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Stereoselective Alkylation of Chiral 2-Imidoylphenols with Organolithium Reagents: Synthesis of Enantiopure 2-Aminoalkylphenols

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In this paper the addition of organolithium reagents to chiral imidoylphenols to prepare enantiopure phenolic Mannich-type bases is described. The experimental data show that this kind of imine is surprisingly reactive toward organolithium reagents, differently from classical imines, and does not need any Lewis acid or base activation. Moreover, interesting results have been obtained with aldimines but more unusually with ketimines. This reaction results in high yields and diastereoselectivities and allows the preparation of aminophenols quaternary at the C-1 carbon atom, which cannot be prepared with the methods available till now. The sense of asymmetric induction has been explained and confirmed in agreement with the results previously obtained by hydride reduction of the same substrates. In some cases this procedure is complementary to the reductive one, allowing the preparation of the diastereomers less abundant in the reduction. The reaction allows the synthesis of one or the other of the two diastereomers, choosing the opportune starting imidoylphenol and the organolithium reagent.

Introduction

The development of efficient enantioselective catalysts applicable to a wide range of reactions represents an important challenge in synthetic organic chemistry.[1]

In previous works it was found that a catalytic amount of enantiopure aminoalkylphenols **3** and aminoalkylnaphthols **4** considerably accelerates the addition of dialkylzincs to aldehydes, affording the corresponding alcohol **2** in good enantiomeric purity[2] (see Scheme 1). The precatalyst aminophenols **3**, known also for their potential utility as pharmaceuticals, insect growth regulators, sterilants, and photochromic and thermochromic molecules,[3] are very accessible compounds, generally obtained by stereoselective reduction of the corresponding 2-imidoylphenols.[2a,b,4] On the other hand, the aminoalky-

SCHEME 1. Enantioselective Catalyzed Alkylation of Aldehydes with Organozinc Reagents

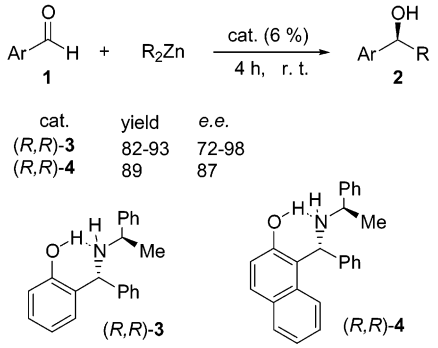

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TABLE 1. Stereoselective Addition of Organolithium Reagents to Chiral Imines (*R*)-5a−f

					method A[a]			method B[a]		
entry	(*R*)-**5**	R	R^1	**6**[b]	**yield**[c] (%)	dr	de	yield[c] (%)	dr	de
1	(*R*)-**5a**	H	Me	(*R,R*)-**6aa**[4a]	95	69/31	38	97	24/76	52
2	(*R*)-**5a**	H	Bu	(*R,R*)-**6ab**	94	68/32	36			
					92[d] (62)	73/27	46			
3	(*R*)-**5b**	Me	Bu	(*R,R*)-**6bb**	68	76/24	52			
4	(*R*)-**5c**	H	Me	(1*S*,1*R*)-**6ca**[2a]	98	65/35	30	98	74/26	48
5	(*R*)-**5c**	H	Bu	(*R,R*)-**6cb**	98	61/39	22	96 (49)	62/38	24
6	(*R*)-**5c**	H	Ph	(1*S*,1*R*)-**6cc**[2a]	96	55/45	10	98 (58)	70/30	40
7	(*R*)-**5c**	H	*t*-Bu	(*R,R*)-**6cd**[2a]	95	63/37	26			
8	(*R*)-**5d**	Me	Bu	(1*S*,1*R*)-**6db**	98	90/10	80	94 (79)	95/5	90
9	(*R*)-**5d**	Me	Ph	(1*S*,1*R*)-**6dc**	94	87/13	74	90 (81)	99/1	98
					90[d]	98/2	96			
10	(*R*)-**5d**	Me	*t*-Bu	(1*S*,1*R*)-**6dd**	80[e]	52/48	4			
11	(*R*)-**5e**	Et	Me	(*R,R*)-**6e a**	95	87/13	74	81 (63)	86/14	72
12	(*R*)-**5e**	Et	Bu	(1*S*,1*R*)- **6eb**	96	78/22	56			
					79[d] (69)	98/2	96			
13	(*R*)-**5e**	Et	Ph	(1*S*,1*R*)-**6ec**	94	86/14	72	96 (68)	79/21	58
14	(*R*)-**5e**	Et	*t*-Bu	(1*S*,1*R*)-**6ed**	93[e]	63/37	26			
15	(*R*)-**5f**	Ph	Me	(*R,R*)-**6fa**	23[e]	77/23	54	81 (61)	81/19	62
16	(*R*)-**5f**	Ph	Bu	(*R,R*)-**6fb**	85[e]	71/29	42	72 (39)	61/39	22
17	(*R*)-**5f**	Ph	*t*-Bu	(1*S*,1*R*)-**6fd**	80[e]	59/41	18			

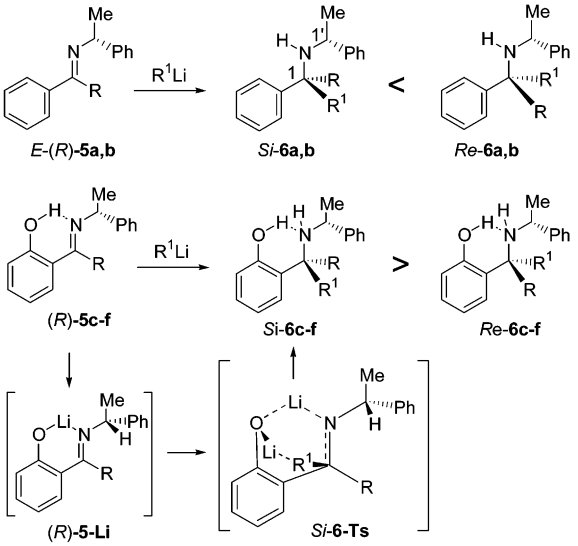
[a] Method A: R^1Li (3.5 equiv), *n*-hexane, 0−40 °C, 1−4 h. Method B: R^1Li (3.5 equiv), TMEDA (3.5 equiv), toluene, 0 °C to rt, 15−60 min. [b] Major diastereomer. In the numbering of compound **6**, the first letter derives from the starting imidoylphenol **5** while the second one shows the organolithium reagent used. [c] Combined yields of the two diastereomers isolated. The yields of the isolated pure major diastereomer are given in parentheses. [d] Reaction performed at − 70 °C for 1 h. [e] Reaction performed at 40 °C for 1−3 h.

lation of electron-rich aromatic compounds (the aromatic Mannich reaction) is an alternative route to aminonaphthols **4** which have catalytic properties similar to those of aminoalkylphenols.[2b,5] Anyway, all these reactions afford only methylene or methine C-1 carbon atom products. The search for quaternary C-1 carbon atom aminoalkylphenols prompted us to explore a new synthetic strategy for their preparation.

The diastereoselective addition of organometallic reagents to the C═N bond of chiral 2-imidoylphenol **5** appears to be an alternative appealing route to obtain enantiomerically pure quaternary C-1 carbon atom aminoalkylphenols **6**. In fact, it is known that the diastereoselective addition of organometallic reagents to imines is one of the key methods for preparing various amines.[6]

The addition of organometallic reagents to ketimines is not widely reported because imines have a propensity to enolize. Enolizable ketimines are generally inert to organometallic reagents and undergo complete enolization in their presence. Therefore, the majority of the literature in this field addresses the addition of organometallic reagents to aldimines, but not to ketimines. Moreover, an additional challenge to this approach is that imines tend to have poor reactivity toward nucleophilic addition and are often activated by the presence of a Lewis acid or by the presence of bases such as TMEDA or (−)-sparteine[6c,f,g] or through substitution of nitrogen with activating groups such as *N*-acyliminium ions and nitrones.

SCHEME 2. Mechanism Hypothesis for the Stereoselective Alkylation of the Imines (*R*)-5a,b and Imidoylphenols (*R*)-5c−f



In this paper, we report the results of our work on the diastereoselective addition of organolithium reagents to chiral 2-imidoylphenols, in which chiral 1-phenylethylamine is used as a convenient chiral auxiliary (see Scheme 2). Due to the intramolecular hydrogen bond, the starting chiral 2-imidoylphenols **5c−f** are stable materials, very accessible, and easily prepared in high yields from (*R*)-1-phenylethylamine and the required *o*-acylphenols under solventless conditions.[7]

Results and Discussion

The results of the diastereoselective alkylation of aldimine (*R*)-**5a,c**, reported in Table 1, are good, but even

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better de's were observed with ketimines (*R*)-**5d**−**f** (up to 96% de).

The alkylation is fast in all the reactions with high yields under both conditions (methods A and B), with the exception in the case of the preparation of (*R*,*R*)-**6fa** (23% yield with method A). The reactions were performed with the same good results in *n*-hexane or toluene, solvents with low coordinating ability for organolithium reagents. In THF the alkylation reaction does not occur. The use of the bulkier 1-naphthylethylamine as chiral auxiliary does not improve the asymmetric induction, and the results are the same using 1-phenylethylamine (1-naphthylethylamine imidoylphenols of 2-hydroxybenzaldehyde and 2-hydroxyacetophenone, treated with butyllithium according to method A, gave de's of 20% and 80%, respectively). Generally better yields and de's were obtained with the use of TMEDA, but good results are obtained in several entries even in the absence of it. The (−)-sparteine serves effectively as the external ligand, showing a dramatic effect on the alkylation of aldimines with alkyllithium (ee up to 91%) as reported in the literature.[6c,f,g] We have observed that, by using the (−)-sparteine in stoichiometric quantities in the alkylation of (*R*)- and (*S*)-**5c** with methyllithium, the same low diastereoselectivity (de = 41%) with both enantiomers of the starting material was obtained, showing any participation of the (−)-sparteine in the reaction. The fast alkylation also in the absence of TMEDA and the lack of effects of the (−)-sparteine on the reaction allow one to hypothesize that the first step of this reaction is the chelation of substrate on a lithium atom, forming the intermediate (R)-**5-Li**. It is more reactive than the starting material toward the nucleophilic alkylation, which occurs intramolecularly through the transition state *Si*-**6-TS** (see Scheme 2). Therefore, the alkylation proceeded smoothly also in the case of ketimines to give the *Si*-**6c**−**f** diastereomers predominantly. The best diastereoselectivities are obtained in the synthesis of aminophenols **6db,dc,ea,ec**. With a lowering of the reaction temperature (−70 °C) as in entries 2, 9, 12, the reaction is still fast and the products show a higher diastereoselectivity, but a consequent lowering of the yields was observed. As seen in Scheme 2 and Table 1, in the case of imine (*R*)-**5a,b** the nucleophilic addition of the organolithium reagent takes place preferentially on the *Re* diastereotopic face of the imine. Conversely, in the case of imidoylphenols (*R*)-**5c**−**f** the alkylation occurs preferentially on the *Si* face of the imine function. This asymmetric induction is the same as that observed in the reduction of the imidoylphenols, where the intramolecular transfer of the hydride occurs preferentially on the less hindered *Si* face of the imine function.[2a,4a] Unique exceptions are the cases of the aminophenols **6-cb,cd**,**fd**, where the major diastereomer obtained was derived from the alkylation on the *Re* face. Moreover, the exchange of R with R^1 on the starting imidoylphenol and on the alkyllithium reagent allows one or the other of the two possible diastereomers to be obtained as the major product (entries 9 and 15). This stereoconvergent synthesis is a confirmation of the hypothesized mechanism of the asymmetric induction.

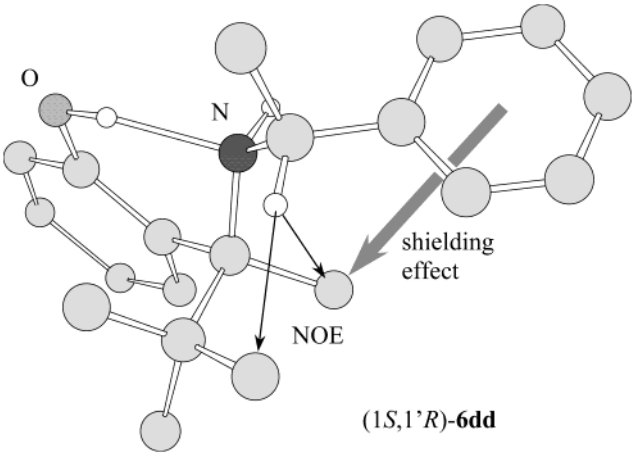

FIGURE 1. The more stable conformation for the aminophenol (1*S*,1′*R*)-**6dd** (PM3 semiempirical level minimization[12]) with the indication of the shielding effect and NOE observed.

Stereochemistry

The diastereomeric ratio was determined by ^{1}H NMR analysis of the amines **6** before and/or after purification. Generally, the ^{1}H NMR spectra of these diastereomeric mixtures show the signals of the two methine protons H-1 and H-1′ of the (*R*,*R*) diastereomers at higher fields than those of the corresponding protons of the (*S*,*R*) diastereomers.[2,5,6f,8] The configurations of the aminophenols (*R*,*R*)-**6ca**−**cd** were attributed to the ^{1}H NMR shielding effects, caused by the Ph-1′ group, on the benzylic hydrogen H-1,[9] in agreement with the most stable conformation obtained with the semiempirical minimization (PM3),[12] or X-ray diffraction on analogous structures.[2d,5,8] Analogously, for *o*-aminophenols **6db**−**fd**, with a quaternary C-1 carbon atom, the conformational analysis, with a systematic search procedure (PM3 semiempirical level minimization),[12] has revealed the preferred more stable conformation reported in Figure 1. Also in this conformation the Ph-1′ group causes a shielding effect on the C-1 group under it,[9] allowing the ^{1}H NMR data of these products to be explained too.

On the basis of these considerations, NOE ^{1}H NMR experiments were carried out on the *o*-aminophenols (1*S*,1′*R*)-**6db,dd** and (*R*,*R*)-**6ea** to have experimental confirmation of configuration and conformation attributions. Inversion of the H-1′ quartet lines enhances the geminal Me-1′ and both the alkyl groups at the C-1 carbon atom signals, validating the results obtained by conformational analysis.

Asymmetric Induction

The sense of asymmetric induction observed in the alkylation of the imine (*R*)-**5a** can be rationalized through a cyclic transition state, *Re*,*Z*-**6aa-TS** (see Figure 2a). After the preliminary formation of a complex between the σ-donor *E*-imine and alkyllithium, an *E* to *Z* isomerization occurs to the more stable *Z*-**5a-Li** followed by the

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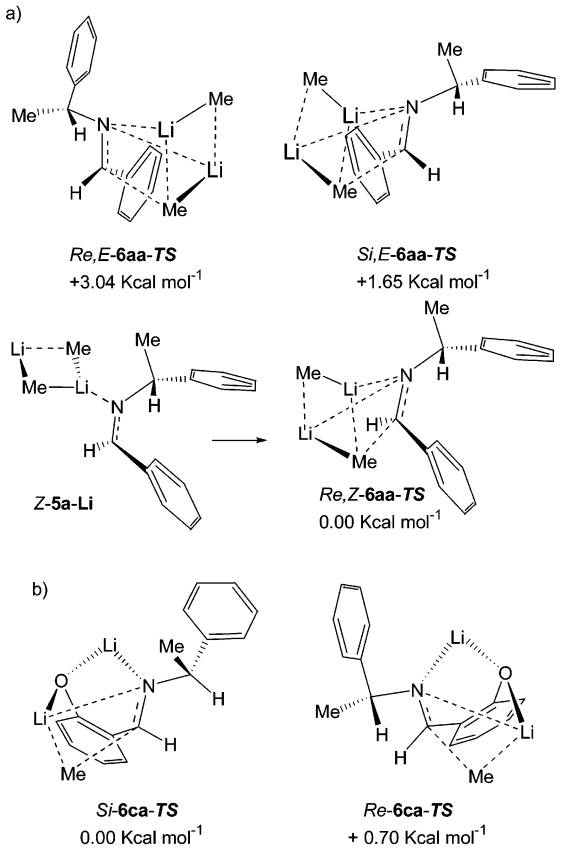
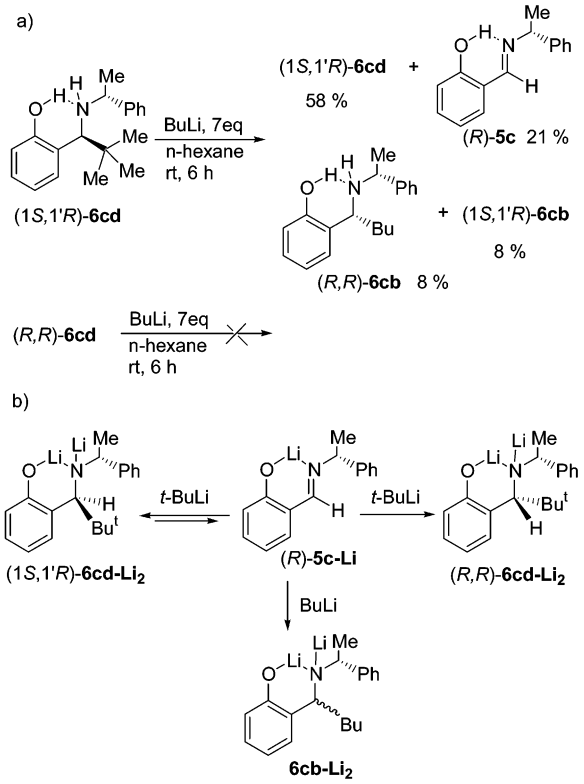


FIGURE 2. The hypothetical more stable *Re* and *Si* transition structures for the alkylation of (a) the imine (*R*)-**5a** and (b) the imidoylphenol (*R*)-**5c** (PM3 semiempirical level minimization[12]).

carbon−carbon bond forming step.[6f,10] The diastereoselectivity is dictated by the orientation of the auxiliary group; the nucleophile attacks preferentially the *Re* less hindered π face of the imine. The alternative *Si,E*- and *Re,E*-**6aa-TS** transition states are more unstable than the *Re,Z*-**6aa-TS** one (see Figure 2a).

The imines (*R*)-**5c**−**f**, capable of acting as bidentate ligands toward lithium ion, react with the organolithium reagents to form reactive imine complexes, e.g., (*R*)-**5-Li**. The bridged lithium atom, coordinated to oxygen and nitrogen atoms, activates the imine function toward the nucleophilic addition, forming a rigid six-membered ring and constraining the imine function in the *E*-configuration. Successively, the complex (*R*)-**5-Li** should coordinate a second molecule of organolithium reagent and convert to the amine **6ca** through a six-membered cyclic transition state, *Si*-**6ca-TS**, more stable than *Re*-**6ca-TS**[10,11] (see Figure 2b). This consideration explains both the sense of asymmetric induction for the alkylation of these substrates and the particular reactivity of these substrates toward the nucleophiles used, due to the role of the oxygen atom in the reaction mechanism.

SCHEME 3. Experimental Evidence (a) and Mechanism Hypothesis (b) for the Epimerization of the Aminophenol 6cd



A unique exception to this kinetic control was observed for the case of aminophenols **6cb,cd,fd**, where the thermodynamically more stable (*R,R*)-**6cb,cd** and (1*S*,1′*R*)-**6fd** are the predominant diastereomers obtained in the reaction. In particular, monitoring the synthesis of the aminophenol **6cd**, following the progress of the reaction by ^{1}H NMR of the reaction mixture aliquot, it is possible to see an initial predominant presence of the kinetically favorite (1*S*,1′*R*)-**6cd** (de = 8%, starting reaction temperature −40 °C). When the temperature was allowed to rise slowly to 40 °C, the complete conversion was observed with the final predominant formation of the thermodynamically more stable (*R,R*)-**6cd** (de = 26%). The hypothesis of the reversibility of the alkylation reaction was ascertained by the experiments shown in the Scheme 3a.

While (*R,R*)-**6cd** is stable in the presence of BuLi, (1*S*,1′*R*)-**6cd** partially eliminates *t*-BuLi to the intermediate (*R*)-**5c-Li**, which adds BuLi to **6cb-Li**$_2$ (see Scheme 3b).

Conclusion

In summary, addition of organolithium reagents to chiral imidoylphenols to prepare enantiopure phenolic Mannich-type bases was explored, which resulted in a high-yielding and quite fast reaction. Owing to the presence of the oxygen atom in the molecule, this class of imines are very reactive toward the nucleophhiles used

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and do not need any Lewis acid or base activation. Good to high diastereoselectivities were observed with aldimines but more unusually with ketimines, and uncommon diastereoisomers were prepared. This reaction allows the preparation of aminophenols quaternary at the C-1 carbon atom, which cannot be prepared with the methods available till now. The sense of asymmetric induction has been explained and confirmed in agreement with the results previously obtained for hydride reduction of the same substrates. The reaction allows the synthesis of one or the other of the two diastereomers, choosing the opportune starting imidoylphenol and the commercially available organolithium reagent. Hypotheses on transition-state models to explain the observed diastereoselectivity were verified by molecular modeling calculations.[12] Further studies with other organometallic reagents are in progress.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, with $CDCl_3$ as solvent at ambient temperature and were calibrated using residual undeuterated solvents as the internal reference. Coupling constants are given in hertz. IR spectra were recorded using an FTIR apparatus.

Materials and Solvents. All reagents were commercially available, were purchased at the highest quality, and were purified by distillation when necessary. Hexane and toluene were distilled and stored on sodium wire before use. The following organolithium reagents were used: MeLi (1.6 M solution in diethyl ether), BuLi (2.5 M solution in hexane), PhLi (1.8 M solution in cyclohexane/diethyl ether, 70/30), *t*-BuLi (1.7 M solution in pentane).

Diastereoselective Alkylation of 2-Imidoylphenols. Synthesis of Aminoalkylphenols (*R*)-6. Typical Procedures. Method A. In the following typical procedure organolithium reagent (7.0 mmol) was added dropwise to a stirred solution of the imine (*R*)-**5** (2.0 mmol) in dry hexane (10 mL) at 0 °C under a nitrogen atmosphere over 15 min. After being stirred for the time required for the complete conversion (1−4 h, following the progress of the reaction by TLC and ^{1}H NMR), allowing the temperature to rise slowly to ambient or higher (40 °C for the preparation of **6dd,ed,fa,fb,fd**), the reaction was quenched with saturated ammonium chloride (20 mL). The reaction mixture was diluted with CH_2Cl_2 (30 mL), and the organic layer was separated, washed with brine, and dried over Na_2SO_4. After removal of the solvent, the yellow oil obtained was subjected to flash column chromatography on silica gel with AcOEt/*n*-hexane (1/30 to 1/5, v/v) to give the pure diastereomers.

Method B. Organolithium reagent (7.0 mmol) was added dropwise to a stirred solution of the imine (*R*)-**5** (2.0 mmol) in dry toluene (10 mL) and TMEDA (7.0 mmol, 1.0 mL) at 0 °C under a nitrogen atmosphere over 15 min. After the mixture was stirred for the time required for the complete conversion (15−60 min, following the progress of the reaction by TLC and ^{1}H NMR), allowing the temperature to rise slowly to ambient, the workup was carried out as described in method A.

The characterization of the prepared unknown aminophenols **6aa**−**fd** follows. Where the major diastereomer only was obtained pure by chromatography, the ^{1}H NMR signals for the minor diastereomers were deduced from the spectra of the crude reaction mixtures or from enriched chromatographic fractions. When it was impossible to isolate the diastereomers with high optical purity, the determination of optical activity was omitted.

Data for (1*R*)-1-phenyl-*N*-[(1′*R*)-1-phenylethyl]pentan-1-amine [(*R,R*)-6ab]: colorless oil; $[\alpha]^{20}_D$ +157.7 (*c* 1.28, $CHCl_3$); IR (neat) ν 2970, 2932, 2862, 1503, 1461, 1256 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, 3 H, J = 7.0 Hz), 1.00−1.25 (m, 4 H), 1.30 (d, 3 H, J = 6.6 Hz), 1.50−1.67 (m, 3 H), 3.31 (t, 1 H, J = 7.0 Hz), 3.52 (q, 1 H, J = 6.6 Hz), 7.20−7.40 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.7, 25.2, 28.6, 38.5, 54.9, 60.0, 126.7, 127.0, 127.2, 127.8, 128.3, 128.4, 144.9, 145.9. Anal. Calcd for $C_{19}H_{25}N$, (267.409): C, 85.34; H, 9.42; N, 5.24. Found: C, 85.27; H, 9.46; N, 5.01.

Data for (1*S*)-1-phenyl-*N*-[(1′R)-1-phenylethyl]pentan-1-amine [(*1S,1′*R)-6ab]: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3 H, J = 6.8 Hz), 1.00−1.32 (m, 4 H), 1.37 (d, 3 H, J = 6.6 Hz), 1.54−1.90 (m, 3 H), 3.74 (t, 1 H, J = 5.5 Hz), 3.75 (q, 1 H, J = 6.2 Hz), 7.20−7.60 (m, 10 H).

Data for (*R,R*)-2-phenyl-*N*-(1-phenylethyl)hexan-2-amine [(*R,R*)-6bb]: colorless oil; $[\alpha]^{20}_D$ +110.33 (*c* 1.15, $CHCl_3$); IR (neat) ν 3025, 2930, 1685, 1602, 1492, 1373, 1267, 762, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (t, 3 H, J = 7.0 Hz), 0.90−1.20 (m, 4H), 1.27 (d, 3 H, J = 6.7 Hz), 1.37 (s, 3 H), 1.58−1.80 (m, 3 H), 3.60 (q, 1 H, J = 6.7 Hz), 7.10−7.40 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 23.1, 26.3, 27.0, 27.3, 41.3, 52.8, 59.5, 126.0, 126.2, 126.5, 126.6, 127.8, 128.1, 147.6, 148.5; API-ES MS *m*/*z* 282 (M^+ + H). Anal. Calcd for $C_{20}H_{27}N$ (281.485): C, 85.35; H, 9.67; N, 4.98. Found: C, 85.37; H, 9.48; N, 7.87.

Data for (2*S*)-2-phenyl-*N*-[(1R)-1-phenylethyl]hexan-2-amine [(*1S,1′*R)-6bb]: colorless oil; $[\alpha]^{20}_D$ +140.95 (*c* 2.0, $CHCl_3$); IR (neat) ν 3024, 2862, 1492, 1446, 1375, 1026, 762, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, 3 H, J = 7.0 Hz), 0.86−1.15 (m, 4H), 1.19 (s, 3 H), 1.20 (d, 3 H, J = 6.6 Hz), 1.26 (m, 3 H), 3.57 (q, 1 H, J = 6.7 Hz), 7.15−7.45 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 23.3, 24.7, 26.4, 27.3, 45.7, 53.2, 59.9, 126.3, 126.4, 126.5, 126.6, 128.1, 128.3, 148.0, 149.6; API-ES MS *m*/*z* 282 (M^+ + H). Anal. Calcd for $C_{20}H_{27}N$ (281.485): C, 85.35; H, 9.67; N, 4.98. Found: C, 85.28; H, 9.50; N, 5.13.

Data for 2-((1*R*)-*1*-{[(1′*R*)-1-phenylethyl]amino}pentyl)-phenol [(*R,R*)-6cb]: colorless oil; IR (neat) ν 2964, 2935, 2859, 1469, 1261, 754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, 3 H, J = 7.0 Hz), 1.00−1.40 (m, 4 H), 1.44 (d, 3 H, J = 6.6 Hz), 1.60−1.80 (m, 2 H), 2.00 (br s, 1 H), 3.43 (t, 1 H, J = 7.0 Hz), 3.72 (q, 1 H, J = 6.8 Hz), 6.72−6.96 (m, 3 H), 7.10−7.45 (m, 6 H), 13.78 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.4, 23.6, 28.3, 35.9, 55.2, 61.0, 116.6, 118.8, 125.5, 126.3, 127.4, 128.2, 128.7, 129.0, 143.5, 157.7. Anal. Calcd for $C_{19}H_{25}NO$ (283.408): C, 80.52; H, 8.89; N, 4.94. Found: C, 80.66; H, 8.81; N, 4.81.

Data for 2-((1*S*)-1-{[(1′R)-1-phenylethyl]amino}pentyl)-phenol [(*1S,1′R*)-6cb]: colorless oil; $[\alpha]^{20}_D$ +71.2 (*c* 1.73, $CHCl_3$); IR (neat) ν 2958, 2930, 2859, 1491, 1474, 1256, 754, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 7.0 Hz), 1.00−1.40 (m, 4 H), 1.49 (d, 3 H, J = 6.6 Hz), 1.60−1.80 (m, 2 H), 2.00 (br s, 1 H), 3.87 (q, 1 H, J = 6.6 Hz), 3.90 (t, 1 H, J = 7.1 Hz), 6.72−6.96 (m, 3 H), 7.10−7.45 (m, 6 H), 13.78 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.3, 22.6, 28.5, 35.1, 54.1, 61.0, 116.8, 118.7, 125.7, 126.5, 127.3, 128.3, 128.6, 128.8, 143.8, 157.4. Anal. Calcd for $C_{19}H_{25}NO$ (283.408): C, 80.52; H, 8.89; N, 4.94. Found: C, 80.27; H, 8.71; N, 4.87.

Data for 2-((1*S*)-1-methyl-1-{[(1′*R*)-1-phenylethyl]-amino}pentyl)phenol [(*1S,1′R*)-6db]: yellow oil; $[\alpha]^{20}_D$ +6.72 (*c* 2.50, $CHCl_3$); IR (neat) ν 2932, 1608, 1458, 1253 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, 3 H, J = 7.2 Hz), 1.05−1.25 (m, 4 H,), 1.33 (d, 3 H, J = 6.7 Hz), 1.37 (s, 3 H), 1.55 (br s, 1 H), 1.80−2.10 (m, 2 H), 3.88 (q, 1 H, J = 6.7 Hz), 6.70−7.60 (m, 9 H), 12.40 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 23.5, 25.4, 26.4, 26.7, 37.3, 53.5, 61.4, 117.7, 119.1, 126.4, 126.9, 127.5, 128.5, 128.6, 130.6, 146.2, 158.3. Anal. Calcd for $C_{20}H_{27}NO$ (297.435): C, 80.76; H, 9.15; N, 4.71. Found: C, 81.87; H, 9.02; N, 4.49.

Data for 2-((1*R*)-1-methyl-1-{[(1′*R*)-1-phenylethyl]-amino}pentyl)phenol [(*R,R*)-6db]: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, 3 H, J = 7.1 Hz), 1.05−1.25 (m, 4 H), 1.30 (d, 3 H, J = 6.6 Hz), 1.47 (s, 3 H), 1.80−2.10 (m, 3 H), 4.00 (q, 1 H, J = 6.7 Hz), 6.70−7.60 (m, 9 H), 12.40 (br s, 1 H).

Data for 2-((1*S*)-1-phenyl-1-{[(1′*R*)-1-phenylethyl]-amino}ethyl)phenol [(1*S*,1′*R*)-6dc]: colorless oil; $[\alpha]^{20}_D$ +63.3 (*c* 2.89, $CHCl_3$); IR (neat) ν 2981, 1583, 1453, 1258, 756, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, 3 H, J = 6.6 Hz), 1.59 (s, 3 H), 2.83 (br s, 1 H), 3.64 (q, 1 H, J = 6.7 Hz), 6.40−7.70 (m, 14 H), 12.70 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 26.6, 53.6, 66.2, 117.1, 118.6, 126.3, 127.0, 127.4, 127.5, 128.4, 128.5, 128.6, 128.8, 132.1, 144.3, 146.7, 157.5; API-ES MS *m/z* 318 (100, M^+ + H). Anal. Calcd for $C_{22}H_{23}NO$ (317.424): C, 83.24; H, 7.30; N, 4.41. Found: C, 83.05; H, 7.47; N, 4.32.

Data for 2-((1*S*)-1-phenyl-1-{[(1′R)-1-phenylethyl]-amino}ethyl)phenol [(*R,R*)-6dc]: see the data for [(*R*,*R*)-**6fa**].

Data for 2-((1*S*)-1,2,2-trimethyl-1-{[(1′R)-1-phenylethyl]-amino}propyl)phenol [(1S,1′R)-6dd]: colorless oil; $[\alpha]^{20}_D$ −41.7 (*c* 0.64, $CHCl_3$); IR (neat) ν 2982, 1603, 1452, 1261, 763, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 9 H), 1.33 (d, 3 H, J = 7.0 Hz), 1.45 (s, 3 H), 2.32 (br d, 1 H, J = 5.9 Hz), 4.02 (dq, 1 H, J = 6.4, 6.2 Hz), 6.80−7.20 (m, 9 H), 13.60 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 22.8, 26.2, 40.2, 54.0, 66.7, 117.1, 117.7, 126.2, 126.9, 127.3, 128.4, 128.9, 129.6, 146.7, 159.2. Anal. Calcd for $C_{20}H_{27}NO$ (297.435): C, 80.76; H, 9.15; N, 4.71. Found: C, 81.32; H, 8.98; N, 4.62.

Data for 2-((1*R*)-1,2,2-trimethyl-1-{[(1′R)-1-phenylethyl]-amino}propyl)phenol [(R,R)-6dd]: colorless oil; $[\alpha]^{20}_D$ +138.2 (*c* 0.73, $CHCl_3$); IR (neat) ν 2963, 1606, 1461, 1295, 751, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 9 H), 1.52 (d, 3 H, J = 6.6 Hz), 1.72 (s, 3 H), 2.04 (br s, 1 H), 3.80−4.00 (m, 1 H), 6.50−7.20 (m, 9 H), 12.20 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 26.5, 27.1, 40.2, 53.0, 67.0, 117.1, 117.4, 126.0, 126.3, 126.9, 128.2, 128.3, 129.8, 145.3, 158.3. Anal. Calcd for $C_{20}H_{27}NO$ (297.435): C, 80.76; H, 9.15; N, 4.71. Found: C, 81.45; H, 8.89; N, 4.84.

Data for 2-((1*R*)-1-methyl-1-{[(1′R)-1-phenylethyl]-amino}propyl)phenol [(R,R)-6ea]: yellow oil; $[\alpha]^{20}_D$ −15.4 (*c* 2.40, $CHCl_3$); IR (neat) ν 2972, 1460, 1257, 754, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.69 (t, 3 H, J = 7.5 Hz), 1.29 (d, 3 H, J = 7.0 Hz), 1.44 (s, 3 H), 1.52−1.70 (m, 1 H), 1.89−2.07 (m, 1 H), 2.00 (br s, 1 H), 4.00 (q, 1 H, J = 6.7 Hz), 6.76−7.42 (m, 9 H), 12.75 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.0, 23.4, 24.2, 34.5, 53.7, 61.8, 117.2, 118.7, 126.4, 127.2, 127.5, 128.7, 129.0, 129.2, 146.7, 158.1; API-ES MS *m/z* 270 (100, M^+ + H). Anal. Calcd for $C_{18}H_{23}NO$ (269.381): C, 80.26; H, 8.61; N, 5.20. Found: C, 80.43; H, 8.52; N, 5.37.

Data for 2-((1*S*)-1-methyl-1-{[(1′R)-1-phenylethyl]-amino}propyl)phenol [(1S,1′R)-6ea]: ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, 3 H, J = 7.6 Hz), 1.28 (d, 3 H, J = 6.7 Hz), 1.37 (s, 3 H), 1.52−1.70 (m, 1 H), 1.89−2.07 (m, 1 H), 2.00 (br s, 1 H), 3.92 (q, 1 H, J = 6.7 Hz), 6.76−6.42 (m, 9 H), 12.75 (br s, 1 H).

Data for 2-((1*S*)-1-ethyl-1-{[(1′R)-1-phenylethyl]amino}-pentyl)phenol [(1S,1′R)-6eb]: colorless oil; $[\alpha]^{20}_D$ −11.0 (*c* 1.48, $CHCl_3$); IR (neat) ν 2970, 1735, 1502, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.54 (t, 3 H, J = 7.3 Hz), 0.88 (t, 3 H, J = 7.1 Hz), 0.92−1.15 (m, 4 H), 1.26 (d, 3 H, J = 6.1 Hz), 1.48 (dq, 1 H, J = 7.2, 13.6 Hz), 1.70−2.20 (m, 3 H), 2.10 (br s, 1H), 3.88 (q, 1 H, J = 6.7 Hz), 6.68−7.60 (m, 9 H), 12.80 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.4, 14.2, 23.0, 23.7, 24.8, 29.4, 30.9, 53.1, 63.9, 117.2, 118.3, 126.5, 127.1, 127.4, 128.3, 128.4, 128.7, 146.0, 158.1; API-ES MS *m/z* 312.0 (M^+ + H, 100). Anal. Calcd for $C_{21}H_{29}NO$ (311.461): C, 80.98; H, 9.38; N, 4.50. Found: C, 81.12; H, 9.50; N, 4.59.

Data for 2-((1*R*)-1-ethyl-1-{[(1′R)-1-phenylethyl]amino}-pentyl)phenol [(*R,R*)-6eb]: colorless oil; IR (neat) ν 2960, 1730, 1493, 1254 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.71 (t, 3 H, J = 7.3 Hz), 0.79 (t, 3 H, J = 7.3 Hz), 0.90−1.20 (m, 4 H), 1.25 (d, 3 H, J = 6.4 Hz), 1.50 (br s, 1 H), 1.80−2.20 (m, 4 H), 3.89 (q, 1 H, J = 6.6 Hz), 6.70−7.20 (m, 9 H), 12.60 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.1, 13.9, 22.8, 23.6, 24.4, 25.8, 29.7, 35.7, 53.3, 117.3, 118.5, 126.6, 126.9, 127.6, 127.8, 128.1; 128.5, 128.7, 158.0. Anal. Calcd for $C_{21}H_{29}NO$ (311.461): C, 80.98; H, 9.38; N, 4.50. Found: C, 80.95; H, 9.42; N, 4.43.

Data for 2-((1*S*)-1-phenyl-1-{[(1′R)-1-phenylethyl]-amino}propyl)phenol [(1S,1′R)-6ec]: yellow oil; IR (neat) ν 2992, 1605, 1267, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.55 (t, 3 H, J = 7.3 Hz), 1.14 (d, 3 H, J = 6.6 Hz), 1.88−2.22 (m, 2 H), 2.64 (br s, 1 H), 3.58 (q, 1 H, J = 6.8 Hz), 6.50−7.50 (m, 14 H), 12.65 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.7, 26.3, 28.3, 53.1, 70.1, 117.3, 118.1, 126.4, 126.6, 127.2, 127.5, 128.2, 128.5, 128.9, 129.0, 130.5, 143.6, 146.5, 158.7. Anal. Calcd for $C_{23}H_{25}NO$ (331.451): C, 83.3; H, 7.60; N, 4.23. Found: C, 83.50; H, 7.32; N, 4.15.

Data for 2-((1*R*)-1-phenyl-1-{[(1′R)-1-phenylethyl]-amino}propyl)phenol [(*R,R*)-6ec]: yellow oil; IR (neat) ν 2971, 2864, 1469, 1271 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.56 (t, 3 H, J = 7.3 Hz), 1.40 (d, 3 H, J = 7.0), 1.88−2.22 (m, 2 H), 2.64 (br s, 1 H), 3.84 (q, 1 H, J = 6.6 Hz), 6.50−7.50 (m, 14 H), 12.65 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.2, 24.7, 28.6, 53.1, 67.4, 117.5, 118.7, 126.7, 126.8, 128.1, 128.2, 128.3, 128.6, 129.4, 129.8, 130.8, 144.2, 146.0, 158.1. Anal. Calcd for $C_{23}H_{25}NO$ (331.451): C, 83.34; H, 7.60; N, 4.23. Found: C, 83.41; H, 7.39; N, 4.30.

Data for 2-((1*S*)-1-ethyl-2,2-dimethyl-1-{[(1′R)-1-phenylethyl]amino}propyl)phenol [(1S,1′R)-6ed]: yellow oil; $[\alpha]^{20}_D$ +37.3 (*c* 1.1, $CHCl_3$); IR (neat) ν 2965, 1493, 1461, 1400, 1245, 756, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.63 (t, 3 H, J = 7.1 Hz), 1.08 (s, 9 H), 1.60 (d, 3 H, J = 6.6 Hz), 1.90−2.30 (m, 2 H), 2.40 (br s, 1 H), 4.15−4.30 (m, 1 H), 6.60−7.40 (m, 9 H), 13.80 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.5, 24.2, 26.7, 26.9, 28.2, 40.5, 52.8, 116.9, 117.8, 125.9, 126.5, 127.2, 128.2, 128.7, 131.1, 146.4, 159.3. Anal. Calcd for $C_{21}H_{29}NO$ (311.461): C, 80.98; H, 9.38; N, 4.50. Found: C, 80.73; H, 9.41; N, 4.62.

Data for 2-((1*R*)-1-ethyl-2,2-dimethyl-1-{[(1′R)-1-phenylethyl]amino}propyl)phenol [(R,R)-6ed]: yellow oil; $[\alpha]^{20}_D$ −100.8 (*c* 0.76, $CHCl_3$); IR (neat) ν 2964, 1606, 1463, 757, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (s, 9 H), 1.10 (t, 3 H, J = 7.3 Hz), 1.38 (d, 3 H, J = 6.6 Hz), 2.05−2.35 (m, 2 H), 2.40 (br s, 1 H), 4.20 (q, 1 H, J = 6.6 Hz), 6.80−7.40 (m, 9 H), 14.00 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 22.1, 25.5, 26.9, 41.3, 54.1, 70.0, 116.9, 117.3, 126.5, 127.5, 128.1, 128.9, 130.6, 136.0, 145.8, 160.2. Anal. Calcd for $C_{21}H_{29}NO$ (311.461): C, 80.98; H, 9.38; N, 4.50. Found: C, 80.80; H, 9.50; N, 4.48.

Data for 2-((1*R*)-1-phenyl-1-{[(1′R)-1-phenylethyl]-amino}ethyl)phenol [(*R,R*)-6fa]: yellow oil; IR (neat) ν 2975, 1600, 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (d, 3 H, J = 6.6 Hz), 1.87 (s, 3 H), 2.85 (br s, 1 H), 3.87 (q, 1 H, J = 7.0 Hz), 6.80−7.40 (m, 14 H), 12.50 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 26.1, 53.3, 64.9, 117.2, 118.6, 125.9, 126.3, 127.0, 127.1, 127.8, 128.1, 128.6, 128.8, 130.4, 145.2, 145.7, 157.9. Anal. Calcd for $C_{22}H_{23}NO$ (317.424): C, 83.24; H, 7.30; N, 4.41. Found: C, 83.32; H, 7.40; N, 4.39.

Data for 2-((1′*R*)-1-phenyl-1-{[(1′R)-1-phenylethyl]-amino}pentyl)phenol [(*R,R*)-6fb]: colorless oil; IR (neat) ν 2961, 2871, 1463, 1282 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (t, 3 H, J = 7.1 Hz), 0.90−1.10 (m, 6H), 1.43 (d, 3 H, J = 6.6 Hz), 1.50 (br s, 1 H), 3.84 (q, 1 H, J = 6.7 Hz), 6.60−7.60 (m, 14 H), 11.75 (br s, 1 H). Anal. Calcd for $C_{25}H_{29}NO$ (359.504): C, 83.52; H, 8.13; N, 3.90. Found: C, 83.61; H, 8.09; N, 4.18.

Data for 2-((1*S*)-1-phenyl-1-{[(1′R)-1-phenylethyl]-amino}pentyl)phenol [(1S,1′R)-6fb]: ^1H NMR (300 MHz, $CDCl_3$) δ 0.65 (t, 3 H, J = 7.0 Hz), 0.90−1.01 (m, 6H), 1.15 (d, 3 H, J = 7.0 Hz), 1.50 (br s, 1 H), 3.58 (q, 1 H, J = 6.7 Hz), 6.60−7.60 (m, 14 H), 11.75 (br s, 1 H).

Data for 2-((1*R*)-2,2-dimethyl-1-phenyl-1-{[(1′R)-1-phenylethyl]amino}propyl)phenol [(1S,1′R)-6fd]: colorless oil; IR (neat) ν 2984, 1616, 1473 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 9 H), 1.30 (d, 3 H, J = 6.7 Hz), 1.55 (br s, 1 H), 4.48 (q, 1 H, J = 6.4 Hz), 6.60−7.60 (m, 14 H), 12.30 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 28.8, 37.5, 54.6, 54.9,

116.0, 117.4, 126.0, 126.6, 126.9, 127.0, 127.2, 128.3, 128.6, 128.7, 131.8, 132.4, 133.0, 160.7, 172.4. Anal. Calcd for $C_{25}H_{29}NO$ (359.504): C, 83.52; H, 8.13; N, 3.90. Found: C, 83.48; H, 8.24; N, 4.16.

Data for 2-((1*R*)-2,2-dimethyl-1-phenyl-1-{[(1′R)-1-phenylethyl]amino}propyl)phenol [(R,R)-6fd]: colorless oil; $[\alpha]^{20}_D$ −19.6 (*c* 0.8, $CHCl_3$); IR (neat) ν 2964, 1606, 1452, 756, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9 H), 1.55 (d, 3 H, $J = 6.6$ Hz), 2.00 (br s, 1 H), 4.57 (q, 1 H, $J = 6.5$ Hz), 6.60−7.60 (m, 14 H), 12.30 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 31.3, 34.9, 60.2, 60.5, 117.3, 117.9, 120.0, 125.4, 126.3, 127.0, 127.1, 128.5, 130.8, 132.3, 132.4, 152.1, 163.4, 172.7. Anal. Calcd for $C_{25}H_{29}NO$ (359.504): C, 83.52; H, 8.13; N, 3.90. Found: C, 83.81; H, 7.98; N, 3.88.

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Supporting Information Available: Computational results (Cartesian coordinates of the optimized geometries, semiempirical PM3 level enthalpies of formation, and imaginary frequencies) for *Z*-**5a-Li**, (*R,R*)-**6dd**, *Re,Z*-**6aa-TS**, *Re,E*-**6aa-TS**, *Si,E*-**6aa-TS**, *Re*-**6ca-TS**, and *Si*-**6ca-TS**. This material is available free of charge via the Internet at http://pubs.acs.org.

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