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Synthesis of enantiopure 2-aminoalkylphenols by stereoselective addition of Grignard reagents to chiral 2-imidoylphenols

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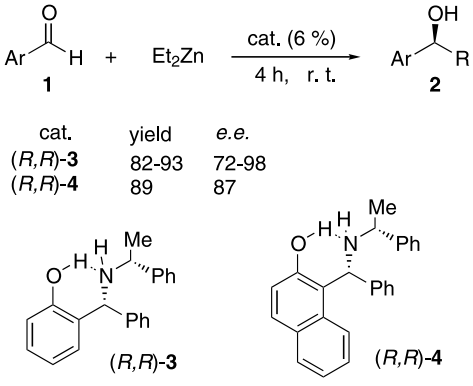
Abstract—The stereoselective addition of Grignard reagents to chiral 2-imidoylphenols affords enantiopure 2-aminoalkylphenols, a class of ligands useful in stereoselective synthesis. Unusually benzyl- and allyl-magnesium chlorides add to ketimines derived from enolizable *o*-acylphenols with high yields and stereoselectivities. In this way a stereogenic quaternary C-1 carbon atom is introduced, which could not be obtained by other methods available till now. The mechanism and the asymmetric induction have been explained in agreement with previously obtained results. © 2002 Published by Elsevier Science Ltd.

1. Introduction

The synthesis of enantiopure amines is an important subject of research because this class of compounds is widespread in biological systems, shows pharmacological activity and has recently found application in asymmetric synthesis as chiral bases, auxiliaries and ligands. The addition of organometallic reagents to chiral imines constitutes an interesting approach to the stereoselective formation of the C–C bond.[1–9] However, this methodology has some drawbacks, owing to the poor electrophilicity of the azomethine carbon and the competition with the enolization in imines containing α-hydrogen. These problems have been partially solved either by activating the C=N bond with a Lewis acid, by converting the imine function to the more reactive iminium salt, nitrone,[10] oximes,[11] or acylimines or alternatively, by using more nucleophilic and less basic reagents, such as organocerium[12] and organocopper[13] compounds. In the literature the additions of organometallic reagents to aldimines are widely reported, while additions to ketimines remain an important challenge. In addition, ketimines can exist in both the *E* and *Z* conformations, so the achievement of high levels of diastereoselectivities is more difficult.

For some time we have been interested in the synthesis of aminoalkylphenols[14–16] and aminoalkylnaphthols,[17] a specific group of amines, since this class of compounds has found application as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde (see Scheme 1).[14,18]

Recently, we have found that organolithium reagents add in very good yields and with high diastereoselectivities to chiral 2-imidoylphenols derived not only from *o*-salicylaldehyde, but more interestingly also from *o*-acylphenols, affording a quaternary stereogenic carbon atom (C-1).[19] Herein, we wish to report our studies on the diastereoselective addition of Grignard reagents to imidoylphenols, prepared from (*R*)-1-phenylethylamine. The use of Grignard reagents is particularly justified in the case of allyl and benzyl organometallics because the corresponding organolithium reagents are not commercially available. In the synthesis of the allylmetal reagents a coupling reaction between the allylmetal



Scheme 1.

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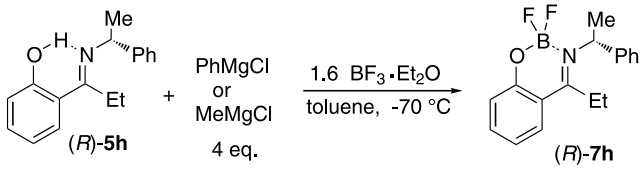
compounds and the allylic halide is a serious complicating factor and no satisfactory preparation of allyllithium appears to be available at present.[20] Generally Grignard reagents have found less application than organolithium compounds because of their poor reactivity towards inactivated imines and their propensity to act as bases with enolizable imines.[21] The more reactive allylmagnesium bromide and benzylmagnesium bromide add to the non-enolizable *N*-(diphenylmethylene)aniline.[22,23] More recently Spero and coworkers reported the stereoselective addition of various Grignard reagents to ketimines prepared from 2-acetylpyridine[24] or methoxyacetone[25] and phenylglycinol as chiral auxiliary, in the presence of $MgBr_2$.

2. Results and discussion

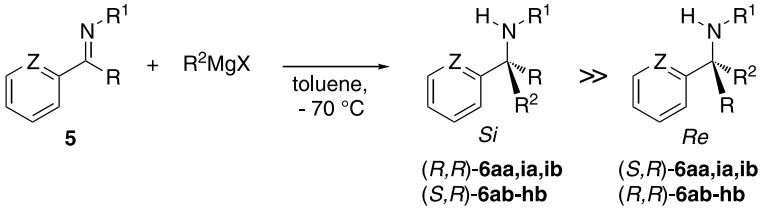
The addition of Grignard reagents was carried out at low temperature (−70°C) in toluene, a non-coordinating hydrocarbon solvent. The results are listed in Table 1. High yields in the addition reaction were obtained both with aldimines (entries 6–12) and enolizable ketimines having a coordinating atom in the aryl group at the *o*-position to the imine function, such as the nitrogen in the pyridine ring (entries 4, 5) and the phenolic oxygen (entries 13–18).

Ketimines react only with the more reactive Grignard reagents derived from stabilized carbanions (allyl- and benzylmagnesium chloride), while with more basic reagents, such as methylmagnesium chloride, the starting material was recovered unchanged, also in the presence of several Lewis acid ($BF_3{\cdot}Et_2O$, $ZnCl_2$, $MgBr_2{\cdot}Et_2O$, $TiCl_4$), since most probably the enolization predominates on the addition. Organolithium reagents appear to be more reactive than Grignard reagents, because MeLi or BuLi also add in high yields to imidoylphenols derived from *o*-acylphenols.[19] When the ketimine (*R*)-**5h** was allowed to react with phenylmagnesium chloride or methylmagnesium chloride in the presence of the boron trifluoride etherate, only the formation of the borate (*R*)-**7h** in high yields was observed, this does not react with the Grignard reagent present (see Scheme 2).



Scheme 2.

Table 1. Synthesis of enantiopure 2-aminoalkylphenols **6** by stereoselective addition of Grignard reagents to chiral 2-imidoylphenols (*R*)-**5**



Entry	**5**	Z	R	R^1	R^2	X	**6**[a]	Time (h)	Yields (%)[b]	Si/Re	D.e.
1	(*R*)-**5a**	CH	H	(*R*)-PhEt	Allyl	Cl	(*R*,*R*)-**6aa**[31]	3	95	42/58	16
2	(*R*)-**5a**	CH	H	(*R*)-PhEt	Benzyl	Cl	(*S*,*R*)-**6ab**	23	18	62/38	24
3	(*R*)-**5b**	N	H	(*R*)-PhEt	Benzyl	Cl	(*S*,*R*)-**6bb**	5	91	57/43	14
4	(*R*)-**5c**	N	Me	(*R*)-PhEt	Allyl	Cl	(*S*,*R*)-**6ca**	4	90	68/32	36
5	(*R*)-**5c**	N	Me	(*R*)-PhEt	Benzyl	Cl	(*S*,*R*)-**6cb**	3	76	91/9	82
6	(*R*)-**5d**	C-OH	H	(*R*)-PhEt	Allyl	Cl	(*S*,*R*)-**6da**	1	94	67/33	34
7	(*R*)-**5d**	C-OH	H	(*R*)-PhEt	Allyl	Br	(*S*,*R*)-**6da**	1	95	75/25	50
8	(*R*)-**5d**	C-OH	H	(*R*)-PhEt	Benzyl	Cl	(*S*,*R*)-**6db**	5	73	62/38	24
9	(*R*)-**5d**	C-OH	H	(*R*)-PhEt	Propyl	Cl	(*S*,*R*)-**6dc**[14]	23	75	63/34	32
10	(*R*)-**5d**	C-OH	H	(*R*)-PhEt	Vinyl	Cl	(*S*,*R*)-**6dd**	23	52	52/48	4
11	(±)-**5e**	C-OH	H	(±)-NpEt	Allyl	Cl	(*S**,*R**)-**6ea**	1	95	61/39	22
12	(±)-**5e**	C-OH	H	(±)-NpEt	Benzyl	Cl	(*S**,*R**)-**6eb**	3	71	76/24	52
13	(*R*)-**5f**	C-OH	Me	(*R*)-PhEt	Allyl	Cl	(*S*,*R*)-**6fa**	3	89	88/12	76
14	(*R*)-**5f**	C-OH	Me	(*R*)-PhEt	Allyl	Br	(*S*,*R*)-**6fa**	3	86	87/13	74
15	(*R*)-**5f**	C-OH	Me	(*R*)-PhEt	Benzyl	Cl	(*S*,*R*)-**6fb**	4	66	95/5	90
16	(±)-**5g**	C-OH	Me	(±)-NpEt	Allyl	Cl	(*S**,*R**)-**6ga**	2	95	91/9	82
17	(*R*)-**5h**	C-OH	Et	(*R*)-PhEt	Allyl	Cl	(*S*,*R*)-**6ha**	3	94	78/22	56
18	(*R*)-**5h**	C-OH	Et	(*R*)-PhEt	Benzyl	Cl	(*S*,*R*)-**6hb**	5	95	99/1	98
19	(*R*)-**5i**	C-OH	Ph	(*R*)-PhEt	Allyl	Cl	(*R*,*R*)-**6ia**	4	78	82/18	64
20	(*R*)-**5i**	C-OH	Ph	(*R*)-PhEt	Benzyl	Cl	(*R*,*R*)-**6ib**	8	40	90/10	80
21	(*R*)-**5j**	C-OMe	Me	(*R*)-PhEt	Allyl	Cl	**6ja**[c]	23	65	58/42[c]	16

[a] Major diastereomer.
[b] Combined yields of the two diastereomers isolated.
[c] Spectroscopic data are insufficient to assign the configuration.

Changing the phenol for naphtholic groups does not afford the same good results. In fact the imidoylnaphthol prepared from (*R*)-1-phenylethylamine and 1′-hydroxy-2′-acetonaphthone adds allylmagnesium chloride only in 40% yield and 77:23 d.r. Moreover, in contrast to aminoalkylphenols, the aminoalkylnaphthol bearing a quaternary stereogenic center is not stable on SiO_2 and eliminates the amine, affording the conjugate alkene. On the other hand the imidoylnaphthol derived from 2′-hydroxy-1′-acetonaphthone does not add allylmagnesium chloride, nor benzylmagnesium chloride.

Low to moderate diastereoselectivities are obtained in the addition of Grignard reagents to aldimines, while a higher increase asymmetric induction is observed with ketimines, because of the major steric hindrance of alkyl groups (d.r. up 99:1, entry 18). This trend is similar to that previously seen in the addition of organolithium reagents. Generally benzylmagnesium chloride affords aminoalkylphenols with better diastereoselectivities than the more reactive allylmagnesium chloride. When the phenol is replaced with a pyridine ring lower stereoselectivity is observed (entries 3–5 compared with entries 8, 13, 15, respectively). However, using imines derived from (*R*)-1-phenylethylamine with a coordinating atom in the other aryl group the addition of organometallic reagents takes place preferentially to the *Si* face of the double bond of the iminic function in all cases.

Entry 21 shows the importance of the free OH group: in fact when it is converted into a methoxy group, the diastereoselectivity of the addition decreases markedly from 76% d.e. to 16% d.e. (entries 13 and 21, respectively). This lowering can be explained observing that the imine (*R*)-**5j** exists as a mixture of *E*/*Z* isomers in a 2:1 ratio,[26] and this invalidates the possibility of a highly stereoselective addition. On the other hand the C=N bond of imidoylphenols is forced in the *E* configuration by the presence of the intramolecular hydrogen bond and the same configuration is retained in the magnesium six-membered chelate complex intermediate (*R*)-**5-Mg**. Changing the chiral auxiliary (*R*)-1-phenylethylamine to the bulkier 1-naphthylethylamine affords a moderate increase in the diastereoselectivity, as does the substitution of Cl with Br in the Grignard reagent.

3. Stereochemistry

The absolute configuration was assigned on the basis of the chemical shifts general trend observed in the ^{1}H NMR spectra and the more stable conformations calculated by molecular modeling. For amines derived from aldimines it can be seen that the methine proton H-1 bound at the new stereogenic center on the C-1 carbon atom in the (*R*,*R*)-diastereomers is always shifted upfield compared to the corresponding proton on the (*S*,*R*) diastereomers. This shift was attributed to the phenyl ring of the auxiliary amine, that exerts a shielding magnetic anisotropy effect on the benzylic H-1 proton in the (*R*,*R*) diastereomers, in agreement with the most stable conformation obtained with semiempirical minimization (PM3),[27] or X-ray diffraction on analogous structure.[17,28] To assign the configuration of compounds with a quaternary stereogenic centre, molecular modeling conformational analysis and NOE experiments were carried out. The more stable conformation was obtained by a systematic search procedure (PM3 semiempirical level minimization). As illustrated in the Fig. 1 for the aminophenol (1*S*,1′*R*)-**6fa**, NOE ^{1}H NMR experiments were carried out.

Irradiation of the H-1′ quartet line enhances the geminal Me-1′ and both the alkyl group signals at the C-1 carbon atom, validating the results obtained by conformational analysis. In this conformation the Ph-1′ group causes a shielding effect on the C-1 group under it, explaining the ^{1}H NMR chemical shift of these products and justifying the configurational assignment.

When imidoylphenols are used as starting materials, an initial acid–base reaction between the phenolic OH and the Grignard reagent takes place, forming a reactive imine–Mg six-membered chelate complex. The bridged magnesium atom coordinates to both the O and N atoms and activates the C–N double bond towards the nucleophilic addition, retaining the *E* configuration (see Scheme 3).

Subsequently, the complex (*R*)-**5-Mg** should coordinate a second molecule of organomagnesium reagent and

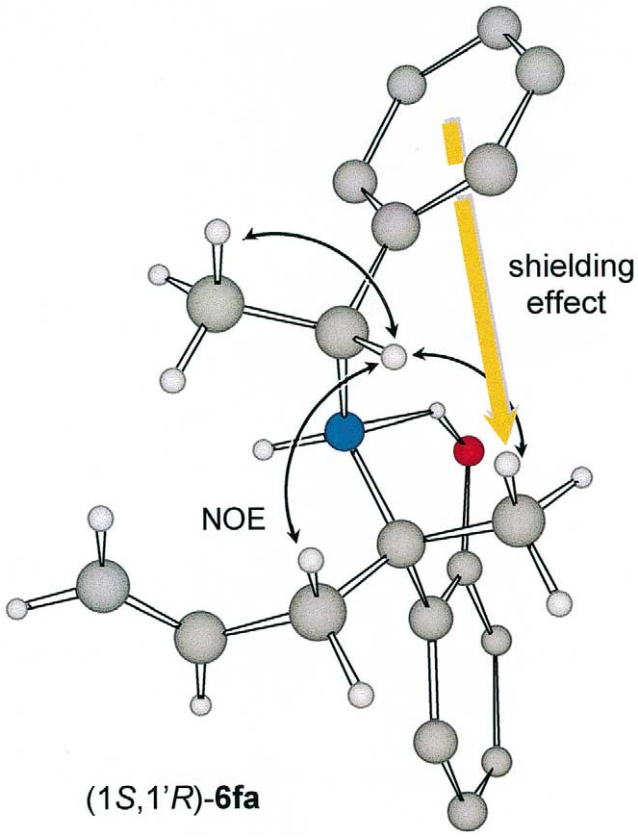
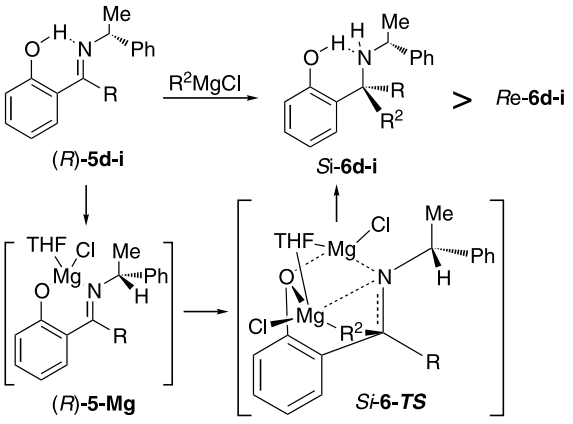


Figure 1. The more stable conformation for the aminophenol (1*S*,1′*R*)-**6fa** (PM3 semiempirical level minimization).



Scheme 3.

convert to the amine **6** through a polycyclic transition state *Si*-**6**-***TS***, which is more stable than *Re*-**6**-***TS*** (see Fig. 2). In this mechanistic hypothesis we have considered that a molecule of THF, derived from the commercial solution of the Grignard reagents, enters the coordination sphere of the magnesium atoms. These transition state models explain both the asymmetric induction and the high reactivity of the imidoyl phenols toward the nucleophiles, as a result of the important role of the oxygen atom in the reaction mechanism. The asymmetric induction is dictated by the orientation of the auxiliary group: the nucleophile preferentially attacks the less hindered *Si*-π face of the imine (see Fig. 2).

The reaction pathway of imines (*R*)-**5b**,**c**, containing a pyridine ring, is similar to that of imidoylphenols and the formation of a five-membered Mg–imine complex is invoked. Also in this case the attack of the Grignard reagents takes place preferentially on the *Si* face of the double bond.

4. Conclusion

In summary, a diastereoselective synthesis of enantiopure aminoalkylphenols by addition of Grignard reagents to chiral 2-imidoylphenols and 2-pyridylimines is reported. These classes of imines are very reactive towards allylmagnesium chloride and benzylmagnesium chloride and the reaction takes place rapidly at low temperature even when enolizable ketimines are used, allowing the construction of a quaternary stereogenic centre with high diastereoselectivity (up 99:1 d.r.) and allowing the preparation of aminophenols that cannot be prepared with organolithium reagents. The sense of asymmetric induction was explained and the absolute configuration of all of the new compounds prepared was assigned.

5. Experimental

5.1. General methods

^{1}H and ^{13}C NMR spectra were recorded at 200 or 300 MHz and 50 or 75 MHz, respectively. Chemical shifts are given in ppm downfield from Me_4Si in $CDCl_3$ solution. Coupling constants are given in Hz. IR spectra were recorded using a FTIR apparatus. Optical rotations were measured in a 1 dm cell at 20°C. All melting points were uncorrected. All reagents were commercially available, were purchased at the highest quality and were purified by distillation when necessary. THF and toluene were distilled and stored on sodium wire before use. The following organometallic reagents were used: AllMgCl (2.0 M, solution in THF), AllMgBr (1.0 M, solution in Et_2O), BnMgCl (2.0 M, solution in THF) VinylMgCl (1.6 M in THF) and PrMgCl (2.0 M, solution in THF). Where only the major diastereomer were obtained pure, the ^{1}H NMR signals for the minor diastereomer were deduced from the spectra of the crude reaction mixture or from enriched chromatographic fractions. When it was impossible to obtain the aminoalkylphenol with high d.r., the determination of the optical rotation was omitted.

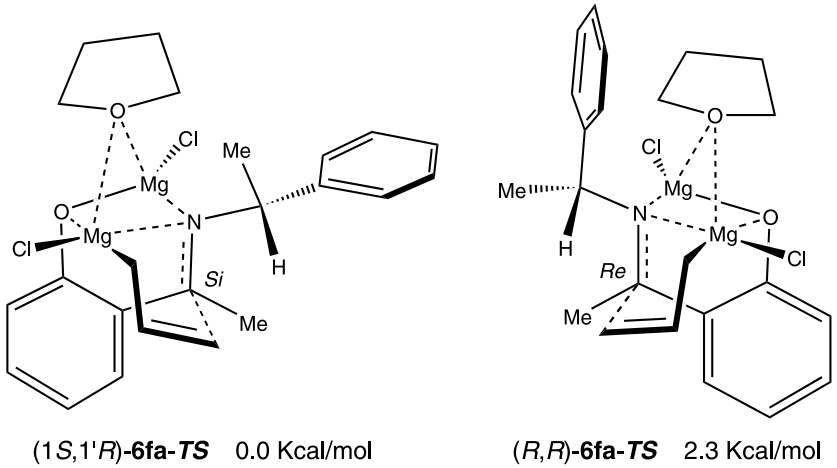


Figure 2. The (1*S*,1′*R*)-**6fa**-***TS*** and (*R*,*R*)-**6fa**-***TS*** transition structures for the allylation of the imidoylphenol (*R*)-**5f** (PM3 semiempirical level minimization).

Imines **5a**–**c**, and **5j** were prepared by mixing the appropriate aldehyde and (*R*)-1-phenylethylamine on acidic Al_2O_3.[29] All imidoylphenols **5d**–**i** were prepared by a solventless procedure.[30]

5.2. General procedure for the addition of Grignard reagents to imines, 5a–j

The imines **5a**–**j** (1.0 mmol) were dissolved in dry toluene (5 mL) under a nitrogen atmosphere and the solution was cooled to −70°C. The Grignard reagent (4.0 mmol) was added dropwise and the reaction mixture was stirred for the time required with the temperature allowed to rise slowly. The reaction mixture was quenched with NH_4Cl saturated solution (5 mL) and extracted with CH_2Cl_2 (2×30 mL). The organic layer was dried with anhydrous Na_2SO_4, then filtered and the solvent was removed under reduced pressure. Chromatographic separation of the crude oil on silica gel with AcOEt/cyclohexane (1/30–1/5, v/v) afforded the pure diastereomers. Amines **6aa**[31] and **6dc**[14] were known compounds. The characterization of the newly prepared **6ab**–**6db** and **6dd**–**6ja** follows.

5.2.1. (1*S*)-2-Phenyl-*N*-[(1*R*)-1-phenylethyl]-1-pyridin-2-ylethan-1-amine, (*S*,*R*)-6bb. Oil; $[\alpha]_D^{20}$ +34.6 (*c* 1.2, $CHCl_3$); IR (liquid film): ν_{max} 3324, 1590, 1370, 1126, 748, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.31 (d, 3H, J=6.6 Hz), 1.89 (br s, 1H), 3.04 (dd, 1H, J=13.2, 7.3 Hz), 3.13 (dd, 1H, J=13.2, 6.6 Hz), 3.75 (q, 1H, J=6.6 Hz), 4.02 (t, 1H, J=7.0 Hz), 6.85–7.50 (m, 13H), 8.65–8.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.8, 42.5, 55.3, 62.9, 121.5, 122.3, 125.9, 126.4, 126.5, 127.9, 128.0, 129.1, 135.6, 138.6, 145.5, 149.0, 162.5. Anal. calcd for $C_{21}H_{22}N_2$ (302.4): C, 83.40; H, 7.33; N, 9.26. Found: C, 83.45; H, 7.30; N, 9.28%.

5.2.2. (1*R*)-2-Phenyl-*N*-[(1*R*)-1-phenylethyl]-1-pyridin-2-ylethan-1-amine, (*R*,*R*)-6bb. ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (d, 3H, J=6.7 Hz), 2.14 (br s, 1H), 2.91 (dd, 1H, J=13.4, 8.2 Hz), 3.01 (dd, 1H, J=13.4, 6.4 Hz), 3.45 (q, 1H, J=6.7 Hz), 3.70 (dd, 1H, J=8.2, 6.4 Hz), 6.90–7.65 (m, 13H), 8.60–8.65 (m, 1H).

5.2.3. (2*S*)-*N*-[(1*R*)-1-Phenylethyl]-2-pyridin-2-ylpent-4-en-2-amine, (*S*,*R*)-6ca. Oil; $[\alpha]_D^{20}$ +30.7 (*c* 1.2, $CHCl_3$); IR (liquid film): ν_{max} 3334, 1638, 1587, 1154, 913, 749, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.31 (d, 3H, J=6.6 Hz), 1.39 (s, 3H), 2.16 (br s, 1H), 2.55–2.75 (m, 2H), 3.78 (q, 1H, J=6.6 Hz), 4.93–5.03 (m, 2H), 5.39–5.56 (m, 1H), 7.03–7.57 (m, 8H), 8.50–8.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.5, 26.8, 45.6, 53.2, 61.1, 117.9, 121.0, 121.3, 126.4, 126.7, 128.2, 135.0, 135.9, 148.3, 148.7, 166.2. Anal. calcd for $C_{18}H_{22}N_2O$ (266.4): C, 81.16; H, 8.32; N, 10.52. Found: C, 81.10; H, 8.35; N, 10.47%.

5.2.4. (2*R*)-*N*-[(1*R*)-1-Phenylethyl]-2-pyridin-2-ylpent-4-en-2-amine, (*R*,*R*)-6ca. ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (d, 3H, J=6.6 Hz), 1.21 (s, 3H), 2.35 (br s, 1H), 2.51 (br d, 2H, J=7.3 Hz), 3.48 (q, 1H, J=6.6 Hz), 4.89–5.02 (m, 2H), 5.48–5.69 (m, 1H), 7.10–7.40 (m, 7H), 7.60–7.70 (m, 1H), 8.60–8.65 (m, 1H).

5.2.5. (2*S*)-1-Phenyl-*N*-[(1*R*)-1-phenylethyl]-2-pyridin-2-ylpropan-2-amine, (*S*,*R*)-6cb. Oil; $[\alpha]_D^{20}$ +62.7 (*c* 1.1, $CHCl_3$); IR (liquid film): ν_{max} 3337, 1587, 1151, 791, 748, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (d, 3H, J=6.6 Hz), 1.43 (s, 3H), 2.32 (br s, 1H), 3.19 (d, 1H, J=12.8 Hz), 3.26 (d, 1H, J=12.8 Hz), 3.91 (q, 1H, J=6.6 Hz), 6.62–6.72 (m, 2H), 7.00–7.45 (m, 11H), 8.55–8.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.7, 26.8, 48.7, 53.2, 62.2, 121.2, 121.3, 126.0, 126.1, 126.5, 127.6, 128.0, 130.4, 135.5, 138.0, 148.0, 148.4, 165.4. Anal. calcd for $C_{22}H_{24}N_2$ (316.4): C, 83.50; H, 7.64; N, 8.85. Found: C, 83.45; H, 7.74; N, 8.81%.

5.2.6. (2*R*)-1-Phenyl-*N*-[(1*R*)-1-phenylethyl]-2-pyridin-2-ylpropan-2-amine, (*R*,*R*)-6cb. ^1H NMR (300 MHz, $CDCl_3$): δ 1.13 (s, 3H), 1.22 (d, 3H, J=6.6 Hz), 2.40 (br s, 1H), 2.99 (d, 1H, J=12.8 Hz), 3.13 (d, 1H, J=12.8 Hz), 3.45 (q, 1H, J=6.6 Hz), 6.70–6.75 (m, 2H), 6.98–7.60 (m, 11H), 8.70–8.76 (m, 1H).

5.2.7. 2-((1*S*)-1-{[(1*R*)-1-Phenylethyl]amino}but-3-enyl)-phenol, (*S*,*R*)-6da. Oil; $[\alpha]_D^{20}$ +43.2 (*c* 0.8, $CHCl_3$); IR (liquid film): ν_{max} 3303, 1638, 1587, 1256, 1096, 922, 755, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (d, 3H, J=6.6 Hz), 2.30 (br s, 1H), 2.49–2.57 (m, 2H), 3.86 (q, 1H, J=6.6 Hz), 3.98 (t, 1H, J=7.0 Hz), 5.10–5.24 (m, 2H), 5.66–5.86 (m, 1H), 6.70–7.40 (m, 9H), 11.50 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.2, 40.3, 54.3, 59.8, 117.0, 119.1, 125.3, 126.6, 127.3, 128.4, 128.5, 128.6, 128.7, 134.6, 143.7, 157.5. Anal. calcd for $C_{18}H_{21}NO$ (267.4): C, 80.86; H, 7.92; N, 5.24. Found: C, 80.80; H, 7.96; N, 5.21%.

5.2.8. 2-((1*R*)-1-{[(1*R*)-1-Phenylethyl]amino}but-3-enyl)-phenol [(*R*,*R*)-6da]. ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (d, 3H, J=7.0 Hz), 2.30 (br s, 1H), 2.38–2.47 (m, 2H), 3.50 (dd, 1H, J=9.3, 5.3 Hz), 3.74 (q, 1H, J=7.0 Hz), 5.10–5.26 (m, 2H), 5.48–5.65 (m, 1H), 6.70–5–7.50 (m, 9H), 11.50 (br s, 1H).

5.2.9. 2-((1*S*)-2-Phenyl-1-{[(1*R*)-1-phenylethyl]amino}-ethyl)phenol, (*S*,*R*)-6db. Oil; $[\alpha]_D^{20}$ +29.4 (*c* 1.2, $CHCl_3$); IR (liquid film): ν_{max} 3305, 1587, 1492, 1255, 1099, 756, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (d, 3H, J=6.6 Hz), 2.10 (br s, 1H), 2.91 (dd, 1H, J=13.9, 9.0 Hz), 3.00 (dd, 1H, J=13.9, 5.9 Hz), 3.72 (q, 1H, J=6.6 Hz), 4.08 (dd, 1H, J=9.0, 5.9 Hz), 6.55–7.30 (m, 14H), 11.80 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.9, 42.3, 54.4, 62.4, 117.2, 119.2, 125.3, 126.3, 126.6, 127.1, 127.5, 128.7, 128.8, 128.9, 129.3, 137.9, 143.8, 157.7. Anal. calcd for $C_{22}H_{23}NO$ (317.4): C, 83.24; H, 7.30; N, 4.41. Found: C, 83.20; H, 7.36; N, 4.35%.

5.2.10. 2-((1*R*)-2-Phenyl-1-{[(1*R*)-1-phenylethyl]amino}-ethyl)phenol, (*R*,*R*)-6db. ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (d, 3H, J=6.6 Hz), 2.07 (br s, 1H), 2.92–3.01 (m, 2H), 3.57–3.75 (m, 2H), 6.60–7.40 (m, 14H), 11.70 (br s, 1H).

5.2.11. 2-((1*R*)-1-{[(1*R*)-1-Phenylethyl]amino}prop-2-enyl)phenol, (*R*,*R*)-6dd. Oil; $[\alpha]_D^{20}$ +2.6 (*c*=0.7, $CHCl_3$, d.r.= 70:30); IR (liquid film): ν_{max} 3298, 1639, 1587,

1254, 1100, 755, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.48 (d, 3H, $J=6.6$ Hz), 2.05 (br s, 1H), 3.80 (q, 1H, $J=6.6$ Hz), 4.13 (d, 1H, $J=7.3$ Hz), 5.05–5.14 (m, 2H), 5.89–6.10 (m, 1H), 6.70–7.50 (m, 9H), 11.50 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.3, 54.9, 63.4, 116.1, 116.9, 119.3, 126.3, 126.9, 127.6, 127.0, 128.8, 128.8, 137.9, 143.3, 157.7. Anal. calcd for $C_{17}H_{19}NO$ (253.3): C, 80.60; H, 7.56; N, 5.53. Found: C, 81.72; H, 7.51; N, 5.48%.

5.2.12. 2-((1*S*)-1-{[(1*R*)-1-Phenylethyl]amino}prop-2-enyl)phenol, (*S*,*R*)-6dd. ^1H NMR (300 MHz, $CDCl_3$): δ 1.50 (d, 3H, $J=6.6$ Hz), 2.05 (br s, 1H), 4.01 (q, 1H, $J=6.6$ Hz), 4.26 (d, 1H, $J=8.4$ Hz), 5.15 (dd, 1H, $J=17.4$, 1.6 Hz), 5.34 (dd, 1H, $J=10.1$, 1.6 Hz), 5.89–6.10 (m, 1H), 6.75–7.40 (m, 9H), 11.50 (br s, 1H).

5.2.13. 2-(1-{[1-(1-Naphthyl)ethyl]amino}but-3-enyl)-phenol, (*S,*R**)-6ea**. Oil; IR (liquid film): ν_{max} 3303, 1638, 1588, 1257, 922, 798, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.59 (d, 3H, $J=6.6$ Hz), 2.56 (t, 2H, $J=7.1$ Hz), 2.60 (br s, 1H), 4.09 (t, 1H, $J=7.1$ Hz), 4.75 (q, 1H, $J=6.6$ Hz), 5.14–5.24 (m, 2H), 5.62–5.83 (m, 1H), 6.70–8.00 (m, 11H), 11.30 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 40.6, 49.6, 59.8, 117.2, 119.2, 119.3, 122.4, 123.0, 125.5, 125.7, 125.8, 126.2, 127.9, 128.6, 128.7, 129.1, 130.8, 134.1, 134.9, 140.1, 157.8. Anal. calcd for $C_{22}H_{23}NO$ (317.4): C, 83.24; H, 7.30; N, 4.41. Found: C, 83.29; H, 7.23; N, 4.52%.

5.2.14. 2-(1-{[1-(1-Naphthyl)ethyl]amino}but-3-enyl)-phenol, (*R,*R**)-6ea**. Oil; ^1H NMR (300 MHz, $CDCl_3$): δ 1.55 (d, 3H, $J=7.0$ Hz), 2.35–2.75 (m, 3H), 3.56 (dd, 1H, $J=9.5$, 4.8 Hz), 4.71 (br q, 1H, $J=7.0$ Hz), 5.20 (d, 1H, $J=16.5$ Hz), 5.21 (d, 1H, $J=10.6$ Hz), 5.50–5.72 (m, 1H), 6.60–8.00 (m, 11H), 12.00 (br s, 1H). Anal. calcd for $C_{22}H_{23}NO$ (317.4): C, 83.24; H, 7.30; N, 4.41. Found: C, 83.15; H, 7.41; N, 4.37%.

5.2.15. 2-(1-{[1-(1-Naphthyl)ethyl]amino}-2-phenylethyl)-phenol, (*S,*R**)-6eb**. Oil; IR (liquid film): ν_{max} 3306, 1588, 1494, 1455, 1257, 910, 755, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (d, 3H, $J=6.6$ Hz), 2.15 (br s, 1H), 3.02 (dd, 1H, $J=13.2$, 9.2 Hz), 3.12 (dd, 1H, $J=13.2$, 5.8 Hz), 4.25 (dd, 1H, $J=9.2$, 5.8 Hz), 4.67 (br q, 1H, $J=6.6$ Hz), 6.70–7.90 (m, 16H), 11.40 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 42.5, 49.8, 62.1, 117.3, 119.2, 122.4, 122.8, 125.5, 125.7, 126.2, 127.1, 127.9, 128.7, 128.8, 128.9, 129.1, 129.2, 129.3, 130.7, 134.1, 137.7, 139.9, 157.8. Anal. calcd for $C_{26}H_{25}NO$ (367.5): C, 84.98; H, 6.86; N, 3.81. Found: C, 84.85; H, 6.97; N, 3.75%.

5.2.16. 2-(1-{[1-(1-Naphthyl)ethyl]amino}-2-phenylethyl)-phenol, (*R,*R**)-6eb**. White crystals; mp 163–166°C (*n*-hexane–AcOEt); ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (d, 3H, $J=7.0$ Hz), 2.47 (br d, 1H, $J=11.4$ Hz), 2.91–3.07 (m, 2H), 3.70 (dd, 1H, $J=8.8$, 6.2 Hz), 4.61 (br s, 1H), 6.45–7.95 (m, 16H), 12.10 (br s, 1H). Anal. calcd for $C_{26}H_{25}NO$ (367.5): C, 84.98; H, 6.86; N, 3.81. Found: C, 85.05; H, 6.97; N, 3.88%.

5.2.17. 2-((1*S*)-1-Methyl-1-{[(1*R*)-1-phenylethyl]amino}-but-3-enyl)phenol, (*S*,*R*)-6fa. Oil; $[\alpha]_D^{20}$ +1.5 (*c* 3.1, $CHCl_3$); IR (liquid film): ν_{max} 3298, 1638, 1608, 1583, 1253, 1092, 752, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (d, 3H, $J=7.0$ Hz), 1.42 (s, 3H), 2.10 (br s, 1H), 2.66–2.88 (m, 2H), 4.01 (q, 1H, $J=7.0$ Hz), 5.21 (d, 1H, $J=10.6$ Hz), 5.22 (d, 1H, $J=16.5$ Hz), 5.60–5.82 (m, 1H), 6.70–7.40 (m, 9H), 12.28 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 26.1, 42.1, 52.9, 60.4, 117.3, 118.7, 119.9, 125.8, 126.5, 127.3, 128.6, 128.8, 129.3, 133.3, 145.5, 157.7. Anal. calcd for $C_{19}H_{23}NO$ (281.4): C, 81.10; H, 8.24; N, 4.98. Found: C, 81.00; H, 8.36; N, 4.87%.

5.2.18. 2-((1*R*)-1-Methyl-1-{[(1*R*)-1-phenylethyl]amino}-but-3-enyl)phenol, (*R*,*R*)-6fa. ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (d, 3H, $J=7.0$ Hz), 1.43 (s, 3H), 2.05 (br s, 1H), 2.40–2.60 (m, 2H), 3.94 (q, 1H, $J=7.0$ Hz), 5.09 (d, 1H, $J=16.8$ Hz), 5.11 (d, 1H, $J=10.3$ Hz), 5.45–5.70 (m, 1H), 6.40–6.70 (m, 9H), 12.70 (br s, 1H).

5.2.19. 2-((1*S*)-1-Methyl-2-phenyl-1-{[(1*R*)-1-phenylethyl]amino}ethyl)phenol, (*S*,*R*)-6fb. Oil; $[\alpha]_D^{20}$ +95.0 (*c* 1.6, $CHCl_3$); IR (liquid film): ν_{max} 3298, 1604, 1582, 1252, 1089, 753, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (d, 3H, $J=6.7$ Hz), 1.51 (s, 3H), 1.98 (br s, 1H), 3.06 (d, 1H, $J=13.1$ Hz), 3.19 (d, 1H, $J=13.1$ Hz), 3.91 (q, 1H, $J=6.7$ Hz), 6.57–7.20 (m, 14H), 11.95 (br s, 1H,); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.2, 25.9, 46.2, 52.7, 61.5, 117.0, 118.5, 126.4, 126.6, 126.8, 127.1, 128.0, 128.3, 128.6, 128.7, 130.7, 136.6, 144.9, 157.4. Anal. calcd for $C_{23}H_{25}NO$ (331.5): C, 83.34; H, 7.60; N, 4.23. Found: C, 83.45; H, 7.51; N, 4.26%.

5.2.20. 2-((1*R*)-1-Methyl-2-phenyl-1-{[(1*R*)-1-phenylethyl]amino}ethyl)phenol [(*R*,*R*)-6fb]. ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (d, 3H, $J=6.7$ Hz), 1.30 (s, 3H), 2.19 (br s, 1H), 2.89 (d, 1H, $J=12.8$ Hz), 3.01 (d, 1H, $J=12.8$ Hz), 3.91 (q, 1H, $J=6.7$ Hz), 6.60–7.35 (m, 14H), 12.80 (br s, 1H).

5.2.21. 2-(1-Methyl-1-{[1-(1-naphthyl)ethyl]amino}but-3-enyl)phenol, (*S,*R**)-6ga**. Oil; IR (liquid film): ν_{max} 3303, 1608, 1583, 1463, 1253, 912, 778, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (s, 3H), 1.50 (d, 3H, $J=6.6$ Hz), 2.28 (br s, 1H), 2.83 (d, 2H, $J=7.0$ Hz), 4.80–4.96 (m, 1H), 5.18 (dd, 1H, $J=9.9$, 2.2 Hz), 5.21 (dd, 1H, $J=17.2$, 1.8 Hz), 5.58–5.82 (m, 1H), 6.70–8.10 (m, 11H), 12.40 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.4, 26.5, 42.1, 47.5, 61.0, 117.6, 119.0, 120.0, 122.5, 123.7, 125.7, 125.9, 126.2, 126.3, 127.7, 128.9, 129.4, 129.6, 130.1, 133.4, 134.1, 142.4, 158.0. Anal. calcd for $C_{23}H_{25}NO$ (331.4): C, 83.34; H, 7.60; N, 4.32. Found: C, 83.21; H, 7.71; N, 4.26%.

5.2.22. 2-((1*S*)-1-Ethyl-1-{[(1*R*)-1-phenylethyl]amino}-but-3-enyl)phenol [(*S*,*R*)-6ha]. Oil; $[\alpha]_D^{20}$ −28.0 (*c* 3.0, $CHCl_3$); IR (liquid film): ν_{max} 3306, 1638, 1606, 1583, 1252, 1094, 753, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.57 (t, 3H, $J=7.5$ Hz), 1.28 (d, 3H, $J=6.6$ Hz), 1.56 (sext, 1H, $J=7.0$ Hz), 1.92 (br sext, 1H,

$J=7.0$ Hz), 2.19 (br s, 1H), 2.75–2.95 (m, 2H), 4.09 (q, 1H, $J=6.6$ Hz), 5.21 (dt, 1H, $J=9.9$, 1.1 Hz), 5.25 (dt, 1H, $J=17.0$, 1.1 Hz), 5.55–5.80 (m, 1H), 6.70–7.40 (m, 9H), 12.75 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.4, 23.5, 29.8, 36.2, 53.0, 63.5, 117.3, 118.4, 119.7, 126.6, 126.9, 127.0, 127.4, 128.6, 128.8, 132.8, 145.8, 158.2. Anal. calcd for $C_{20}H_{25}NO$ (295.4): C, 81.31; H, 8.53; N, 4.74. Found: C, 81.45; H, 8.62; N, 4.62%.

5.2.23. 2-((1*R*)-1-Ethyl-1-{[(1*R*)-1-phenylethyl]amino}-but-3-enyl)phenol, (*R*,*R*)-6ha. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, 3H, $J=7.3$ Hz), 1.28 (d, 3H, $J=6.6$ Hz), 2.05–2.35 (m, 3H), 2.65–2.75 (m, 2H), 3.96 (q, 1H, $J=6.6$ Hz), 4.84–4.98 (m, 2H), 5.25–5.45 (m, 1H), 6.70–7.40 (m, 9H), 12.70 (br s, 1H).

5.2.24. 2-((1*S*)-1-Ethyl-2-phenyl-1-{[(1*R*)-1-phenylethyl]-amino}ethyl)phenol, (*S*,*R*)-6hb. Oil; $[\alpha]_D^{20}$ +83.51 (*c* 1.2, $CHCl_3$); IR (liquid film): ν_{max} 3306, 1605, 1583, 1251, 1078, 753, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.68 (t, 3H, $J=7.3$ Hz), 1.37 (d, 3H, $J=6.7$ Hz), 1.80 (q, 2H, $J=7.3$ Hz), 2.33 (br s, 1H), 3.15 (d, 1H, $J=13.4$ Hz), 3.40 (d, 1H, $J=13.4$ Hz), 4.11 (q, 1H, $J=6.7$ Hz), 6.56–7.30 (m, 14H), 12.65 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.8, 25.4, 26.6, 41.1, 52.4, 65.4, 117.2, 118.1, 118.5, 126.4, 126.5, 127.4, 127.8, 128.6, 128.7, 128.9, 130.5, 136.7, 145.1, 158.3. Anal. calcd for $C_{24}H_{27}NO$ (345.5): C, 83.44; H, 7.88; N, 4.05. Found: C, 83.32; H, 7.96; N, 4.12%.

5.2.25. 2-((1*R*)-1-Phenyl-1-{[(1*R*)-1-phenylethyl]amino}-but-3-enyl)phenol, (*R*,*R*)-6ia. Oil; $[\alpha]_D^{20}$ +52.9 (*c* 1.6, $CHCl_3$); IR (liquid film): ν_{max} 3296, 1604, 1583, 1251, 912, 756, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.32$ (d, 3H, $J=6.7$ Hz), 2.75 (br s, 1H), 3.09 (d, 2H, $J=7.0$ Hz), 3.87 (q, 1H, $J=6.7$ Hz), 4.83 (dd, 1H, $J=17.1$, 1.5 Hz), 4.93 (dd, 1H, $J=10.2$, 1.4 Hz), 5.20–5.45 (m, 1H), 6.75–7.70 (m, 14H), 11.85 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.6, 41.0, 53.4, 66.6, 117.7, 119.0, 119.8, 126.6, 126.8, 127.0, 127.4, 127.7, 128.2, 128.9, 129.2, 129.6, 133.0, 144.2, 146.0, 158.0. Anal. calcd for $C_{24}H_{25}NO$ (343.5): C, 83.93; H, 7.34; N, 4.08. Found: C, 84.03; H, 7.25; N, 4.03%.

5.2.26. 2-((1*S*)-1-Phenyl-1-{[(1*R*)-1-phenylethyl]amino}-but-3-enyl)phenol [(*S*,*R*)-6ia]. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.18$ (d, 3H, $J=6.6$ Hz), 2.77 (dd, 1H, $J=14.5$, 6.8 Hz), 2.80 (br s, 1H), 2.99 (dd, 1H, $J=14.5$, 7.0 Hz), 3.65 (q, 1H, $J=6.6$ Hz), 4.75 (dd, 1H, $J=16.8$, 1.5 Hz), 4.85 (br d, 1H, $J=8.1$ Hz), 5.22–5.45 (m, 1H), 6.60–7.60 (m, 14H), 12.40 (br s, 1H).

5.2.27. 2-((1*R*)-1,2-Diphenyl-1-{[(1*R*)-1-phenylethyl]-amino}ethyl)phenol [(*R*,*R*)-6ib]. Oil; $[\alpha]_D^{20}$ +61.8 (*c* 2, $CHCl_3$); IR (liquid film): ν_{max} 3310, 1583, 1494, 1252, 754, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (d, 3H, $J=6.6$ Hz), 2.65 (br s, 1H), 3.70–3.85 (m, 2H), 4.18 (q, 1H, $J=6.6$ Hz), 6.39–6.44 (m, 2H), 6.80–7.45 (m, 17H), 11.20 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 42.2, 53.6, 66.6, 117.5, 118.9, 126.4, 126.5, 126.6, 126.7, 127.0, 127.3, 127.7, 127.8, 128.8, 129.1, 130.2, 130.7, 135.3, 144.5, 146.1, 157.7. Anal. calcd for $C_{28}H_{27}NO$ (393.5): C, 85.46; H, 6.92; N, 3.56. Found: C, 85.58; H, 6.87; N, 3.69%.

5.2.28. 2-((1*S*)-1,2-Diphenyl-1-{[(1*R*)-1-phenylethyl]-amino}ethyl)phenol, (*S*,*R*)-6ib. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (d, 3H, $J=6.6$ Hz), 2.68 (br s, 1H), 3.39 (d, 1H, $J=13.9$ Hz), 3.70 (d, 1H, $J=13.9$ Hz), 3.86 (q, 1H, $J=6.6$ Hz), 6.30–7.50 (m, 19H), 11.25 (br s, 1H).

5.2.29. *N*-[1-(2-Methoxyphenyl)-1-methylbut-3-enyl]-*N*-[(1*R*)-1-phenylethyl]amine, major diastereomer. Oil; $[\alpha]_D^{20}$ +66.9 (*c* 0.97, $CHCl_3$); IR (liquid film): ν_{max} 3360, 1638, 1598, 1237, 1028, 910, 752, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (d, 3H, $J=6.6$ Hz), 1.52 (s, 3H), 2.40 (dd, 1H, $J=13.4$, 7.9 Hz), 2.81 (dd, 1H, $J=13.4$, 6.8 Hz), 3.00 (br s, 1H), 3.39 (s, 3H), 3.44 (q, 1H, $J=6.6$ Hz), 4.83–4.96 (m, 2H), 5.34–5.54 (m, 1H), 6.60–7.30 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.3, 26.6, 45.1, 53.5, 54.1, 59.9, 110.6, 116.5, 119.9, 126.2, 126.3, 127.8, 128.0, 128.6, 133.1, 135.6, 147.9, 157.5. Anal. calcd for $C_{20}H_{25}NO$ (295.4): C, 81.31; H, 8.53; N, 4.74. Found: C, 81.25; H, 8.63; N, 4.62%.

5.2.30. *N*-[1-(2-Methoxyphenyl)-1-methylbut-3-enyl]-*N*-[(1*R*)-1-phenylethyl]amine, minus diastereomer. Oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (s, 3H), 1.16 (d, 3H, $J=6.9$ Hz), 2.54 (dd, 1H, $J=13.3$, 7.9 Hz), 2.75 (br s, 1H), 2.88 (dd, 1H, $J=13.3$, 6.6 Hz), 3.44 (q, 1H, $J=6.9$ Hz), 3.88 (s, 3H), 4.85–5.00 (m, 2H), 5.44–5.65 (m, 1H), 6.90–7.40 (m, 9H). Anal. calcd for $C_{20}H_{25}NO$ (295.4): C, 81.31; H, 8.53; N, 4.74. Found: C, 81.39; H, 8.65; N, 4.78%.

5.3. Addition of MeMgCl and PhMgCl to imidoyophenol (*R*)-5h in the presence of $BF_3{\cdot}Et_2O$: formation of the borate, (*R*)-7h

(*R*)-**5h** (0.253g, 1.0 mmol) was dissolved in dry toluene (5 mL), under a nitrogen atmosphere and $BF_3{\cdot}Et_2O$ (0.2 mL, 1.6 mmol) was added. The solution was stirred for 10 min at room temperature, then cooled to −70°C and the Grignard reagent (4.0 mmol) was added dropwise. The reaction mixture was stirred for 4 h and the temperature slowly allowed to rise. The reaction mixture was quenched with NH_4Cl saturated solution (5 mL) and extracted with CH_2Cl_2 (2×30 mL). The organic layer was dried with anhydrous Na_2SO_4, then filtered and the solvent was removed under reduced pressure. Chromatographic purification of the crude oil on silica gel with AcOEt/cyclohexane (1/9–1/1, v/v) afforded the borate (*R*)-**7h** in 88% yield: Oil; IR (liquid film): ν_{max} 1644, 1610, 1561, 1318 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, 3H, $J=7.7$ Hz), 1.98 (d, 3H, $J=6.7$ Hz), 2.66–3.00 (m, 2H), 5.72 (q, 1H, $J=6.7$ Hz), 6.90–7.60 (m, 9H). Anal. calcd for $C_{17}H_{18}BF_2NO$ (301.1): C, 67.80; H, 6.02; N, 4.65. Found: C, 67.65; H, 6.17; N, 4.62%.

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