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Synthesis of enantiomerically enriched amines by chiral ligand mediated addition of organolithium reagents to imines

Sonia Arrasate, Esther Lete* and Nuria Sotomayor

Departamento de Química Orgánica II, Facultad de Ciencias, Universidad del País Vasco, Apdo. 644, 48080 Bilbao, Spain

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Abstract—The effect of the imine and ligand structure on the enantioselective addition of organolithiums to imines has been studied. Thus, (−)-sparteine-mediated additions of MeLi and/or *n*-BuLi to *p*-anisidine derived phenylimine **1a** afforded the corresponding amines with modest e.e.s. The use of bulkier or more reactive imines (naphthyl or tosyl imines) resulted in loss of enantioselectivity. The best enantioinduction with this ligand was obtained with enolizable imines **8** and **10**. When bis(oxazolidines) were used as chiral ligands, a strong influence of their structure in the enantioselectivity of the addition of MeLi and *n*-BuLi to phenylimine **1a** was observed. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The asymmetric 1,2-addition of organometallic reagents to imines is a powerful tool to form carbon–carbon bonds and simultaneously introduce a new stereogenic centre in organic molecules.[1] Thus, it provides ready access to enantiomerically enriched amines bearing a stereogenic centre at the α-position, a characteristic structural feature in many biologically active compounds. These optically active amines are also important compounds because of their broad range of applications (as chiral auxiliaries, resolving agents and building blocks for the synthesis of natural and unnatural compounds) and their pharmacological properties.[2]

In this regard, strategies based on the use of external chiral ligands to achieve the asymmetric synthesis of amines are especially attractive. Different types of bidentate and tridentate ligands have been reported to promote the enantioselective addition of organolithium reagents to the carbon–nitrogen double bond: *O*,*O*′-dialkyldihydro-benzoins,[3] β-aminoethers derived from amino acids such as phenylalanine and phenylglycine[3a,b,4]or (*S*)-proline and (*S*)-valine,[5] (−)-sparteine,[6] bis(oxazolidines),[6,7] bis(aziridines),[8] oxazoline derivatives.[9] These additions have been performed under stoichiometric or catalytic conditions and the enantioselectivity is known to depend on the structure of the imine as well as that of the ligand. Interesting applications of this type of chiral ligand-mediated reactions have been reported by Tomioka, who has developed new procedures for the synthesis of β-lactams[10] and tetrahydroisoquinolines.[11] Another recent contribution by Snieckus[12] illustrates the potential of this methodology with an asymmetric synthesis of tetrahydroisoquinolin-1-ones using a (−)-sparteine mediated benzamide lateral metalation–imine addition sequence.

As part of a research program aimed at the development of asymmetric synthesis of nitrogen heterocycles, we were faced with the task of preparing enantiomerically pure amines. Herein, we report details of our results on the asymmetric addition of organolithium reagents to imines in the presence of several types of chiral ligands.[13]

2. Results and discussion

The chiral ligand (−)-sparteine appeared to be a suitable starting point for our work. This naturally occurring alkaloid is inexpensive, available in large quantities and it can function as a bidentate ligand for the chiral modification of cations in carbanion pairs. However, there are only a few examples in the literature in which the use of this chiral ligand in the asymmetric addition of organolithium reagents to imines has been studied. For instance, Denmark[6] reported that (−)-sparteine induced the enantioselective addition of an organolithium reagent (methyllithium, *n*-butyllithium, and

* Corresponding author. Tel.: 34 94 6012576; fax: 34 94 4648500; e-mail: qopleexe@lg.ehu.es

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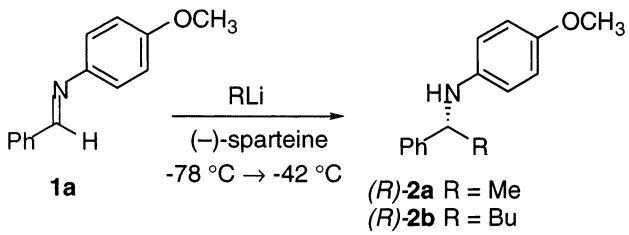
phenyllithium) to *N*-aryl imines derived from 3-phenylpropionaldehyde, in both stoichiometric and catalytic quantities, though the procedure has not been extended to other imines. (–)-Sparteine has also been successfully employed as a chiral ligand in the reaction of *n*-butyllithium with benzaldehyde *N*-(metallo)imines.[14]

Therefore, we decided to investigate in more detail the use of (–)-sparteine as a chiral ligand and/or catalyst for the organolithiums addition to imines. Thus, the influence of the imine structure, as well as the effect of the experimental conditions (solvent, use of catalytic, stoichiometric or greater amounts of the ligand, temperature, etc.) in the stereoselectivity of these processes was studied.

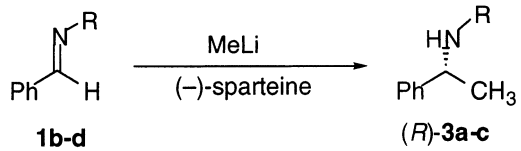
We initiated our study with *p*-anisidine derivatives as the arylimines, as shown in Scheme 1, expecting convenient oxidative removal of the *p*-methoxyphenyl group to liberate a primary amine. As summarized in Table 1, we carried out the addition of low halide MeLi and *n*-BuLi to a solution of arylimine **1a** and (–)-sparteine in Et_2O at −78°C, obtaining the corresponding enantiomerically enriched amines (*R*)-**2a** and (*R*)-**2b**.[15] In both cases, higher enantioinduction was obtained when the reaction was performed with an excess of the chiral ligand (entries 3–6, 8–9). Also, the use of non-coordinating solvents, such as toluene, hexane or *i*-Pr_2O (entries 5, 6, 9) or the order of addition of the reagents (entries 4, 8) had no significant influence on the optical yields. Lower reaction temperatures (–94°C) did not improve the results.

We next turned our attention to the influence of the imine structure on the enantioinduction. Previous work had shown a strong influence of the *N*-substituent on the imine, so we decided to test the sparteine-mediated addition of MeLi to imines **1b**–**1d** (Scheme 2, Table 2). Although Tomioka had reported a significant improvement of the e.e. (90 versus 58%) when imine **1b** was used as a substrate for the addition of MeLi in the presence of aminoethers as chiral ligands,[3a,4c] the (–)-sparteine (2.6 equiv.) mediated addition of MeLi to **1b** showed completely different behavior, obtaining amine (*R*)-**3a** in only 9% e.e. (entry 1). Similarly, the use of the naphthylamine-derived imine **1c** did not improve the results obtained with **1a**, leading to modest enantioselectivities (entries 2, 3). The use of tosylimine **1c** resulted in the formation of racemic mixtures. Thus, the *p*-methoxyphenyl group seems to be the most appropriate *N*-substituent for sparteine-mediated addition to phenylimines **1**. The use of bulkier or more electrophilic imines resulted in a significant decrease of enantioselectivity.

In order to improve the enantioselectivities obtained with (–)-sparteine, our next concern was to study the influence of the ligand structure. In this context, bis(oxazolidines) and aminoethers have been reported to be the most promising types of ligands. While this work was in progress,[13] Denmark reported a comparative study of bis(oxazolidine)-mediated addition of MeLi to imines, showing that although the ligand bite angle has only a small effect on the enantioselectivity, the size of the substituents on the bridge is more important, obtaining the best results for arylimines with larger groups.[7] These results correlate quite well with our findings (Table 3, Scheme 3). Thus, when oxazolidine **5b**, with bulky *tert*-butyl groups on C(4), and methyl groups on the bridge carbon, was used with MeLi, amine (*R*)-**2a** was obtained with a reasonable 74% e.e.,[16] although reaction with *n*-BuLi proceeded with much lower enantioselectivity (29% e.e.) (entries 4, 10). The nature of the C(4)-substituents also plays an important role, as ligand **5c**, with phenyl groups on C(4), provided lower enantioselectivity than **5b** for the addition of MeLi and *n*-BuLi (entries 5, 11). Interest-



Scheme 1.



Scheme 2.

Table 1. (–)-Sparteine mediated addition of organolithiums to imine **1a**

Entry	R	Solvent	(−)-Sparteine (equiv.)	Yield (%)	e.e. (%)
1	Me	Et_2O	0.5	97	11
2	Me	Et_2O	1.0	85	3
3	Me	Et_2O	2.6	79	32
4	Me[a]	Et_2O	2.6	89	32
5	Me	Toluene	2.6	80	31
6	Me	Hexane	2.6	99	34
7	*n*-Bu	Et_2O	0.6	99	25
8	*n*-Bu[a]	Et_2O	2.6	99	29
9	*n*-Bu	*i*-Pr_2O	2.6	85	29

[a] Imine was added over a mixture of RLi-(–)-sparteine complex

Table 2. (−)-Sparteine-mediated addition of MeLi to imines **1b–d**

Entry	R	Solv.	Prod.	Yield (%)	e.e. (%)	Conf.
1	2-Me-4(OMe)Ph	Et_2O	**3a**	95	9	*R*
2	1-Naphthyl	Et_2O	**3b**	99	19	*R*[a]
3	1-Naphthyl	Hexane	**3b**	99	23	*R*
4	Ts	Et_2O	**3c**	80	0	–

[a] Configuration established by analogy.[11b]

Table 3. Ligand mediated addition of organolithiums to imine **1a**

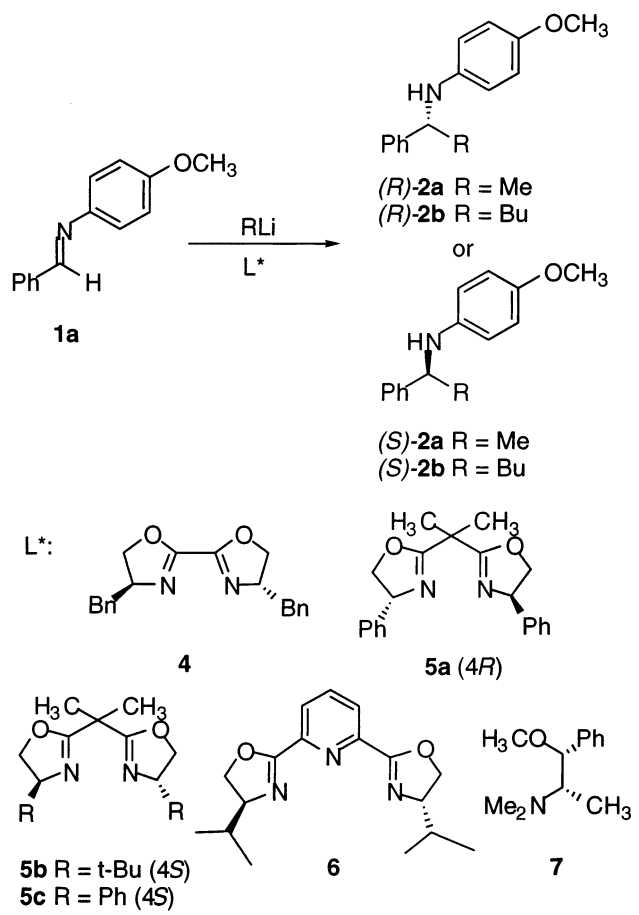
Entry	R	Solvent	L*	Yield %	e.e. (%)	Conf.
1[a]	*n*-Bu	Et_2O	**4**	98	5	*R*
2	*n*-Bu	Toluene	**4**	95	3	*R*
3	*n*-Bu	Toluene	**5a**	95	14	*S*
4[b]	*n*-Bu	Toluene	**5b**	96	29	*R*
5	*n*-Bu	Toluene	**5c**	74	3	*R*
6	*n*-Bu	Toluene	**6**	78	3	*R*
7	Me	Toluene	**4**	39	1	*R*
8[c]	Me	Et_2O	**5a**	86	7	*S*
9	Me	Toluene	**5a**	91	19	*S*
10	Me	Toluene	**5b**	93	74	*R*[d]
11	Me	Toluene	**5c**	93	44	*R*
12	Me	Toluene	**6**	92	2	*R*
13	Me	Hexane	**7**	99	34	*S*
14	Me[e]	Hexane	**7**	84	20	*S*

[a] 80% of ligand **4** was recovered.
[b] 52% of ligand **5c** was recovered.
[c] 63% of ligand **5a** was recovered.
[d] Reported by Denmark with 67% e.e.[7]
[e] MeLi was added over a solution of imine **1** and ligand **7**.

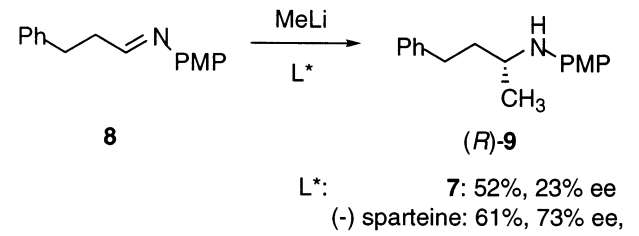
ingly, when addition of MeLi or *n*-BuLi was carried out in the presence of **5a**, the amines of *S* configuration were obtained, although with lower e.e. (entries 3, 8, 9). The use of bis(oxazolidine) **4**, with no bridge between rings, resulted in a dramatic decrease of enantioselectivity, obtaining nearly racemic products in the addition of both MeLi and *n*-BuLi (entries 1, 2, 7). This result could be attributed to the difficulty of both nitrogen atoms of **4** being coplanar, precluding the complexation with lithium. The result obtained with **6** in which, besides probable lack of coplanarity, the pyridine ring would leave nitrogen atoms too far away from each other (entries 6, 12) would be along these lines. It is also of note that the chiral ligands could be recovered from the reaction mixtures, and re-used, as shown in selected examples (entries 1, 4, 8).

As stated above, in a different approach, aminoethers are another kind of promising ligand for asymmetric addition of organolithiums to *p*-anisidine imines. In this area, Tomioka[3] has developed several aminoethers, though best results were obtained with tridentate ligands. Also, aminoalcohols derived from proline have been used successfully, using *N*-(metallo)imines as substrates.[14] Thus, we decided to test aminoalcohol **7** as ligand, which was prepared in high yield from *N*-methylephedrine. Interestingly, when imine **1a** was added over a mixture of **7** and MeLi in hexane at −78°C, the amine (*S*)-**2a** was obtained, with opposite configuration to amine obtained with (−)-sparteine or bis(oxazolidines), although with modest enantioselectivity (34% e.e., entry 13). Inverse addition conditions resulted in poorer e.e. (entry 14).

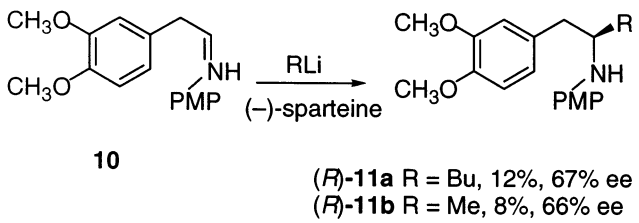
Finally, we tried to extend this methodology to different imines (Schemes 4 and 5). Denmark reported that the best enantioselectivities in the addition of organolithium reagents to alkyl imines, as hydrocinamaldehyde imine **8**, were obtained with (−)-sparteine,[1g,6] although oxazolidines gave also very good enantioinduction in the addition of MeLi.[7] Thus, addition of MeLi to **8** using aminoalcohol **7** yielded amine (*R*)-**9**, the same configuration obtained with sparteine, but with a lower e.e. (Scheme 4). In this case, no inversion of enantioinduction using **7** was observed. However, we were more interested in the preparation of enantiomerically enriched 1-substituted phenethylamines, that would be interesting precursors in the synthesis, for instance, of enantiomerically enriched fused isoquinoline alkaloids.[17] Thus, imine **10** was prepared from homoveratraldehyde and *p*-anisidine, and reacted with MeLi or *n*-BuLi in the presence of (−)-sparteine, amines **11a** and **11b** were obtained with 67 and 66% e.e., respectively.[18] The low yields obtained, however, are attributed to the instability of imine **10**, which decomposes readily and has to be used immediately, without purification.



Scheme 3.



Scheme 4.



Scheme 5.

3. Conclusion

The structure of the imine is of great relevance in the enantioselective (–)-sparteine-mediated additions of MeLi and/or *n*-BuLi to imines. Thus, non-enolizable *p*-anisidine-derived phenylimine **1a** provided the corresponding amines (*R*)-**2** with modest e.e.s. The use of bulkier or more reactive imines (naphthyl or tosyl imines) resulted in partial or complete loss of enantioselectivity. With this ligand, the best enantioinduction was obtained with enolizable imines **8** and **10**. When bis(oxazolidines) were used as chiral ligands, a strong influence of their structure in the enantioselectivity of the addition of MeLi and *n*-BuLi to phenylimine **1a** was observed. The use of bis(oxazolidine) **5a**, having (4*S*)-configuration, or aminoether **7**, leads to amines with (*S*)-configuration.

4. Experimental

4.1. (–)-Sparteine-mediated addition of MeLi to imines. Typical procedure

A solution of MeLi (1.4 mL of a 0.96 M solution in Et_2O, 1.3 mmol) was added to a cold solution of (–)-sparteine (0.4 mL, 1.5 mmol) in Et_2O (12 mL), and the mixture was stirred at −78°C for 30 min. A solution of naphthyl imine **1c** (136 mg, 0.6 mmol) in Et_2O (12 mL) was added and the resulting solution was allowed to warm up to −42°C and stirred at this temperature for 2 h. The reaction was quenched by addition of water (10 mL), and allowed to warm to rt. The mixture was separated, the aqueous extracted with Et_2O (3×10 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent followed by purification by column chromatography (silica gel, 15% hexane/AcOEt) gave (*R*)-*N*-(1-methylbenzyl)-*N*-(1-naphthyl)amine **3b**, as a white solid that was recrystallized from hexane (140 mg, 96%): $[\alpha]_D^{20} = -3.3$ ($c = 2.8$, CH_2Cl_2); mp (hexane): 94–96°C; ^{1}H NMR ($CDCl_3$) 1.71 (d, $J = 6.3$ Hz, 3H, CH_3), 4.68–4.76 (m, 2H, NH, C<u>H</u>CH$_3$), 6.42–6.45 (m, 1H, Harom), 7.24–7.54 (m, 9H, Harom), 7.83–7.86 (m, 1H, Harom), 7.97–8.00 (m, 1H, Harom); ^{13}C NMR 25.2, 53.5, 105.9, 117.2, 119.7, 123.1, 124.7, 125.6, 125.7, 126.5, 126.9, 128.3, 128.6, 128.7, 129.3, 134.2, 141.9, 144.8; MS(EI) *m*/*z* (rel. intens.): 247 (M^+, 44), 232 (16), 144 (12), 143 (100), 127 (15), 115 (22), 106 (10), 105 (93), 103 (12), 97 (10), 85 (38), 83 (54), 81 (12), 79 (26), 77 (27), 71 (28), 69 (25), 57 (55), 56 (12), 55 (29), 51 (11). The enantiomeric excess was determined by CSP HPLC to be 19% (Chiralcel OD, 3% hexane/2-propanol, 0.5 mL/min) $t_r(S) = 18.2$ (40.7%) min; $t_r(R) = 29.1$ min (59.3%).

4.2. Oxazolidine-mediated addition of RLi to imines. Typical procedure

A solution of *n*-BuLi (0.8 mL of a 0.62 M solution in hexane, 0.5 mmol) was added to a cold solution of **5a** (79 mg, 0.2 mmol) in Et_2O (5 mL) and the mixture was stirred at −94°C for 30 min. A solution of imine **1a** (55 mg, 0.2 mmol) in Et_2O (5 mL) was added and the resulting solution was stirred at this temperature for 3 h. The reaction was quenched by addition of MeOH (10 mL) and allowed to warm to rt. The mixture was separated, extracted with Et_2O (3×10 mL) and the combined organic layers were washed with brine and

dried over Na_2SO_4. Evaporation of the solvent followed by purification by column chromatography (silica gel, 30% hexane/AcOEt) gave (*S*)-*N*-(1-butylbenzyl)-*N*-(4-methoxyphenyl)amine (**3b**),[3a] as an oil (61 mg, 95%): $[\alpha]_D^{20}=-1.9$ ($c=1.2$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 1.05–1.11 (m, 3H, CH_3), 1.43–1.53 (m, 4H, CH_2-C<u>H</u>$_2$-C<u>H</u>$_2$-CH_3), 1.93–1.96 (m, 2H, C<u>H</u>$_2$-CH_2-CH_2-CH_3), 3.81 (s, 3H, OCH_3), 4.08 (s, 1H, NH), 4.42 (t, $J=6.7$ Hz, 1H, CHN), 6.67 (d, $J=8.9$ Hz, 2H, Harom), 6.87 (d, J = 8.9 Hz, 2H, Harom), 7.3–7.5 (m, 5H, Harom) ^{13}C NMR ($CDCl_3$) 13.8, 22.4, 28.3, 38.4, 55.4, 58.9, 114.4, 114.6, 126.3, 126.6, 128.3, 141.6, 144.4, 151.7; MS(EI) *m*/*z* (rel. intens.): 269 (M^+, 19), 213 (16), 212 (100), 134 (6), 123 (7), 108 (8), 91 (23). The e.e. was determined by CSP HPLC to be 14% (Chiralcel OD, 3% hexane/2-propanol, 0.6 mL/min) $t_r(R)=11.0$ min (57%); $t_r(S)=$ 12.0 min (43%).

4.3. Synthesis of (−)-(1*R*,2*S*)-*N*,*O*-dimethylephedrine 7

(−)-(1*R*,2*S*)-Methylephedrine (841 mg, 4.7 mmol) was added to a suspension of NaH (468 mg, 18.7 mmol) in THF (60 mL) and the mixture was stirred at rt for 2 h. MeI (0.3 mL, 5.2 mmol) was added and the resulting mixture was stirred for 4 days. Water was added and the mixture was separated, extracted with Et_2O (3×20 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent followed by purification by column chromatography (silica gel, AcOEt) gave aminoether **7**, as a yellow oil (844 mg, 93%): $[\alpha]_D^{20}=-60.0$ ($c=7.7$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 0.94 (d, $J=6.7$ Hz, 3H, CHC<u>H</u>$_3$), 2.29 (s, 6H, N(C<u>H</u>$_3$)$_2$), 2.55–2.65 (m, 1H, C<u>H</u>CH_3), 3.17 (s, 3H, OCH_3), 4.33 (d, $J=3.2$ Hz, 1H, $CHOCH_3$), 7.13–7.29 (m, 5H, Harom); ^{13}C NMR ($CDCl_3$) 7.5, 41.4, 56.3, 64.8, 83.9, 126.3, 126.7, 127.8, 140.7; MS(EI) *m*/*z* (rel. intens.): 149 (13), 97 (6), 91 (12), 87 (11), 85 (63), 83 (100), 72 (47), 71 (12), 69 (12), 58 (9), 57 (9), 56 (9), 55 (17).

4.4. Addition of MeLi to imine 8 mediated by 7. Synthesis of (*R*)-9

A solution of MeLi (1.6 mL of a 1.4 M solution in Et_2O, 2.2 mmol) was added to a cold solution of (−)-**7** (194 mg, 1 mmol) in Et_2O (11 mL), and the mixture was stirred at −90°C for 30 min. A solution of imine **8**, freshly prepared from 3-phenylpropionaldehyde (0.15 mL, 1.1 mmol) and *p*-anisidine (137 mg, 1.1 mmol) in Et_2O (11 mL) was added and the resulting solution was stirred at this temperature for 1 h. The reaction was quenched by addition of MeOH (10 mL), and allowed to warm to rt. The mixture was separated, extracted with Et_2O (3×10 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent followed by purification by column chromatography (silica gel, 20% hexane/AcOEt) gave (*R*)-*N*-(4-methoxyphenyl)-*N*-(1-methyl-3-phenylpropyl)amine **9**[6] as a yellow oil (148 mg, 52%): $[\alpha]_D^{20}=-9.1$ ($c=1.2$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 1.28 (d, $J=6.3$ Hz, 3H, CH_3), 1.75–1.89 (m, 1H, C<u>H</u>$_a$H$_b$CHNH), 1.92–2.03 (m, 1H, CH_a<u>H</u>$_b$CHNH), 2.82 (t, $J=7.7$ Hz, 2H, C<u>H</u>$_2$$CH_2$CHNH), 3.18 (s, 1H, NH), 3.45–3.53 (m, 1H, C<u>H</u>CH_3NH), 3.83 (s, 3H, OCH_3), 6.61 (d, $J=9.1$ Hz, 2H, Harom), 6.87 (d, $J=9.1$ Hz, 2H, Harom), 7.27–7.38 (m, 5H, Harom); ^{13}C NMR ($CDCl_3$) 20.7, 32.4, 38.7, 48.7, 55.6, 114.6, 114.8, 125.7, 128.2, 128.3, 141.6, 141.9, 151.7; MS(EI) *m*/*z* (rel. intens.): 257 (5), 256 (33), 255 (M^+, 76), 240 (11), 150 (100), 134 (5), 122 (6), 108 (7), 104 (28), 91 (25), 89 (8), 73 (59), 65 (5), 59 (48). The enantiomeric excess was determined by CSP HPLC to be 23% (Chiralcel OD, 2% hexane/2-propanol, 0.5 mL/min) $t_r(R)=$ 23.6 (61.5%) min; $t_r(S)=$ 26.6 min (38.5%).

4.5. (−)-Sparteine mediated addition of RLi to imine 10. Synthesis of phenethylamines 11

A solution of RLi (3.5 mmol) was added to a cold solution of (−)-sparteine (0.94 mL, 4.1 mmol) in Et_2O (16 mL), and the mixture was stirred at −78°C for 30 min. A solution of imine **8**, immediately prepared from homoveratraldehyde (285 mg, 1.6 mmol) and *p*-anisidine (195 mg, 1.6 mmol) in the presence of Na_2SO_4, in Et_2O (16 mL) was transferred via cannula, and the resulting solution was stirred at this temperature for 2 h. The reaction was quenched by addition of water, and allowed to warm to rt. The mixture was separated, extracted with Et_2O (3×10 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent followed by purification by column chromatography (silica gel, 60% hexane/AcOEt) gave amines **11a** and **11b**. (−)-(*R*)-*N*-[2-(3,4-Dimethoxyphenyl)-1-butylethyl]-*N*-(4-methoxyphenyl)amine **11a** (65 mg, 12%): $[\alpha]_D^{20}=-23.2$ ($c=0.3$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 0.88 (t, $J=6.9$ Hz, 3H, $CH_2CH_2CH_2$C<u>H</u>$_3$), 1.26–1.54 (m, 6H, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$-CH_3), 2.75–2.78 (m, 2H, C<u>H</u>$_2$CHN), 3.21 (broad s, 1H, N<u>H</u>), 3.51–3.57 (m, 1H, CH_2C<u>H</u>N), 3.75 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.54–6.59 (m, 2H, Harom), 6.64–6.67 (m, 2H, Harom), 6.71–6.80 (m, 3H, Harom); ^{13}C NMR ($CDCl_3$ 14.1, 22.7, 28.3, 33.8, 39.3, 54.4, 55.8, 55.8, 111.0, 112.9, 114.6, 115.0, 121.5, 131.1, 141.9, 147.4, 148.6, 151.7; MS(EI) *m*/*z* (rel. intens.): 343 (M^+), 193 (13), 192 (100), 149 (8), 136 (11). The e.e. was determined by CSP HPLC to be 67% (Chiralcel OD, 5% hexane/2-propanol, 0.7 mL/min) $t_r(R)=16.6$ (83.3%) min; $t_r(S)=18.4$ min (16.7%).

(−)-(*R*)-*N*-[2-(3,4-Dimethoxyphenyl)-1-methylethyl]-*N*-(4-methoxyphenyl)amine **11b** (12 mg, 8%, 34% conversion):%): $[\alpha]_D^{20}=-3.5$ ($c=0.3$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 1.18 (d, $J=6.3$ Hz, 3H, CH_3), 2.71 (dd, $J=9.2$, 13 Hz, 1H, CH_a<u>H</u>$_b$CHN), 3.14 (dd, $J=6.6$, 13 Hz, 1H, C<u>H</u>$_a$H$_b$CHN), 3.61–3.68 (m, 1H, CH_2C<u>H</u>N), 3.76 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.65–6.84 (m, 7H, Harom); ^{13}C NMR ($CDCl_3$): 20.3, 41.7, 50.4, 55.8, 55.9, 111.1, 112.8, 114.9, 115.2, 121.5, 131.0, 141.3, 147.5, 148.7, 152.1; MS(EI) *m*/*z* (rel. intens.): 301 (M^+, 2), 151 (14), 150 (100), 135 (5), 119 (3), 108 (4), 77 (4). The enantiomeric excess was determined by CSP HPLC to be 66% (Chiralcel OD, 4% hexane/2-propanol, 1 mL/min) $t_r(R)=24.8$ (83%) min; $t_r(S)=26.7$ min (17%).

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