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Synthesis of enantiomerically enriched β-amino alcohol derivatives via asymmetric lithiation of *O*-benzyl carbamates–imine addition using (−)-sparteine complexes

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Abstract—The asymmetric lithiation of *O*-benzyl carbamates–imine addition sequence using *sec*-butyllithium/(−)-sparteine complexes has been studied. The reactions proceed with high diastereoselectivity, giving the *threo* β-amino alcohol derivatives with modest to good e.e. The best enantioinduction was obtained with *O*-benzyl carbamates bearing methoxy substituents on the aromatic ring.

1. Introduction

Because of the widespread utility in different fields of chemistry, for example medicinal chemistry[1] and especially as building blocks, chiral catalysts and auxiliaries in stereoselective synthesis,[2] optically active β-amino alcohols and their derivatives are of great importance and interest. Thus, different routes have been developed in order to synthesise these compounds.[3] In this regard, strategies based on asymmetric deprotonation–substitution sequences[4] using organolithium species complexed to (−)-sparteine are especially attractive. Hoppe[5] found that chiral carbamates, bearing hetero-substituents in the β or γ positions, are deprotonated by *sec*-butyllithium/TMEDA with efficient selection between the diastereotopic α-methylene protons. This stereoselectivity could be enhanced or overridden by means of *sec*-butyllithium/(−)-sparteine, which exhibits a strong preference for abstraction of the pro-*S* proton. Thus, the deprotonation–substitution sequence on (*R*)-2-(*N*,*N*-dibenzylamino)alkyl carbamates with *sec*-butyllithium/(−)-sparteine proceeds with a high degree of chiral recognition to form β-amino alcohols with >95% e.e. after reaction with electrophiles. In this case, the internal diastereoselectivity in favour of the pro-*S* proton is raised from 7:1 to 20:1 in the presence of (−)-sparteine. Another possible method is the use of chiral α-amino carbanions as organometallic reagents in the nucleophilic addition to prochiral aldehydes or ketones, and subsequent hydrolysis to the β-amino alcohols. Thus, Beak[6] reported the controlled asymmetric synthesis of β-amino alcohols with high enantioenrichments from *N*-Boc-*N*-(*p*-methoxyphenylbenzylamine and benzaldehyde in an asymmetric lithiation–substitution sequence mediated by (−)-sparteine. The authors also found that this approach could be extended to the synthesis of vicinal diamines using the imine *N*-benzylidene-*p*-methoxyaniline as electrophile. In a similar way, Martens[7] has recently carried out the reaction of *N*-Boc-pyrrolidin-2-lithium, generated by the use of *sec*-butyllithium/(−)-sparteine complex, to bicyclic imines.

However, to our knowledge, the addition of chiral α-oxycarbanions to prochiral imines has not been reported so far even though this synthetic pathway would also give the possibility of forming β-amino alcohols with control of the two stereogenic centres.[8] Herein, we wish to report the stereoselective intermolecular addition of chiral α-oxybenzyllithium, generated by deprotonation of *O*-benzyl carbamates, to imines using (−)-sparteine complexes.[9]

2. Results and discussion

We initiated our study by examining the diastereoselectivity of the addition of lithiated *O*-benzyl carbamates **2** to benzylidene-*p*-anisidine **3** as shown in Scheme 1. We selected a carbamate protecting group to favour depro-

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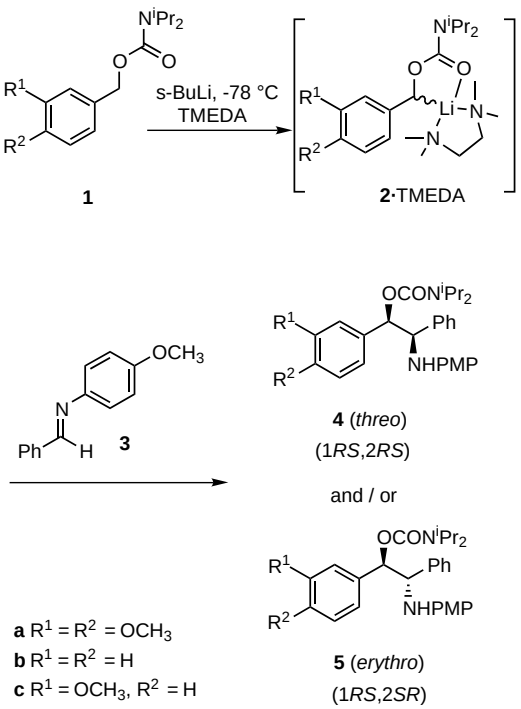


Scheme 1.

tonation, as it is known that in the presence of TMEDA this group increases the kinetic acidity of the α-protons and stabilizes the lithio derivatives by chelation.[10] Thus, racemic α-oxybenzyllithium compounds **2**, stabilised by complexation with TMEDA, were generated, as previously described, by deprotonation of the lithiated *O*-benzyl carbamates **1** with *sec*-BuLi in Et_2O at 78°C in the presence of TMEDA over five minutes. Alkylation of **2** with the *p*-anisidine-derived imine **3** resulted in the formation of *N*,*O*-protected *threo* and *erythro* β-amino alcohols **4** and **5**. As summarised in Table 1, a strong influence of the alkylation conditions on the stereoselectivity was observed. Thus, when the reaction mixture was stirred for two hours at −78°C, and allowed to warm to room temperature before quenching, the *erythro* β-amino alcohol derivatives **5a**–**c** were obtained as major products, though with modest diastereoselectivity (entries 1, 4, and 6). However, when α-oxybenzyllithium **2a** was treated with imine **3** at –78°C for 48 h, complete reversal of the stereochemical outcome was observed and the *threo* β-amino alcohol derivative **4a** was obtained as a single diastereomer, albeit in moderate yield (33%). Nevertheless, an increase on the reaction time considerably improved the yield of **4a** to 64% (entries 2 and 3). This reversal of stereoselection could also be observed on carbamate **1b**, obtaining the *threo* β-amino alcohol derivative **2b** as the major product, though with almost no diastereoselectivity (entry 5).

The relative stereochemistry of the *N*,*O*-protected *threo* and *erythro* β-amino alcohols **4** and **5** was determined by the analysis of the values of the vicinal H_1–H_2 coupling constants, as has been described for related compounds.[11] Thus, the coupling constants for *threo* compounds **4a**–**c** have larger values (9.5 Hz) than those for the *erythro* products **5a**–**c** (5.1–5.9 Hz), which is consistent with a larger dihedral angle in the preferred conformation.[12] The stereochemical outcome of the reaction could be explained in terms of the most favourable transition state for the addition. We can assume that the α-oxybenzylcarbanion **2** is stabilised by coordination of lithium to the carbonyl oxygen. Therefore, if the imine approaches anion **2** with coordination of the nitrogen atom to the lithium metal, an approach from the *Si* face would be more favourable, minimising the repulsion between the two phenyl groups in the transition state. Similar diastereoselectivity has been reported in the addition of α-aminobenzyllithium salts to benzylidene-*p*-anisidine.[13]

Once it had been established that the addition of α-lithiated carbamates **2** to imine **3** could be carried out with control of diastereoselectivity, we focused on the enantioselectivity of the reaction. The pioneering work of Hoppe[10] had shown that enantioselective deprotonation reactions of carbamates could be carried out with organolithiums in the presence of the chiral diamine (−)-sparteine. In this context, whereas the lithium derivatives of secondary benzyl *N*,*N*-dialkylcarbamates are configurationally stable at −70°C, this is not necessarily true for lithiated primary benzyl carbamates.[4d] In fact, although the lithium derivative of carbamate **1b** proved to be configurationally stable under Hoffmann test conditions,[14] Hoppe has concluded that it is probable that both epimeric lithium complexes [(*S*)-**2b** (−)-sparteine and (*R*)-**2b** (−)-sparteine] equilibrate even at –70°C. In a series of experiments, carbamate **1b** was deprotonated with *s*-BuLi in the presence of (−)-sparteine, and quenched by the addition of CO_2, followed by esterification with diazomethane. The methoxycarbonyl derivatives were obtained with modest e.e. in Et_2O (14%), which was improved in hexane up to 82%. Thus, in accord with the (*S*)-configuration of the methoxycarbonyl derivative obtained, the

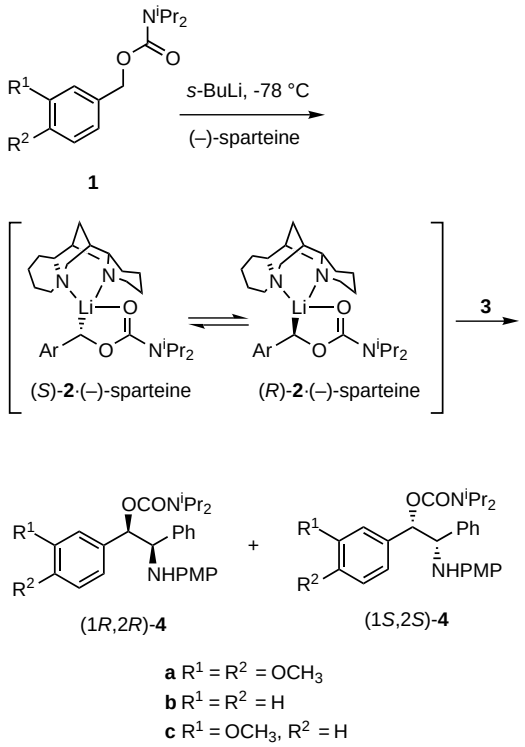
Table 1. Addition of α-oxybenzyllithiums to imine **3**

Entry	Substrate	R^1	R^2	Conditions	Yield (%)	Ratio **4**:**5**
1	**1a**	OCH_3	OCH_3	Et_2O, −78°C, 2 h; −78°C→rt	67	33:67
2	**1a**	OCH_3	OCH_3	Et_2O, −78°C, 48 h	33	>95:5
3	**1a**	OCH_3	OCH_3	Et_2O, −78°C, 72 h	64	>95:5
4	**1b**	H	H	Et_2O, −78°C, 2 h; −78°C→rt	97	27:73
5	**1b**	H	H	Et_2O, −78°C, 48 h	41	59:41
6	**1c**	OCH_3	H	Et_2O, −78°C, 2 h; −78°C→rt	73	28:72

configuration of the favoured ion-pair was assumed to be (*S*).[4d,15]

With these precedents in mind, benzyllithium salts **2** were generated by deprotonation with *sec*-BuLi/(–)-sparteine (1.1 equiv.) at –78°C over 5 min, and allowed to react with imine **3** under various experimental conditions (Table 2). The first interesting feature of these reactions was that, in direct contrast to the results obtained with TMEDA, when the reaction mixtures were kept at –78°C for 2 h and allowed to warm to rt before quenching, in all cases, the *threo* isomers **4a**–**c** were obtained as the major diastereomers (entries 1, 6, and 8), although with modest e.e. When the temperature was kept at –78°C for 6 h, an improvement in diastereoselection was observed and **4a** and **4c** were obtained as single diastereomers, though the e.e.s were still only moderate (entries 2 and 10). The best diastereo- and enantioselectiviy was achieved when an excess of the *sec*-BuLi/(–)-sparteine complex was used (2.2 equiv.), and the reaction was quenched at low temperature. Thus, *threo* compounds **4a** and **4c** were obtained as single diastereomers with e.e.s of 56 and 76%, respectively. In both cases, the enantiomeric purity of the products was significantly improved after crystallisation from hexane/2-propanol to 96 and 91% e.e., respectively (Scheme 2). The use of less coordinating solvents, such as toluene (entries 4, 8, and 12) or hexane (entry 5) resulted in a loss of enantioselection. It is also worth mentioning that in the case of carbamate **1b**, poor e.e.s were obtained under all the conditions tested (entries 6–8).[16]

The formation of the *threo* products (*R*,*R*)-**4a**–**c** could be explained assuming that, as stated by Hoppe for **1b**, the favoured ion pair is (*S*)-**2**, which reacts with imine **3** with retention of configuration. Although the stereochemical course of the electrophilic substitution of chiral benzyllithium compounds is still unclear, it has been established that some electrophiles show strong tendencies for stereoinversion (alkyl and acyl halides, CO_2, carbon disulphide, silyl and stannyl chlorides) while others for stereoretention (protonation with alcohols or acids, reaction with aldehydes or esters).[4d] In the latter case, it can be assumed that a pre-association of the reagent at the cation occurs.[17] Although addition of chiral α-oxycarbanions to prochiral imines has not been reported, Beak has demonstrated that a chiral α-amino benzyllithium generated from *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamine reacts with benzylidene-*p*-anisidine **3** with retention of configuration.[6]



Scheme 2.

3. Conclusion

The addition of α-oxybenzyllithium salts derived from *O*-benzyl carbamates, to benzylidene-*p*-anisidine in the presence of TMEDA at –78°C is diastereoselective, occurring preferentially from the *Si* face. The use of

Table 2. (−)-Sparteine mediated addition of α-oxybenzyllithiums to imine **3**

Entry	Substrate	R^1	R^2	Solvent	Temperature	Yield (%)	D.r	E.e. (%)
1	**1a**	OCH_3	OCH_3	Et_2O	−78°C→rt	38	72:28	46
2	**1a**	OCH_3	OCH_3	Et_2O	−78°C	79	>95:5	35
3	**1a**	OCH_3	OCH_3	Et_2O[a]	−78°C	84	>95:5	56 (96)[b]
4	**1a**	OCH_3	OCH_3	Toluene	−78°C→rt	72	>95:5	46
5	**1a**	OCH_3	OCH_3	Hexane	−78°C	37	>95:5	8
6	**1b**	H	H	Et_2O	−78°C→rt	56	77:23	9
7	**1b**	H	H	Et_2O[a]	−78°C	13	>95:5	15
8	**1b**	H	H	Toluene	−78°C→rt	39	71:29	10
9	**1c**	OCH_3	H	Et_2O	−78°C→rt	31	>95:5	30
10	**1c**	OCH_3	H	Et_2O	−78°C	45	>95:5	33
11	**1c**	OCH_3	H	Et_2O[a]	−78°C	67	>95:5	76 (91)[b]
12	**1c**	OCH_3	H	Toluene	−78°C→rt	32	67:33	7

[a] 2.2 equiv. of *sec*-BuLi/ (–)-sparteine were used
[b] E.e. after recrystallisation

sec-butyllithium/(−)-sparteine complexes does not change the sense of diastereoselectivity and enables the reaction to be conducted enantioselectively, giving the enantioenriched *threo*-β-amino alcohol derivatives with modest to good e.e. The stereochemical outcome of the reaction can be explained assuming that, as has been observed in previous studies, the favoured ion pair would have (*S*)-configuration, and subsequent addition takes place with stereoretention.

4. Experimental

4.1. General procedure for TMEDA-mediated addition of α-oxybenzyllithiums to imine 3

A solution of *s*-BuLi (1.1 mmol) was added to a cold solution of TMEDA (0.16 mL, 1.1 mmol) and carbamates **1a**–**c** (1 mmol) in Et_2O (10 mL), and the mixture was stirred at –78°C for 5 min. A solution of imine **3** (1 mmol) in Et_2O (10 mL) was added and the resulting solution was stirred at –78°C for 2 h, allowed to warm to rt. The reaction was quenched by addition of 2 M HCl (10 mL). The mixture was separated, extracted with Et_2O (3×10 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, and dried over Na_2SO_4. Evaporation of the solvent followed by purification by column chromatography (silica gel) gave a mixture of *threo*-**4a**–**c** and *erythro*-**5a**–**c**.

4.1.1. (1*RS*,2*RS*)-4a and (1*RS*,2*SR*)-5a. According to the general procedure, carbamate **1a** (407 mg, 1.38 mmol) was treated with *sec*-BuLi (1.2 mL of a 1.27 M solution in hexanes, 1.52 mmol), TMEDA (0.23 mL, 1.52 mmol) and imine **3** (324 mg, 1.52 mmol). After work-up, purification by column chromatography (silica gel, 35% hexane/ethyl acetate) gave a mixture of (1*RS*,2*RS*)-**4a** (1*RS*,2*SR*)-**5a** in a 33:67 ratio, (estimated by integration of representative signals of the ^{1}H NMR spectrum of the mixture) (467 mg, 67%). Analytical samples of both diastereomers were obtained by column chromatography followed by crystallisation from Et_2O.

4.1.1.1. (1*RS*,2*RS*)-*O*-(*N*,*N*-Diisopropylcarbamoyl)-*N*-(*p*-methoxyphenyl)-1-(3,4-dimethoxyphenyl)-2-phenyl-2-aminoethanol, 4a. Mp (Et_2O) 130–132°C; ^{1}H NMR ($CDCl_3$) 0.85 (d, J=5.5 Hz, 6H, 2×CH_3), 1.09 (d, J=6.3 Hz, 6H, 2×CH_3), 3.48–3.59 (m, 2H, 2×CH), 3.72 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.94 (dd, J=9.5, 5.5 Hz, 1H, H-2), 5.35 (d, J=9.5 Hz, 1H, H-1), 6.56–6.61 (m, 2H, Harom.), 6.71–6.77 (m, 5H, Harom.), 7.06–7.16 (m, 5H, Harom.); ^{13}C NMR ($CDCl_3$) 19.8 (CH_3), 21.2 (CH), 55.2, 55.6 (OCH_3), 69.1 (C-2), 73.6 (C-1), 110.2, 110.4, 113.7, 119.5, 127.2, 127.7, 129.6, 129.8 (Carom.-H), 135.1, 135.2, 138.7 (Carom.-C, Carom.-N), 147.6, 148.2, 157.6 (Carom.-O), 163.6 (CO); IR (CH_2Cl_2) 3326, 1608 cm^{-1}; MS (EI) m/z (rel. intensity) 340 (15), 212 (9), 196 (9), 149 (12) 128 (59), 105 (20), 91 (22), 87 (15), 86 (72), 85 (73), 84 (10), 83 (100), 82 (8), 77 (15), 73 (9), 71 (18), 70 (10), 69 (16), 58 (10), 57 (35), 55 (20). Anal. calcd for $C_{30}H_{38}N_2O_5$: C, 71.12; H, 7.56; N, 5.53. Found C, 70.95; H, 7.75; N, 5.23%.

4.1.1.2. (1*RS*,2*SR*)-*O*-(*N*,*N*-Diisopropylcarbamoyl)-*N*-(*p*-methoxyphenyl)-1-(3,4-dimethoxyphenyl)-2-phenyl-2-aminoethanol 5a. Mp (Et_2O) 69–71°C; ^{1}H NMR ($CDCl_3$) 0.78 (d, J=5.9 Hz, 6H, 2×CH_3), 0.92 (d, J=6.3 Hz, 6H, 2×CH_3), 3.38–3.43 (m, 2H, 2×CH), 3.75 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.87 (broad s, 1H, NH), 5.09 (d, J=5.9 Hz, 1H, H-2), 5.37 (d, J=5.9 Hz, 1H, H-1), 6.72–6.79 (m, 3H, Harom.), 6.86–6.94 (m, 4H, Harom.), 7.17–7.23 (m, 3H, Harom.), 7.43–7.47 (m, 2H, Harom.); ^{13}C NMR ($CDCl_3$) 19.2 (CH_3), 21.1 (CH), 55.3, 55.6, 55.7 (OCH_3), 71.5 (C-2), 73.6 (C-1), 109.9 110.5, 114.3, 119.2, 127.1, 127.4, 127.6, 129.7 (Carom.-H), 134.6, 137.4, 138.2 (Carom.-C, Carom.-N), 147.9, 148.6, 156.8 (Carom.-O), 160.8 (CO); IR (CH_2Cl_2) 3234, 1627 cm^{-1}; MS (EI) m/z (rel. intensity) 341 (10), 340 (42), 297 (9), 212 (14), 149 (9), 139 (6), 129 (9), 128 (100), 91 (16), 86 (89), 58 (9).

4.1.2. (1*RS*,2*RS*)-4b and (1*RS*,2*SR*)-5b. According to the general procedure, carbamate **1b** (109 mg, 0.46 mmol) was treated with *sec*-BuLi (0.70 mL of a 0.71 M solution in hexanes, 0.51 mmol), TMEDA (0.07 mL, 0.51 mmol) and imine **3** (111 mg, 0.5 mmol). After work-up, purification by column chromatography (silica gel, 25% hexane/ethyl acetate gave a mixture of (1*RS*,2*RS*)-**4b** (1*RS*,2*SR*)-**5b** in a 27:73 ratio, (estimated by integration of representative signals of the ^{1}H NMR spectrum of the mixture) (200 mg, 97%). Analytical samples of both diastereomers were obtained by column chromatography followed by crystallisation from Et_2O.

4.1.2.1. (1*RS*,2*RS*)-*O*-(*N*,*N*-Diisopropylcarbamoyl)-*N*-(*p*-methoxyphenyl)-1,2-diphenyl-2-aminoethanol 4b. Mp (Et_2O) 117–119°C; ^{1}H NMR ($CDCl_3$) 0.85 (d, J=5.9 Hz, 6H, 2×CH_3), 1.12 (d, J=6.3 Hz, 6H, 2×CH_3), 3.46–3.53 (m, 2H, 2×CH), 3.77 (s, 3H, OCH_3), 4.99 (dd, J=6.3, 9.5 Hz, 1H, H-2), 5.41 (d, J=9.5 Hz, 1H, H-1), 6.67–6.72 (m, 4H, Harom.), 7.03–7.29 (m, 10H, Harom.); ^{13}C NMR ($CDCl_3$) 19.7 (CH_3), 21.4 (CH), 55.3 (OCH_3), 69.2 (C-2), 73.9 (C-1), 113.7 126.9, 127.3, 127.8, 129.7, 129.9 (Carom.-H), 135.4, 138.6, 142.7 (Carom.-C, Carom.-N), 157.6 (Carom.-O), 163.8 (CO); IR (CH_2Cl_2) 3307, 1608 cm^{-1}; MS (EI) m/z (rel. intensity) 446 (M^+, 1), 340 (21), 339 (10), 213 (6), 212 (34), 211 (9), 197 (7), 196 (11), 149 (12). Anal. calcd for $C_{28}H_{34}N_2O_3$: C 75.31, H 7.67, N 6.27. Found C 74.87, H 7.96, N 5.94%.

4.1.2.2. (1*RS*,2*SR*)-*O*-(*N*,*N*-Diisopropylcarbamoyl)-*N*-(*p*-methoxyphenyl)-1,2-diphenyl-2-aminoethanol 5b. Mp (Et_2O) 139–141°C; ^{1}H NMR ($CDCl_3$) 0.79–0.94 (m, 12H, 4×CH_3), 3.44–4.49 (m, 2H, 2×CH), 3.78 (s, 3H, OCH_3), 5.04 (d, J=5.1 Hz, 1H, H-2), 5.42 (d, J=5.1 Hz, 1H, H-1), 6.82 (d, J=8.9 Hz, 2H, Harom.), 6.98 (d, J=8.9 Hz, 2H, Harom.), 7.18–7.50 (m, 10H, Harom.); ^{13}C NMR ($CDCl_3$) 19.2 (CH_3), 21.1 (CH), 55.3 (OCH_3), 72.3 (C-2), 73.5 (C-1), 114.4 (Carom.-C), 126.7, 127.0, 127.3, 127.6, 128.0, 129.7 (Carom.-H),

137.2, 138.3, 142.1 (Carom.-C, Carom.-N), 156.9 (Carom.-O), 160.8 (CO); IR (CH_2Cl_2) 3378, 1619 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 341 (9), 340 (36), 339 (19), 212 (20), 211 (7), 196 (11), 149 (7), 129 (9), 128 (100), 105 (7), 91 (10), 86 (80) 79 (9), 77 (11), 58 (9).

4.1.3. (1*RS*,2*RS*)-4c and (1*RS*,2*SR*)-5c. According to the general procedure, carbamate **1c** (121 mg, 0.46 mmol) was treated with *sec*-BuLi (0.53 mL of a 0.96 M solution in hexanes, 0.51 mmol), TMEDA (0.07 mL, 0.5 mmol) and imine **3** (111 mg, 0.5 mmol). After work-up, purification by column chromatography (silica gel, 30% hexane/ethyl acetate) gave a mixture of (1*RS*,2*RS*)-**4c** (1*RS*,2*SR*)-**5c** in a 28:72 ratio, (estimated by integration of representative signals of the ^1H NMR spectrum of the mixture) (160 mg, 73%). Analytical samples of both diastereomers were obtained by column chromatography followed by crystallisation from Et_2O.

4.1.3.1. (1*RS*,2*RS*)-*O*-(*N*,*N*-Diisopropylcarbamoyl)-*N*-(*p*-methoxyphenyl)-1-(3-methoxyphenyl)-2-phenyl-2-aminoethanol 4c. Mp (Et_2O) 148–150°C; ^1H NMR ($CDCl_3$) 0.85 (d, $J=5.9$ Hz, 6H, 2×CH_3), 1.10 (d, $J=6.3$ Hz, 6H, 2×CH_3), 3.48–3.53 (m, 2H, 2×CH), 3.67 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.98 (dd, $J=9.5$, 6.3 Hz, 1H, H-2), 5.38 (d, $J=9.5$ Hz, 1H, H-1), 6.59–6.71 (m, 6H, Harom.), 6.81–6.87 (m, 2H, Harom.), 7.00–7.19 (m, 5H, Harom.); ^{13}C NMR ($CDCl_3$) 19.9 (CH_3) 21.4 (CH), 55.1, 55.4 (OCH_3), 69.3 (C-2), 73.9 (C-1), 112.5 112.9, 113.8, 119.7, 127.4, 127.9, 128.9, 129.7, 129.8 (Carom.-H), 135.4, 138.7, 144.3 (Carom.-C, Carom.-N), 157.6, 159.2 (Carom.-O), 163.7 (CO); IR (CH_2Cl_2) 1602 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 340 (25), 212 (13), 149 (6), 128 (100), 109 (6), 91 (12), 86 (94), 77 (9), 58 (10). Anal. calcd for $C_{29}H_{36}N_2O_4$: C 73.08, H 7.61, N 5.87. Found C 73.19, H 7.58, N 5.58%.

4.1.3.2. (1*RS*,2*SR*)-*O*-(*N*,*N*-Diisopropylcarbamoyl)-*N*-(*p*-methoxyphenyl)-1-(3-methoxyphenyl)-2-phenyl-2-aminoethanol 5c. Mp (Et_2O) 99–101°C; ^1H NMR ($CDCl_3$): 0.81 (d, $J=5.9$ Hz, 6H, 2×CH_3), 0.93 (d, $J=6.3$ Hz, 6H, 2×CH_3), 3.46–3.55 (m, 2H, 2×CH), 3.72 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 5.08 (d, $J=5.2$ Hz, 1H, H-2), 5.38 (d, $J=5.2$ Hz, 1H, H-1), 5.45 (broad s, 1H, NH), 6.71–6.82 (m, 4H, Harom.), 6.92–6.98 (m, 3H, Harom.), 7.14–7.19 (m, 4H, Harom.), 7.46–7.50 (m, 2H, Harom.). ^{13}C NMR ($CDCl_3$) 19.2 (CH_3), 21.1 (CH), 55.0, 55.3 (OCH_3), 72.1 (C-2), 73.4 (C-1), 112.0 112.8, 114.4, 119.1, 127.0, 127.6, 128.9, 129.6, 129.7 (Carom.-H), 137.2, 138.2, 143.8 (Carom.-C, Carom.-N), 156.9, 159.3 (Carom.-O), 160.8 (CO). IR (CH_2Cl_2) 1613 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 340 (13), 212 (15), 149 (12), 128 (86), 121 (13), 91 (18), 87 (12), 86 (100), 83 (76), 77 (18), 58 (12).

4.2. General procedure for (−)-sparteine-mediated addition of α-oxybenzyllithiums to imine 3

A solution of *sec*-BuLi (2.2 mmol) was added to a cold solution of (−)-sparteine (2.2 mmol) in Et_2O (5 mL), and the resulting solution was stirred at –78°C for 20 min. A solution of carbamates **1a**–**c** (1 mmol) in Et_2O (10 mL) was added, and the mixture was stirred at –78°C for 5 min. A solution of imine **3** (1.1 mmol) in Et_2O (10 mL) was added and the resulting solution was stirred for 6 h. The reaction was quenched at low temperature by addition of 2 M HCl (10 mL), and the mixture was allowed to warm up to rt. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, and dried over Na_2SO_4. Evaporation of the solvent followed by purification by column chromatography (silica gel) gave enantioenriched (1*R*,2*R*)-**4a**–**c**, whose spectroscopic data were identical to those of the racemates.

4.2.1. (1*R*,2*R*)-*O*-(*N*,*N*-Diisopropylcarbamoyl)-*N*-(*p*-methoxyphenyl)-1-(3,4-dimethoxyphenyl)-2-phenyl-2-aminoethanol 4a. According to the general procedure, carbamate **1a** (128 mg, 0.43 mmol) was treated with *sec*-BuLi (0.73 mL of a 1.3 M solution in hexanes, 0.95 mmol), (−)-sparteine (0.2 mL, 0.95 mmol) and imine **3** (100 mg, 0.47 mmol). After work-up, purification by column chromatography (silica gel, 35% hexane/ethyl acetate) gave (1*R*,2*R*)-**4a** as a white solid (183 mg, 84%). The enantiomeric excess was determined by CSP HPLC to be 56% (Chiralcel OD, 10% hexane/2-propanol, 0.8 mL/min) $t_r(S,S)=15.9$ min (22.2%); $t_r(R,R)=28.0$ (77.8%) min. After crystallisation from 1% hexane/2-propanol, the e.e. was improved to 96% (Chiralcel OD, 10% hexane/2-propanol, 0.8 mL/min) $t_r(S,S)=15.9$ min (2.2%); $t_r(R,R)=28.0$ min (97.8%). $[\alpha]_D^{20}=-19.1$ ($c=0.2$, $CHCl_3$).

4.2.2. (1*R*,2*R*)-*O*-(*N*,*N*-Diisopropylcarbamoyl)-*N*-(*p*-methoxyphenyl)-1,2-diphenyl-2-aminoethanol 4b. According to the general procedure, carbamate **1b** (119 mg, 0.5 mmol) was treated with *sec*-BuLi (0.86 mL of a 1.27 M solution in hexanes, 1.1 mmol), (−)-sparteine (0.26 mL, 1.1 mmol) and imine **3** (117 mg, 0.56 mmol). After work-up, purification by column chromatography (silica gel, 35% hexane/ethyl acetate) gave (1*R*,2*R*)-**4b** as a white solid (29 mg, 13%). The enantiomeric excess was determined by CSP HPLC to be 15% (Chiralcel OD, 10% hexane/2-propanol, 0.7 mL/min) $t_r(R,R)=8.6$ min (57.8%); $t_r(S,S)=21.9$ min (42.2%). $[\alpha]_D^{20}=-26.5$ ($c=0.1$, CH_2Cl_2).

4.2.3. (1*R*,2*R*)-*O*-(*N*,*N*-Diisopropylcarbamoyl)-*N*-(*p*-methoxyphenyl)-1-(3-methoxyphenyl)-2-phenyl-2-aminoethanol 4c. According to the general procedure, carbamate **1c** (80 mg, 0.30 mmol) was treated with *sec*-BuLi (0.67 mL of a 0.98 M solution in hexanes, 0.66 mmol), (−)-sparteine (0.13 mL, 0.66 mmol) and imine **3** (70 mg, 0.33 mmol). After work-up, purification by column chromatography (silica gel, 30% hexane/ethyl acetate) gave (1*R*,2*R*)-**4a** as a white solid (96 mg, 67%). The enantiomeric excess was determined by CSP HPLC to be 76% (Chiralcel OD, 8% hexane/2-propanol, 0.6 mL/min) $t_r(R,R)=15.6$ min (87.8%); $t_r(S,S)=21.3$ min (12.2%). After crystallisation from 2% hexane/2-propanol, the e.e. was improved up to 91% (Chiralcel OD, 8% hexane/2-propanol, 0.6 mL/min) $t_r(R,R)=15.6$ min (95.6%); $t_r(S,S)=21.3$ min (4.4%). $[\alpha]_D^{20}=-102.2$ ($c=0.5$, $CHCl_3$).

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