Addition of Grignard Reagents to Chiral 1,2-Bisimines: A Diasteroselective Preparation of Unsymmetrical 1,2-Diamines

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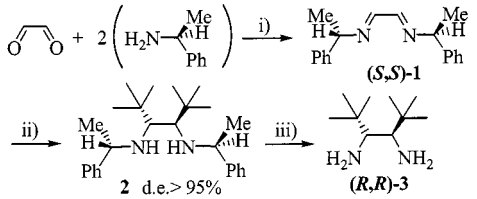
A diastereoselective synthesis of *tert*-butyl-1,2-diamines has been developed from the addition of *tert*-butylmagnesium chloride to the 1,2-bisimines derived from glyoxal and chiral amines such as 1-(*S*)-ethylphenylamine, 1-(*S*)-phenylpropylamine or 1-(*S*)-(*p*-chlorophenyl)ethylamine. The influence of solvent, temperature and chiral auxiliaries on the chemical reactivity and stereoselectivity has been fully studied. Evidence of a dynamic kinetic resolution during the bis-addition process of the organometallic, leading to the 1,2-di-*tert*-butylethanediamine,[1] as a single diastereomer, has been demonstrated. This resolution has been applied with high diastereoselectivities to the synthesis of unsymmetrical disubstituted 1,2-diamines, by addition of one equivalent of *tert*-butylmagnesium chloride, followed by one equivalent of a second Grignard reagent. Several chiral 1-*tert*-butyl-1,2-diamines have also been synthesized by monoaddition of *tert*-butylmagnesium chloride to the bisimines, followed by hydride reduction of the chiral intermediate imines.

Introduction

In recent years, vicinal diamines have played an increasingly important role in organic chemistry[2] particularly due to their use as chiral auxiliaries or as precursors for the synthesis of a broad family of bidentate ligands. Numerous preparations of symmetrical or unsymmetrical 1,2-diamines have been developed.

We recently reported a diastereoselective synthesis of (*R*,*R*)-1,2-diamino-1,2-di-*tert*-butylethane **3**, by reverse addition of the chiral (*S*,*S*)-1,2-bisimine **1** to a suspension of *tert*-butylmagnesium chloride (Scheme 1). This reaction gave one single diastereomer **2**, which upon hydrogenolysis led to the (*R*,*R*)-diamine **3**.[1] The high diastereoselectivity of this reaction induced us to fully study the addition of *tert*-butylmagnesium chloride to chiral 1,2-bisimines derived from glyoxal.



Scheme 1. i) $MgSO_4$, CH_2Cl_2; ii) *t*BuMgCl, hexane, 50 °C; iii) HCO_2NH_4, 10% $Pd(OH)_2/C$, EtOH reflux

In this paper, we wish to report these results and their application to the synthesis of new unsymmetrical 1,2-diamines.

The addition of Grignard or zinc reagents to the carbon-nitrogen double bonds of the chiral 1,2-bisimine **1**[3,5] derived from glyoxal and (*S*) [or (*R*)] methylbenzylamine, has previously been studied by Neumann et al. They showed that addition of allyl magnesium chloride to **1** at –78 °C gave a 6:1 diastereomeric mixture.[4] A few years later, Savoia and Coll. improved this reaction by using allylzinc bromide and obtained the same major diastereomer in 93.5% yield.[5] Addition of phenyl magnesium chloride or methyl magnesium bromide at low temperature was also studied by Simpkins and co-workers.[6] These reagents furnished a mixture of diastereomers from which the major one was isolated in 47% and 35% yield, respectively. In all these studies, the same stereochemistry was observed, affording the (1*R*,2*R*) diamine, starting from the (*S*,*S*)-bisimine **1**.

The monoaddition of *tert*-butyl organometallics to 1,2-iminoesters has previously been reported by Kagan et al.[8] tom Dieck[7] also described a similar type of addition to 1,2-bisimines, but with no stereochemical information. One diastereoselective example of addition of *tert*-butylzincates was described by Savoia et al.,[9] who obtained the 1-(2-pyridyl)-*tert*-butyl amine with 50% *de*.

Results and Discussion

Study of the Reactivity

Our initial attempts to study the reactivity of *tert*-butylmagnesium chloride towards the bisimine **1** showed that the first addition occurred rapidly at low temperature (–78 °C) in many solvents (hexane, toluene, ether or THF). Indeed, dropwise addition of the Grignard reagent to a solution of **1** in the appropriate solvent, followed by immediate reverse quenching in a saturated aqueous solution of ammonium chloride, gave quantitatively the monoadduct **5** (Scheme 2). However, in the bis-addition process, introduction of the second *tert*-butyl group appeared to be more difficult and

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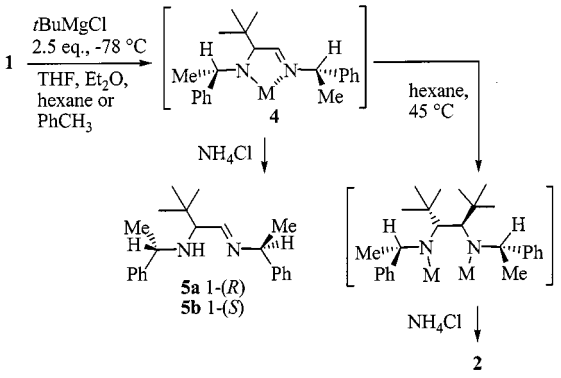
we soon noticed that it was closely related to the nature of the solvent and the addition temperature. A temperature above +35 °C was necessary in toluene to obtain the diamine **2** and no reaction occurred below +45 °C in hexane. The difference of reactivity between these two non-polar solvents was probably due to their ability to solubilise the Grignard reagent (the reaction was homogeneous in toluene and heterogeneous in hexane). However, some side-reactions occurred when the bis-addition was performed in toluene, although not in hexane. Surprisingly, all our attempts to perform the addition in polar solvents such as THF or ether, gave exclusively the monoadduct **5**, even upon heating (65 °C in THF).

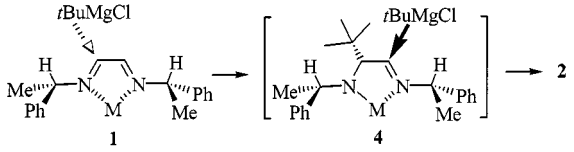


Scheme 2. Influence of solvent and temperature

In these bis-additions, it was found that the second addition goes through the rigid five-membered chelate **4** which plays an important role in providing an activation of the imine double bond (Scheme 2).[10] We demonstrated in our case, in contrary to the other Grignard reagents previously used (PhMgCl, AllylMgCl or MeMgCl), that generation of this chelate was essential, although not always sufficient, to allow the addition of the second *tert*-butyl group.

Study of the Diastereoselectivity

According to the results obtained for the addition of the allyl or phenyl moiety, the stipulated more stable conformation of the bisimine **1** is the one where the C–H benzylic bond and the C=N bond are coplanar (Scheme 3).[10] The stereochemistry of the first addition of *tert*-butylmagnesium chloride should be controlled by steric interactions with the organometallic group approaching the bis-imine **1** from the less-hindered methyl face. The second addition to intermediate **4** would then be controlled both by the first *tert*-butyl group added and by the chiral auxiliary on the remaining imine (Scheme 3). According to this model, the diamine **2** with an (*R*,*R*) configuration was expected, and indeed obtained, as confirmed by X-ray spectroscopy.[1]



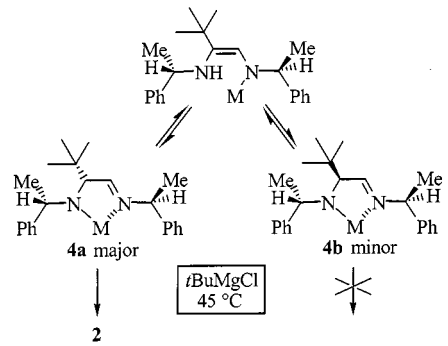
Scheme 3. Control of the diastereoselectivity

Nevertheless, the model described above became less obvious when we checked the diastereomeric purity of the monoadduct **5** by running the addition in hexane at 20 °C. Indeed, **5** was obtained with a much lower *de* (40%) than that observed for the final diamine **2** (>95%).[11] This result led us to modify the stereocontrol pathway proposed in Scheme 3. Indeed, if the second addition (**4** → **2**) seemed completely directed to the opposite side of the *tert*-butyl group (no "meso" compound was ever observed with **2**), it was clear that the first addition was not efficiently controlled by the chiral auxiliary. However, this surprising result was clarified by the following experiments: the addition of *tert*-butylmagnesium chloride performed in THF at –40 °C and quenched at 20 °C gave a 77:23 mixture of **5a:5b** (Table 1, entry 3) whereas the same reaction maintained and quenched at –40 °C gave a 1:1 mixture (Table 1, entry 1). Therefore, we considered that an equilibration should occur between the two intermediates **4a** and **4b** at 20 °C (Scheme 4). We postulated that only the intermediate **4a** could react with a second equivalent of Grignard reagent (in hexane at 50 °C), providing the (1*R*,2*R*) diamine **2**. In **4b**, the bulkiness of the *tert*-butyl group and the chiral auxiliary should prevent the addition of the second organometallic. This system led to a dynamic kinetic resolution of **4a** and **4b** to give **2**. Such a hypothesis was confirmed by performing the addition of a 1:1 mixture of **5a**:**5b**, to a suspen-

Table 1. Monoaddition to **1** in THF, temperature dependent equilibration

entry	*T* addition [°C]	*T* quenching [°C]	ratio **5a/5b**[a]
1	–40	–40	50:50
2	–40	–10	50:50
3	–40	20	77:23
4	20	20	78:22

[a] All these reactions gave quantitatively the monoadduct **5** and the ratios were measured by ^{1}H NMR (400 MHz) of the crude reaction mixture.



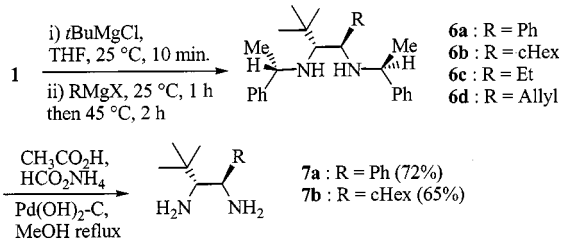
Scheme 4. Dynamic kinetic resolution

sion of *t*BuMgCl (2.5 equiv.) in hexane at 50 °C. After 30 min., 67% of diamine **2** (*de* = 100%), 12% of **5a** and 22% of **5b** were obtained. If no equilibration had occurred, we should have recovered 50% of **5b** and no more than 50% of **2**, which was not the case. In all these reactions, according to the (1*R*,2*R*) absolute configuration obtained for the diamine **2**, the (*R*) configuration on the carbon bearing the *tert*-butyl group was assigned for the major diastereomer **5a**.

The mechanism of the equilibration still remained unexplained. Nevertheless, it could go through an intermediate enamine by intra- or intermolecular deprotonation of the carbon bearing the *tert*-butyl group in **4**. Evidence of formation of this intermediate could not be confirmed since no trace of enamine was observed by ^{1}H NMR spectroscopy.

Synthesis of Unsymmetrical 1,2-Diamines

From the results above, we thought that the equilibrium between **4a** and **4b** could also be displaced by addition of a second, different Grignard reagent, less hindered and more reactive than *tert*-butylmagnesium chloride, thus affording unsymmetrical disubstituted 1,2-diamines (Scheme 5). We considered that this reaction might give a major (1*R*,2*R*) diastereomer, which would be a further confirmation of the dynamic kinetic resolution. This hypothesis was supported by adding 1.5 equivalent of *tert*-butylmagnesium chloride to the bisimine **1**, at 25 °C in THF, followed by the addition of PhMgCl, cHexMgCl, EtMgBr or AllylMgBr and heating for 2 h at 45 °C. Compounds **6a**–**6d** were obtained in high diastereomeric excesses and in good yields (Table 2). The more hindered phenyl and cyclohexyl Grignard reagents (entries 1 and 2) gave only one diastereomer detectable by ^{1}H and ^{13}C NMR spectroscopy. Even the less-hindered EtMgBr (entry 3) and the more reactive allylMgBr (entry 4) gave **6c** and **6d**, respectively, with good *de*. Deprotection of the chiral auxiliary groups on diamines **6a** and **6b** was



Scheme 5. Synthesis of unsymmetrical 1,2-diamines

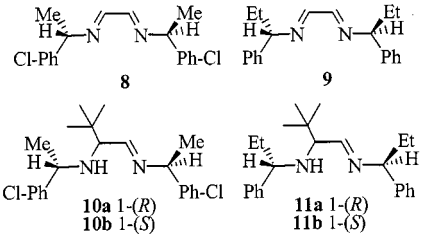
Table 2. Synthesis of disubstituted unsymmetrical 1,2-diamines by dynamic kinetic resolution

entry	RMgX	diamine	yield [%]	*dr*[a]
1	PhMgCl	**6a**	89	>95:5
2	cHexMgCl	**6b**	80	>95:5
3	EtMgBr	**6c**	88	92:8
4	AllylMgBr	**6d**	77	91:9

[a] The ratios were measured by ^{1}H NMR (400 MHz) of the crude reaction mixture.

performed in refluxing methanol and acidic conditions (acetic acid) with ammonium formate and palladium hydroxide. The free diamines **7a** and **7b** were obtained in 72 and 65% yield, respectively, by this procedure.

We were also interested in the preparation of the enantiopure mono-*tert*-butyl diamines **12**, **13** and **14** (Scheme 6), by reduction of the intermediate imines. For this purpose, we studied the effect of the temperature and the chiral auxiliary on the diastereoselectivity of the monoaddition. Evidence of a temperature-dependent equilibrium between **4a** and **4b** was first demonstrated by running the additions in THF (where only the monoadduct could be obtained) at higher temperatures. We observed that this equilibrium was displaced towards the major intermediate **4a** when the temperature was higher. The diastereomeric ratio changed from 78:22 (Table 3, entry 1) at 20 °C to 89:11 (entry 2) at 50 °C.



Scheme 6

Table 3. Influence of the temperature and chiral auxiliary on the monoaddition

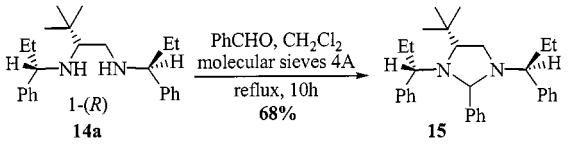
entry	bisimine	solvent	*T* [°C]	ratio
1	**1**	THF	20	78:22 (**5a**:**5b**)
2	**1**	THF	50	89:11 (**5a**:**5b**)
3	**8**	THF	20	88:12 (**10a**:**10b**)
4	**9**	THF	20	90:10 (**11a**:**11b**)
5	**9**	Et_2O	20	88:12 (**11a**:**11b**)
6	**9**	hexane	20	80:20 (**11a**:**11b**)
7	**9**	THF	50[a]	96:4 (**11a**:**11b**)

[a] Addition and quenching have been performed at the same temperature.

To study the effect of the chiral auxiliary upon the diastereoselectivity of the monoaddition, we also synthesized the bisimines **8** and **9** derived from (*S*)-1-(*p*-chlorophenyl)ethylamine and (*S*)-1-phenylpropylamine (Scheme 6). The first experiments were run at 20 °C and showed that the two bisimines **8** and **9** (Table 3, entries 3, 4) gave better diastereomeric ratios (88:12 and 90:10) than the bisimine **1** (entry 1). A study of the solvent effect using **9** demonstrated that polar solvents such as THF or Et_2O gave a better *dr* (entries 4, 5 and 6). Finally, the best result was obtained for **11** (*dr* 96:4) by performing the addition on the bisimine **9**, at 50 °C in THF (entry 7).

The reduction of imines **5**, **10** and **11** by sodium borohydride in ethanol afforded the corresponding crude amines in 75–95% yield (Scheme 7). However, a partial epimerization was sometimes detected in this reduction step (Table 4).

Separation by chromatography over silica gel gave each diastereomer of amines **12**, **13** and **14** in high purity. Finally, the diamine **14a** was easily obtained in an optically pure form in 85% yield from the bisimine **9**, in a two step procedure under the best conditions described above followed by separation of the minor isomer.

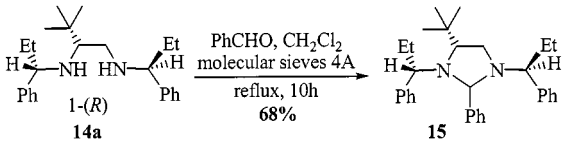


Scheme 7

Table 4. Reduction of the intermediate imines with $NaBH_4$

Imine	*de* [%]	diamine	Yield [%]	*de* [%]
5	48	**12**	84	46
10	64	**13**	77	60
11	80	**14**	95	72
11	92	**14**	89	90

Determination of the absolute configuration of the major diastereomers was achieved with diamine **14a**. Formation of the corresponding aminal **15** by refluxing **14a** with benzaldehyde in CH_2Cl_2 afforded a white solid, in 68% yield, which was recrystallized from pentane (Scheme 8). The ORTEP diagram of **15** (Figure 1) confirmed the (*R*) configuration on the carbon bearing the *tert*-butyl, as previously predicted for **5a**.



Scheme 8

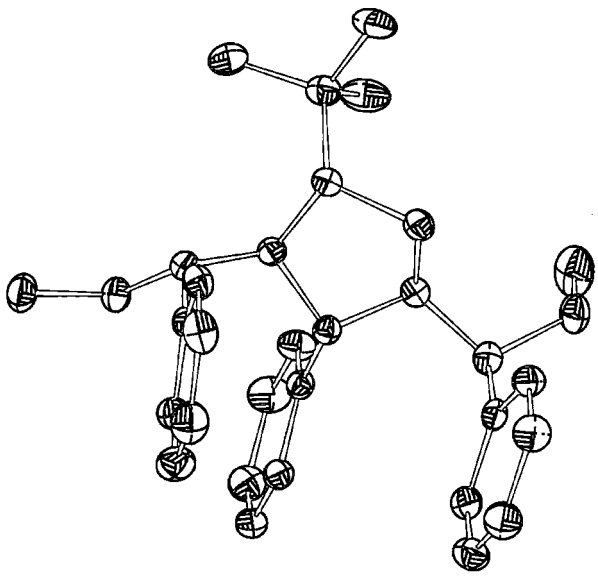


Figure 1. ORTEP diagram of **15**

Conclusion

Evidence of a dynamic kinetic resolution giving diastereomerically pure diamine **2** during the bis-addition of *tert*-butylmagnesium chloride to the chiral bisimine **1** was demonstrated. We showed from this study the existence of a temperature-dependent equilibrium between the two chelated intermediates **4a** and **4b**. The diastereoselectivity of the monoaddition was increased by using the bisimine **9** and was shown to be higher in polar solvents and at higher temperatures. Several new unsymmetrical 1-*tert*-butyl-1,2-diamines were obtained in an optically pure form by reduction of the intermediate imines followed by chromatographic separation. This resolution has also been applied to the highly diastereoselective synthesis of new unsymmetrically disubstituted 1,2-diamines.

Experimental Section

General Remarks: Experiments involving organometallics were carried out in dried glassware under a positive pressure of dry N_2 or Ar. – THF was distilled from sodium-benzophenone ketyl. – *tert*-Butylmagnesium chloride (2 M in Et_2O), phenylmagnesium chloride (2 M in THF) and sodium borohydride (powder, 98%) were purchased from Aldrich. – *c*Hexylmagnesium chloride (1.43 M in Et_2O) and allylmagnesium bromide (1.77 M in Et_2O) were prepared from the corresponding halide. – *n*-Hexane, dichloromethane and absolute ethanol were used in analytical grade. – Optical purity of the chiral amines: (*S*)-1-ethylphenylamine, *ee* = 99.3%; (*S*)-1-(*p*-chlorophenyl)ethylamine, *ee* = 99.5%; (*S*)-1-phenylpropylamine, *ee* = 99.4%. – Column chromatography: Merck silica gel 60, 0.040–0.063 mm. – NMR spectra were recorded on a Bruker ARX 400 or AC 200 Q instrument, with $CDCl_3$ as solvent. – Optical rotations were measured on a Perkin–Elmer 141.

Typical Procedure for the Synthesis of Bisimines: To a solution of amine (2 mmol) in CH_2Cl_2 (5 mL) were added at 0 °C a 40% aqueous solution of glyoxal (145 mg, 1 mmol), anhydrous magnesium sulfate (0.5 g) and formic acid (5 μL). The mixture was stirred for 30 min at 20 °C. The suspension was filtered and concentrated under vacuum at 20 °C to give the crude bisimines which were subsequently stored at –20 °C.

***N,N'*-Bis[(*S*)-1-ethylphenyl]ethanediimine (1):** 1.97 g (96%) of an orange oil were obtained from 16 mmol of (α)-(*S*)-benzylmethylamine – $C_{18}H_{20}N_2$ (264.37). – ^{1}H NMR: δ = 1.60 (d, *J* = 6.7 Hz, 6 H), 4.53 (q, *J* = 6.7 Hz, 2 H), 7.24–7.38 (m, 10 H), 8.07 (s, 2 H).
***N,N'*-Bis[(*S*)-1-(*p*-chlorophenyl)ethyl]ethanediimine (8):** 3.19 g (95%) of a pale yellow solid were obtained from 20 mmol of (α)-(*S*)-1-(*p*-chlorophenyl)propylamine. – $C_{18}H_{18}Cl_2N_2$ (333.3). – ^{1}H NMR: δ = 1.56 (d, *J* = 6.7 Hz, 6 H), 4.50 (q, *J* = 6.7 Hz, 2 H), 7.28–7.33 (m, 8 H), 8.05 (s, 2 H). – ^{13}C NMR: δ = 24.5, 69.4, 128.4, 129.1, 133.4, 142.5, 161.2.

***N,N'*-Bis[(*S*)-1-phenylpropyl]ethanediimine(9):** 2.88 g (99%) of a pale yellow oil were obtained from 20 mmol of (α)-(*S*)-phenylpropylamine. – $C_{20}H_{24}N_2$ (292.46). – ^{1}H NMR: δ = 0.89 (t, *J* = 7.2 Hz, 6 H), 1.97 (m, 4 H), 4.14 (t, *J* = 7.1 Hz, 2 H), 7.25–7.34

(m, 10 H), 8.05 (s, 2 H) – ^{13}C NMR: δ = 11.4, 31.3, 127.5, 127.6, 128.9, 143.3, 161.4.

Typical Procedure for the Monoaddition of *tert*-Butylmagnesium Chloride: To a solution of bisimine (1 mmol) in 15 mL of solvent was added dropwise, 0.6 mL (1.2 equiv.) of a solution of *tert*-butylmagnesium chloride (2 M in ether). The mixture was stirred for 15 min. at the appropriate temperature, quenched with satd. NH_4Cl (5 mL) and stirred for 15 min. The aqueous layer was separated and extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford quantitatively the crude imines.

1-Amino-1-*tert*-butyl-*N,N'*-bis[(*S*)-1-ethylphenyl]-2-iminoethane (5): A mixture of diastereomers, not separable (pale yellow oil). – ^{1}H NMR: **(5a)** δ = 1.00 (s, 9 H), 1.33 (d, *J* = 6.6 Hz, 3 H), 1.54 (d, *J* = 6.6 Hz, 3 H), 2.90 (d, *J* = 5.6 Hz, 1 H), 3.70 (q, *J* = 6.6 Hz, 1 H), 4.33 (q, *J* = 6.6 Hz, 1 H), 7.2–7.4 (m, 10 H), 7.63 (d, *J* = 5.6 Hz, 1 H). – **(5b)** δ = 0.92 (s, 9 H), 1.37 (d, *J* = 6.6 Hz, 3 H), 1.58 (d, *J* = 6.6 Hz, 3 H), 2.70 (d, *J* = 5.1 Hz, 1 H), 3.70 (q, *J* = 6.6 Hz, 1 H), 4.47 (q, *J* = 6.6 Hz, 1 H), 7.20–7.40 (m, 10 H), 7.79 (d, *J* = 5.1 Hz, 1 H).

1-Amino-1-*tert*-butyl-*N,N'*-bis[(*S*)-1-(*p*-chlorophenyl)ethyl]-2-iminoethane (10): A mixture of diastereomers, not separable (pale yellow oil). – ^{1}H NMR: **(10a)** δ = 0.93 (s, 9 H), 1.25 (d, *J* = 6.5 Hz, 3 H), 1.41 (d, *J* = 6.6 Hz, 3 H), 1.92 (s, 1 H), 2.83 (d, *J* = 5.5 Hz, 1 H), 3.58 (q, *J* = 6.5 Hz, 1 H), 4.17 (q, *J* = 6.6 Hz, 1 H), 7.20–7.40 (m, 10 H), 7.52 (d, *J* = 5.5 Hz, 1 H). – **(10b)** δ = 0.84 (s, 9 H), 1.26 (d, *J* = 6.5 Hz, 3 H), 1.48 (d, *J* = 6.5 Hz, 3 H), 1.92 (s, 1 H), 2.56 (d, *J* = 5.0 Hz, 1 H), 3.58 (q, *J* = 6.5 Hz, 1 H), 4.37 (q, *J* = 6.5 Hz, 1 H), 7.05–7.30 (m, 10 H), 7.72 (d, *J* = 5 Hz, 1 H).

1-Amino-1-*tert*-butyl-*N,N'*-bis[(*S*)-1-phenylpropyl]-2-iminoethane (11): A mixture of diastereomers, not separable (pale yellow oil). – ^{1}H NMR: **(11a)** δ = 0.72 (t, *J* = 7.3 Hz, 3 H), 0.86 (t, *J* = 7.3 Hz, 3 H), 0.98 (s, 9 H), 1.50–2.00 (m, 4 H), 2.94 (d, *J* = 5.7 Hz, 1 H), 3.35 (dd, *J* = 8.1 and 5.2 Hz, 1 H), 3.90 (dd, *J* = 7.7 and 5.8 Hz, 1 H), 7.00–7.40 (m, 10 H), 7.55 (d, *J* = 5.7 Hz, 1 H). – **(11b)** δ = 0.79 (t, *J* = 7.4 Hz, 3 H), 0.86 (t, *J* = 7.4 Hz, 3 H), 0.87 (s, 9 H), 1.50–2.00 (m, 4 H), 2.68 (d, *J* = 5 Hz, 1 H), 3.45 (dd, *J* = 7.6 and 6 Hz, 1 H), 4.10 (dd, *J* = 8 and 5.6 Hz, 1 H), 7.02–7.30 (m, 10 H), 7.70 (d, *J* = 5 Hz, 1 H).

Typical Procedure for the Synthesis of Diamines: To a solution of bisimine **1** (1 mmol) in THF (15 mL) was added dropwise a solution of *tert*-butylmagnesium chloride (0.75 mL, 1.5 equiv., 2 M in ether). The mixture was stirred for 10 min. at 25 °C and the second Grignard reagent (1.5 equiv.) was then added dropwise. The mixture was stirred for 1 h at 25 °C and 2 h at 45 °C, quenched with satd. NH_4Cl (8 mL) and stirred vigorously for 15 min. The aqueous layer was separated and extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford the crude diamines.

(*R*,*R*)-1-*tert*-Butyl-1,2-bis{[(*S*)-1-ethylphenyl]amino}-2-phenylethane (6a): Purification by chromatography on silica gel (cHex/Et_2O, 95:5) gave 355 mg (89%), as a colorless oil. – $[\alpha]_D^{20}$ = –171 (*c* = 0.8, CH_2Cl_2). – ^{1}H NMR: δ = 0.85 (s, 9 H), 1.25 (d, *J* = 6.6 Hz, 3 H), 1.35 (d, *J* = 6.6 Hz, 3 H), 2.50 (d, *J* = 4 Hz, 1 H), 3.40 (m, 2 H), 3.60 (q, *J* = 6.6 Hz, 1 H), 6.92 (dd, *J* = 8 and 2 Hz, 2 H), 7.22–7.45 (m, 13 H). – ^{13}C NMR: δ = 24.0, 25.2, 28.3, 37.0, 54.8, 59.1, 59.4, 68.4, 69.3, 127.6, 127.7, 128.4, 128.6, 128.7, 145.8, 146.5, 147.6. – $C_{28}H_{36}N_2$ (400.60): calcd. C 83.95, H 9.06, N 6.99; found C 83.98, H 9.17, N 6.90.

(*R*,*R*)-1-*tert*-Butyl-1,2-bis{[(*S*)-1-ethylphenyl]amino}-2-cyclohexylethane (6b): Purification by chromatography on silica gel (cHex/Et_2O, 95:5) led to 320 mg (80%), as a colorless oil. . – $[\alpha]_D^{20}$ = +4 (*c* = 0.8, CH_2Cl_2). – ^{1}H NMR: δ = 0.76 (s, 9 H), 1.03–1.80 (m, 10 H), 1.29 (d, *J* = 6.6 Hz, 3 H), 1.34 (d, *J* = 6.6 Hz, 3 H), 2.03 (d, *J* = 4 Hz, 1 H), 2.27 (dd, *J* = 4 and 3 Hz, 1 H), 3.66 (q, *J* = 6.6 Hz, 1 H), 3.77 (q, *J* = 6.6 Hz, 1 H), 7.20–7.50 (m, 10 H). – ^{13}C NMR: δ = 23.9, 24.6, 27.1, 27.4, 27.5, 27.6, 32.5, 36.6, 45.6, 57.6, 58.9, 59.0, 65.5, 127.0, 127.5, 127.7, 128.5, 132.8, 146.9, 147.9. – $C_{28}H_{48}N_2$ (406.65): calcd. C 82.70, H 10.41, N 6.89; found C 82.74, H 10.52, N 6.64.

(*R*,*R*)-1-*tert*-Butyl-1,2-bis{[(*S*)-1-ethylphenyl]amino}-2-ethylethane (6c): Purification by chromatography on silica gel (cHex/Et_2O, 95:5) gave 310 mg (88%), as a pale yellow oil. . – $[\alpha]_D^{20}$ –53 = (*c* = 1.7, CH_2Cl_2). – ^{1}H NMR: δ = 0.46 (t, 3 H, *J* = 7.4 Hz), 0.80 (s, 9 H), 1.32 (d+d+m, 8 H, *J* = 6.6 Hz), 1.60 (m, 2 H), 2.06 (d, 1 H, *J* = 2 Hz), 2.16 (dt, 1 H, *J* = 2 and 6.3 Hz), 3.80 (t+t, 2 H, *J* = 6.6 Hz), 7.20–7.40 (m, 10 H). – ^{13}C NMR: δ = 10.9, 24.2, 25.1, 25.9, 28.0, 36.6, 55.2, 59.4, 64.5, 127.1, 127.7, 128.4, 128.5, 146.0, 147.7. – $C_{24}H_{36}N_2$ (352.56): calcd. C 81.76, H 10.29, N 7.95; found C 81.83, H 10.43, N 7.69.

(*R*,*R*)-2-Allyl-1-*tert*-butyl-1,2-bis{[(*S*)-1-ethylphenyl]amino}ethane (6d): Purification by chromatography on silica gel (cHex/Et_2O, 95:5) gave 280 mg (77%), as a pale yellow oil. . – $[\alpha]_D^{20}$ –55 = (*c* = 2, CH_2Cl_2). – ^{1}H NMR: δ = 0.76 (s, 9 H), 1.34 (d + d + m, *J* = 6.6 Hz, 7 H), 1.47 (m, 1 H), 1.62 (m, 1 H), 1.82 (m, 1 H), 2.05 (m, 2 H), 2.30 (m, 1 H), 3.78 (q, *J* = 6.6 Hz, 1 H), 3.84 (q, *J* = 6.6 Hz, 1 H), 4.44 (d, *J* = 17 Hz, 1 H), 4.77 (d, *J* = 10 Hz, 1 H), 5.29 (m, 1 H), 7.20–7.40 (m, 10 H). – ^{13}C NMR: δ = 24.5, 25.0, 27.7, 36.6, 37.7, 53.0, 54.8, 59.3, 64.5, 116.5, 127.0, 127.6, 127.7, 128.2, 128.4, 136.9, 145.8, 147.8. – $C_{25}H_{36}N_2$ (364.57): calcd. C 82.36, H 9.95, N 7.68; found C 82.37, H 10.17, N 7.22.

Typical Procedure for the Hydrogenolysis: To a solution of diamine (1 mmol) in methanol (10 mL) were added 230 μL (4 equiv.) of acetic acid, 378 mg (6 equiv.) of ammonium formate and 100 mg (10% mol) of $Pd(OH)_2$-C (20% wt.). The mixture was refluxed for 6 h with vigorous stirring, filtered and concentrated. The residue was stirred vigorously for 15 min. in a mixture of ether (30 mL) and saturated aqueous K_2CO_3 (10 mL). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated to give the crude free diamine.

(*R*,*R*)-1,2-Diamino-1-*tert*-butyl-2-phenylethane (7a): 600 mg were obtained from 1.54 g of **6a**. Purification by chromatography on silica gel (Et_2O, then Et_2O/EtOH, 7:3) gave 533 mg (72%) of **7a** as a colorless oil. – $[\alpha]_D^{20}$ = –16 (*c* = 2.5, CH_2Cl_2). – ^{1}H NMR: δ = 1.04 (s, 9 H), 1.70 (s, 4 H), 2.57 (d, *J* = 2 Hz, 1 H), 4.24 (d, *J* = 2 Hz, 1 H), 7.20–7.40 (m, 5 H). – ^{13}C NMR: δ = 27.6, 35.2, 55.4, 65.2, 126.4, 126.7, 128.3, 128.5, 147.5. – $C_{12}H_{20}N_2$ (192.30): calcd. C 74.95, H 10.48, N 14.57; found C 75.02, H 10.55, N 14.42.

(*R*,*R*)-1,2-Diamino-1-*tert*-butyl-2-cyclohexylethane (7b): 372 mg were obtained from 1 g of **6b**. Purification by chromatography on silica gel (Et_2O, then Et_2O/EtOH, 7:3) gave 320 mg (65%) of **7b** as a colorless oil. – $[\alpha]_D^{20}$ = +12 (*c* = 2.8, CH_2Cl_2). – ^{1}H NMR: δ = 0.91 (s, 9 H), 1.21–1.90 (m, 11 H), 2.42 (d, *J* = 1 Hz, 1 H), 2.64 (dd, *J* = 6.5 and 1 Hz, 1 H). – ^{13}C NMR: δ = 26.5, 26.6, 26.9, 29.2, 30.3, 35.1, 44.3, 54.5, 59.5. – $C_{12}H_{26}N_2$ (198.35): calcd. C 72.66, H 13.21, N 14.12; found C 72.70, H 13.29, N 13.97.

Typical Procedure for the Reduction of Imines: To a solution of imine (1 mmol) in EtOH (10 mL) was added slowly at 0 °C sodium borohydride (115 mg, 3 mmol). The mixture was stirred for 4 h at 20 °C then neutralized by slow addition of NH_4Cl (0.5 g). The suspension was stirred for 10 h, filtered through celite and concentrated. The residue was diluted with Et_2O (30 mL) and satd. NaOH (10 mL) was added. The mixture was stirred vigorously for 3 h. The aqueous layer was separated and extracted with ether. The combined organic layers were washed with water, dried over $MgSO_4$, filtered and concentrated to give the crude diamines in 75–95%

yield. Purification by flash-chromatography on silica gel (cHex to cHex/Et_2O, 7:3) allowed the separation of the two diastereomers.

1-*tert*-Butyl-1,2-bis{[(*S*)-1-ethylphenyl]amino}ethane (12): Obtained from the imine **5**. – **(12a)** (pale yellow oil). – $[\alpha]_D^{20} = -58$ (c = 2.5, CH_2Cl_2). – ^{1}H NMR: δ = 0.91 (s, 9 H), 1.06 (d, J = 6.6 Hz, 3 H), 1.40 (d, J = 6.6 Hz, 3 H), 2.07 (dd, J = 11.6 and 8.7 Hz, 1 H), 2.27 (dd, J = 8.7 and 2.7 Hz, 1 H), 2.43 (dd, J = 11.6 and 2.7 Hz, 1 H), 3.35 (q, J = 6.6 Hz, 1 H), 3.84 (q, J = 6.6 Hz, 1 H), 7.20–7.40 (m, 10 H). – ^{13}C NMR: δ = 24.2, 24.5, 27.3, 35.4, 49.0, 58.0, 64.2, 126.5, 126.8, 127.1, 128.1, 128.4, 146.0, 147.0. – $C_{22}H_{32}N_2$ (324.503): calcd. C 81.43, H 9.94, N 8.63; found C 81.08, H 10.5, N 8.05. – **(12b)** (pale yellow oil). – $[\alpha]_D^{20} = -83$ (c = 2.4, CH_2Cl_2). – ^{1}H NMR: δ = 0.85 (s, 9 H), 1.34 (d, J = 6.6 Hz, 3 H), 1.37 (d, J = 6.6 Hz, 3 H), 2.10 (dd, J = 5.4 and 4.1 Hz, 1 H), 2.46 (dd, J = 11.9 and 5.4 Hz, 1 H), 2.62 (dd, J = 11.9 and 4.1 Hz, 1 H), 3.72 (q, J = 6.6 Hz, 1 H), 3.77 (q, J = 6.6 Hz, 1 H), 7.24–7.40 (m, 10 H). – ^{13}C NMR: δ = 24.6, 25.0, 27.5, 34.7, 48.2, 56.3, 58.9, 63.2, 126.7, 126.9, 128.1, 128.2, 146.4. – $C_{22}H_{32}N_2$ (324.503): calcd. C 81.43, H 9.94, N 8.63; found C 81.45, H 10.16, N 8.08.

1-*tert*-Butyl-1,2-bis{[(*S*)-1-(*p*-chlorophenyl)ethyl]amino}ethane (13): Obtained from the imine **10**. – **(13a)** (pale yellow oil). – $[\alpha]_D^{20} = -61$ (c = 2.7, CH_2Cl_2). – ^{1}H NMR: δ = 0.87 (s, 9 H), 1.02 (d, J = 6.5 Hz, 3 H), 1.31 (d, J = 6.6 Hz, 3 H), 1.97 (dd, J = 11.2 and 8.7 Hz, 1 H), 2.15 (dd, J = 8.7 and 2.5 Hz, 1 H), 2.35 (dd, J = 11.2 and 2.5 Hz, 1 H), 3.30 (q, J = 6.5 Hz, 1 H), 3.75 (q, J = 6.6 Hz, 1 H), 7.00–7.30 (m, 8 H). – ^{13}C NMR: δ = 24.2, 24.4, 26.9, 35.4, 49.1, 57.8, 58.4, 64.5, 127.9, 128.4, 128.5, 132.1, 132.4, 144.6, 145.5. – $C_{22}H_{30}Cl_2N_2$ (393.392): calcd. C 67.17, H 7.69, N 7.12; found C 67.03, H 7.35, N 6.85. – **(13b)** (pale yellow oil). – $[\alpha]_D^{20} = -93$ (c = 3.4, CH_2Cl_2). – ^{1}H NMR: δ = 0.80 (s, 9 H); 1.27 (d, J = 6.5 Hz, 3 H), 1.30 (d, J = 6.5 Hz, 3 H), 2.00 (dd, J = 5.3 and 4.2 Hz, 1 H), 2.40 (dd, J = 12 and 5.3 Hz, 1 H), 2.54 (dd, J = 12 and 4.2 Hz, 1 H), 3.65 (q, J = 6.5 Hz, 1 H), 3.70 (q, J = 6.5 Hz, 1 H), 7.11–7.30 (m, 8 H). – ^{13}C NMR: δ = 24.7, 25.0, 26.9, 34.7, 48.2, 54.4, 55.8, 58.3, 63.2, 128, 128.3, 132.2, 144.8. – $C_{22}H_{30}Cl_2N_2$ (393.392): calcd. C 67.17, H 7.69, N 7.12; found C 67.28, H 7.62, N 6.49.

1-*tert*-Butyl-1,2-bis{[(*S*)-1-phenylpropyl]amino}ethane (14): Obtained from the imine **11**. – **(14a)** (pale yellow oil). – $[\alpha]_D^{20} = -51$ (c = 2.3, CH_2Cl_2). – ^{1}H NMR: δ = 0.60 (t, J = 7.5 Hz, 3 H), 0.80 (t, J = 7.4 Hz, 3 H), 0.88 (s, 9 H), 1.10 (s, 1 H), 1.35 (m, 3 H), 1.66 (m, 1 H), 1.80 (m, 1 H), 2.07 (dd, J = 11.7 and 8.3 Hz, 1 H), 2.25 (dd, J = 8.3 and 2.8 Hz, 1 H), 2.3 (dd, J = 11.7 and 2.8 Hz, 1 H), 3.03 (dd, J = 7.6 and 5.8 Hz, 1 H), 3.54 (dd, J = 8.2 and 6 Hz, 1 H), 7.13–7.32 (m, 10 H). – ^{13}C NMR: δ = 11.0, 11.8, 27.3, 27.8, 31.5, 36.0, 49.3, 64.3, 65.3, 66.1, 126.9, 127.9, 128.2, 128.4, 128.6, 144.8, 146.1. – $C_{24}H_{36}N_2$ (352.556): calcd. C 81.76, H 10.29, N 7.95; found C 81.44, H 10.27, N 7.87. – **(14b)** (pale yellow oil). – $[\alpha]_D^{20} = -90$ (c = 3.1, CH_2Cl_2). – ^{1}H NMR: δ = 0.73 (t, J = 7.4 Hz, 3 H), 0.86 (s, 9 H), 0.88 (t, J = 7.4 Hz, 3 H), 1.35 (s, 1 H), 1.50–1.80 (m, 5 H), 2.00 (dd, J = 4.7 and 2 Hz, 1 H), 2.40 (dd, J = 11.9 and 4.7 Hz, 1 H), 2.62 (dd, J = 11.9 and 2 Hz), 3.40 (m, 2 H), 7.20–7.40 (m, 10 H). – ^{13}C NMR: δ = 11.3, 27.3, 28.0, 31.6, 32.0, 35.1, 48.5, 63.3, 66.2, 127.1, 127.8, 128.2, 128.4, 128.5, 145.0, 145.4. – $C_{24}H_{36}N_2$ (352.556): calcd. C 81.76, H 10.29, N 7.95; found C 81.52, H 10.26, N 7.86.

Aminal 15: To a solution of diamine **14a** (168 mg, 0.5 mmol) in CH_2Cl_2 (1 mL), were added 55 μL of benzaldehyde and molecular sieves 4Å. The mixture was refluxed for 10 h, filtered and concentrated to give 221 mg of crude aminal **15**. Purification by silica gel chromatography (cHex/Et_2O, 95:5) afforded 150 mg (68%) of the aminal as a colorless oil that crystallized within a few hours. Colorless crystals suitable for an X-ray diffraction study were obtained by recrystallization from pentane. – $[\alpha]_D^{20} = +7.8$ (c = 2.6, CH_2Cl_2). – ^{1}H NMR: δ = 0.43 (t, J = 7.2 Hz, 3 H), 0.53 (t, J = 7.2 Hz, 3 H), 0.97 (s, 9 H), 1.19–1.40 (m, 3 H), 1.60 (m, 1 H), 1.85 (t, J = 8.4 Hz, 1 H), 2.68 (dd, J = 9.2 and 2 Hz, 1 H), 2.75 (dd, J = 8 and 2 Hz, 1 H), 2.90 (t, J = 7.6 Hz, 1 H), 3.63 (dd, J = 9.2 and 6.4 Hz, 1 H), 4.10 (s, 1 H), 6.86–7.62 (m, 15 H). – ^{13}C NMR: δ = 10.4, 11.0, 25, 25.9, 26.7, 35.0, 44.9, 60.5, 67.0, 67.7, 78.2, 126.3, 126.5, 127.9, 128.3, 129, 132.1, 137.2, 138.6, 143.9. – $C_{31}H_{40}N_2$ (440.66): calcd. C 84.49, H 9.15, N 6.36; found C 84.57, H 9.11, N 6.23.

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[11] All the diastereomeric ratios in this study were determined by ^{1}H NMR spectroscopy of the crude reaction mixtures as the two diastereomers of the imines **5**, **10** and **11** were not separable by chromatography on silica gel.

[12] Crystallographic data (excluding structure factors) for the structure of **15** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-117666. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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