A Practical and Efficient Synthesis of Enantiomerically Pure Di-*tert*-butylethanediamine

Sylvain Roland,* Pierre Mangeney, Alex Alexakis

Laboratoire de Chimie des Organo-Eléments, tr 44–45, 2 ème ét., Université P. et M. Curie, 4, Place Jussieu, 75252 Paris Cedex 05, France
Fax +33(1)44277567; E-mail: sroland@ccr.jussieu.fr
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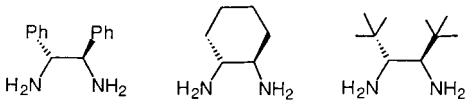
Abstract: A diastereoselective synthesis of 1,2-diamino-1,2-di-*tert*-butylethane has been developed by addition of *tert*-butyl magnesium chloride to a chiral bis-imine derived from glyoxal and (*S*)-methylbenzylamine. Addition of the bis-imine to the Grignard reagent in hexane at 50 °C gave only one diastereomer detectable by ^{1}H and ^{13}C NMR. Hydrogenolysis of the phenylethyl groups led to the expected free diamine **3** in good yields. The absolute configuration (*R,R*) of the carbons bearing the *tert*-butyl groups has been confirmed by X-ray spectroscopy.

Key words: chiral 1,2-diimine, diastereoselective addition, Grignard reagent, hydrogenolysis, ligand precursor

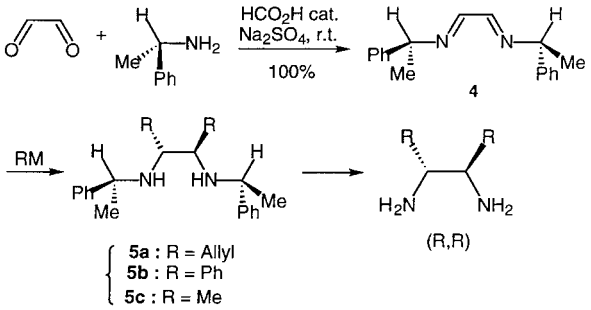
In recent years, numerous applications have been developed in asymmetric synthesis using vicinal diamines as the source of chirality. One of their major interest lies in their use as precursors for the synthesis of a broad family of bidentate ligands.[1] Many reactions have also been described using these diamines as chiral auxilaries and protecting groups of aldehydes.[2]

Most of these applications generally use the framework of diphenyldiaminoethane (**1**) or diaminocyclohexane (**2**) whose preparations were fully described.[3] However, in several of our projects, we were in need of new 1,2 diamines. We were particularly interested in obtaining 1,2-diamino-1,2-di-*tert*-butylethane (**3**) because of its increased steric bulk and absence of benzylic protons.



1 **2** **3**

Syntheses of enantiomerically pure diamines have been mainly developed through resolution of racemic diamines. Nevertheless, asymmetric synthesis of vicinal diamines is an attractive alternative solution, and few methods have been thus far reported. The addition of Grignard or zinc reagents to the carbon–nitrogen double bonds of the chiral 1,2-bis-imine precursor **4**[4,6] derived from glyoxal and (*S*)- [or (*R*)]-methylbenzylamine, followed by removal of the phenylethyl group, has been shown to be an attractive method for the preparation of these compounds (Scheme 1). The first example was described by Neumann et al.[5] who showed that addition of allylmagnesium chloride gave a 6:1 mixture of two diastereomers. A few years later, Savoia and co-workers[6] improved this reaction by using allylzinc bromide and obtained 93.5% of the major diastereomer **5a**, characterized by X-ray crystallography. Addition of phenylmagnesium chloride and methylmagnesium bromide was also studied by Simpkins and co-workers.[7] These reagents gave a mixture of diastereomers from which **5b** and **5c** were respectively isolated in 47% and 35% yield.

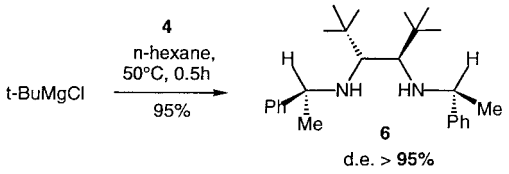


Scheme 1

We were attracted by the use of this procedure to develop a diastereoselective synthesis of 1,2-diamino-1,2-di-*tert*-butylethane (**3**) by addition of *tert*-butylmagnesium chloride to the chiral 1,2-bis-imine **4**. To our knowledge, only one method was described in the literature for the synthesis of **3**,[8] by coupling of nitriles or *N*-(trimethylsilyl)imines promoted by $NbCl_4$(THF). In this procedure the diamine was isolated as a 1.3:1 mixture of the (d,l:meso) diastereoisomers and the (+)-diamine was obtained pure in 18% yield by resolution with (–)-mandelic acid.[9]

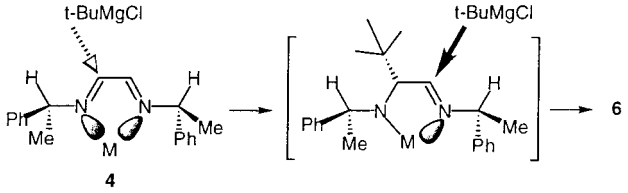
Our initial attempts to study the reactivity of *tert*-butylmagnesium chloride towards the bis-imine showed that the first *tert*-butyl group added easily at low temperature (–70 °C) whereas a temperature above +45 °C was necessary for the second addition. This high temperature seemed at first sight to be incompatible with obtaining the expected pure diamine **6**. Indeed, dropwise addition at –70 °C of *tert*-butylmagnesium chloride to the bis-imine, followed by heating to +45 °C, generally led to a mixture of compounds in which the major isomer **6** could be detected by ^{1}H NMR. Unfortunately, isolation of this latter compound by chromatography on silica gel was not efficient. Our best result was obtained by carrying out the addition in hexane where about 50% of this major diastereomer was formed.[10] We stipulated then that reverse addition of the bisimine to the Grignard reagent at a temperature above 45 °C could increase the rate of the second addition and avoid the formation of by-products which probably arose from the degradation of the interme-

diate imine. Indeed, addition of the chiral (*S*,*S*)-1,2-bis-imine **4** to a suspension of *tert*-butylmagnesium chloride in hexane at 50°C, led very cleanly in 0.5 h to a single diastereomer **6** with no other compound detectable by ^{1}H and ^{13}C NMR.



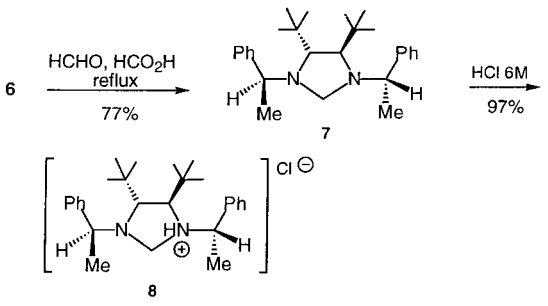
Scheme 2

In these additions, it was postulated that the metal generates a rigid five-membered chelate with the two nitrogen atoms, providing an activation of the imine double bonds as well as an improvement of the stereocontrol. According to the results obtained in additions of the allyl or phenyl group,[6,7] the more stable conformation of this complex was stipulated to be the one where the C–H benzylic bond and the C=N bond are coplanar (Scheme 3). Following this model, the stereoisomer **6** was effectively the expected one. Indeed, due to steric bulk, the first addition is directed on the least hindered methyl side. The second addition is then controlled both by the first *t*-butyl group added and the chiral auxiliary.



Scheme 3

The diamine **6** was obtained as an oil and all our attempts to get crystals for X-ray spectroscopy failed. Nevertheless, with the intention of carrying out the methylation of **6** by the Eischweiler-Clarke procedure, we obtained the aminal **7** as a white solid in 77% isolated yield. The monohydrochloride **8**, obtained by treatment of **7** with hydrochloric acid, was then recrystallized twice in ethyl acetate to give colourless crystals suitable for the analysis (Scheme 4). The ORTEP diagram of **8** is shown in the Figure, and clearly confirms the expected (*R*,*R*) absolute configuration of the carbons bearing the *t*-butyl groups.



Scheme 4

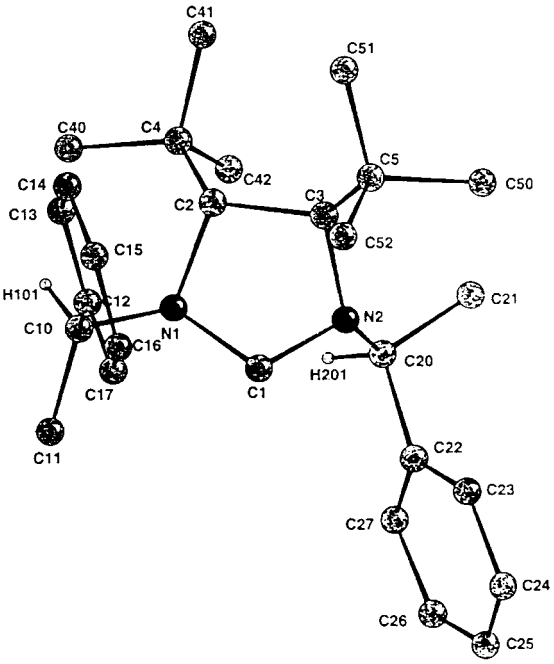
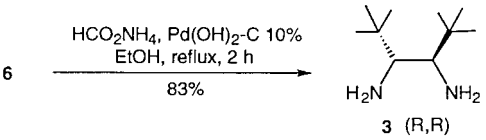


Figure ORTEP diagram of compound **8**

Deprotection of the chiral auxilary groups was performed from the crude diamine **6**, using ammonium formate[11] and palladium hydroxide in refluxing ethanol. This reaction gave the free diamine **3** in 2 h (Scheme 5).



Scheme 5

In conclusion, we developed an efficient synthesis of 1,2-diamino-1,2-di-*tert*-butylethane from glyoxal and (*S*)-methylbenzylamine. This diamine was obtained optically pure in three steps with short reaction times, no intermediate purification and 75% overall yield. We believe that the easy availability of diamine **3** will render it as attractive as **1** and **2** for testing a new carbon framework. Synthetic applications using this diamine are under investigation.

Experiments involving organometallics were carried out under a positive pressure of dry N_2 or under Ar. (*S*)-(–)-α-methylbenzylamine (98%) was purchased from Aldrich. *tert*-Butylmagnesium chloride 2M in Et_2O was purchased from Aldrich. Palladium hydroxide 20% on activated charcoal was purchased from Fluka. Hexane was of analytical grade type and used without special drying or distillation. NMR spectra were recorded on a Brucker ARX 400 or AC 200 Q instrument, in $CDCl_3$ as the solvent. Optical rotations were measured on a Perkin-Elmer 141.

***N*,*N*′-Bis[(*S*)-1-phenylethyl]ethanediimine (4)**

The previously reported procedures starting from 40% aq glyoxal[4] or glyoxal trimer[6] can be followed; However, we wish to present a faster modified procedure:

A mixture of 40% aq glyoxal (1.13 mL, 7.8 mmol), (α)-(*S*)-methylbenzylamine (2.06 mL, 16 mmol), formic acid (50 μL) and anhyd $MgSO_4$ (4 g) in CH_2Cl_2 (15 mL), was stirred for 15 min. at 25 °C. The suspension was filtered over Celite. The filtrate was concentrated and the residue dissolved in cyclohexane (15 mL), dried (Na_2SO_4), filtered and concentrated to give 1.97 g (96 %) of **4** as an orange oil. (store at –20 °C).

$C_{18}H_{20}N_2$ (M = 264.37).

^{1}H NMR: δ = 1.6 (d, 6H, *J* = 6.7 Hz), 4.53 (q, 2H, *J* = 6.7 Hz), 7.24–7.38 (m, 10H), 8.07 (s, 2H).

_N_,_N_′-Bis[(*S*)-1-phenylethyl]-(*R*,*R*)-1,2-diamino-1,2-di-*tert*-butylethane (6)

A solution of 100 mL (0.2 mol) of *t*-butylmagnesium chloride (2M in Et_2O) in hexane (1 L) was heated to 50 °C and stirred for 15 min. At this temperature was added dropwise a solution of diimine **4** (18.5 g, 0.07 mol) in hexane (300 mL). The mixture was stirred 0.5 h at 50 °C then cooled to 20 °C, quenched with sat. NH_4Cl (300 mL), diluted with Et_2O (300 mL) and stirred for 30 min. The aqueous layer was extracted with Et_2O (2 × 200 mL). The combined organic layers were dried (K_2CO_3), filtered over silica gel (Et_2O) and concentrated to give 25.2 g (95%) of crude **6** as an orange oil.

$[\alpha]_D^{25}$ = +31.6 (*c* = 0.364, $CHCl_3$).

^{1}H NMR: δ = 0.83 (s, 18H), 1.3 (d, 6H, *J* = 6.4 Hz), 2.4 (s, 2H), 3.75 (q, 2H, *J* = 6.4 Hz), 7.15–7.45 (m, 10H).
^{13}C NMR: δ = 23.6, 35.9, 57.1, 62.2, 126.5, 126.9, 128.2, 147.9.
$C_{26}H_{40}N_2$ (380.615): calcd. C 82.05, H 10.59, N 7.36; found C 80.99, H 10.01, N 7.19.

(1*R*,2*R*)-*N*,*N*′-Bis[(*S*)-1-phenylethyl]-1,2-di-*tert*-butylimidazolidine (aminal) (7)

The crude diamine **6** (380 mg, 1 mmol) was dissolved in formic acid (380 μL, 10 mmol) and 400 μL (5 mmol) of 37% aq formaldehyde. The solution was stirred under reflux for 5 h. After cooling, H_2O (1 mL) and Et_2O (2 mL) were added and the mixture was neutralised under stirring by slow addition of solid K_2CO_3 until the gas evolution stopped. The aqueous layer was separated and extracted with Et_2O (3 × 3 mL). The combined organic layers were dried on K_2CO_3, filtered and concentrated. Purification by chromatography on silica gel (*c*-Hex : EtOAc, 98:2) led to 300 mg (77%) of the expected aminal as a colourless oil that crystallizes after a few hours.

$[\alpha]_D^{25}$ = + 68.6 (*c* = 0.37, $CHCl_3$). mp = 78 °C.

^{1}H NMR: δ = 0.92 (s, 18H), 1.35 (d, 6H, *J* = 7 Hz), 3.08 (s, 2H), 3.59 (s, 2H), 4.12 (q, 2H, *J* = 7 Hz), 7.15–7.45 (m, 10H).
^{13}C NMR: δ = 23.3, 29.1, 36.1, 61.5, 68.2, 75.3, 126.6, 127.9, 128.3, 146.3.
$C_{27}H_{40}N_2$ (392.626): calcd. C 82.60, H 10.27, N 7.13; found C 82.47, H 10.17, N 7.03.

Aminal Monohydrochloride 8

To a solution of 281 mg (0.72 mmol) of aminal **7** in Et_2O (2 mL) were added 6 M HCl (3 mL). A white precipitate appeared and the mixture was stirred for 15 min at 20 °C. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried ($MgSO_4$) filtered and concentrated to give 301 mg (97%) of the expected chlorohydride as a white crystalline solid. The crude was recrystallized twice in EtOAc to give colourless crystals suitable for X-ray crystallography.

$[\alpha]_D^{25}$ = +103.2 (*c* = 0.155, CH_2Cl_2), mp = 226 °C.

^{1}H NMR: δ = 0.46 (s, 9H). 1.26 (d, 3H, *J* = 6.5 Hz), 1.45 (s, 9H), 1.65 (s, 1H), 2.0 (d, 3H, *J* = 7.2 Hz), 3.24 (d, 1H, *J* = 3.5 Hz), 3.5 (dd, 1H, *J* = 6.9, 3.5 Hz), 3.85 (dd, 1H, *J* = 9.5, 8.3 Hz), 4.53 (dd, 1H, *J* = 9.5, 5 Hz), 4.75 (q, 1H, *J* = 6.5 Hz), 4.86 (m, 1H), 7.18–7.64 (m, 10H).
^{13}C NMR: δ = 18.0, 23.5, 28.7, 29.9, 35.5, 35.6, 59.0, 63.7, 69.0, 69.9, 72.2, 127.6, 128.6, 129.1, 130.8, 132.7, 146.4.

$C_{27}H_{41}N_2Cl$ (429.087): calcd. C 75.58, H 9.63, N 6.53; found C 75.52, H 9.58, N 6.65.

(*R*,*R*)-1,2-Diamino-1,2-di-*tert*-butylethane (3)

To a solution of diamine **6** (2 g, 5.3 mmol) in EtOH (50 mL) were added (0.5 g,10% mol) of $Pd(OH)_2$–C 20% wt. and 2 g (31.6 mmol, 6 eq.) of anhyd ammonium formate. The mixture was refluxed 2 h with vigourous stirring under inert atmosphere, filtered and concentrated. The residue was dissolved in Et_2O (25 mL), stirred 15 min on K_2CO_3, filtered and concentrated to give 943 mg of crude **3** as an orange liquid. Distillation under reduced pressure led to 760 mg (83%) of pure **3** as a colourless liquid.

bp = 240 °C. $[\alpha]_D^{25}$ = –15 (*c* = 0.145, CH_2Cl_2). $[\alpha]_{lit}$ = +12 for the (*S*,*S*) diamine.[9]

^{1}H NMR: δ = 0.88 (s, 18H), 2.69 (s, 2H), 3.8 (s, 4H).

^{13}C NMR: δ = 27.0, 35.8, 57.6.

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