Pergamon

Tetrahedron 54 (1998) 14255–14264

TETRAHEDRON

Proton Abstraction and Electrophilic Quench at C-2 of Imidazolidines

Iain Coldham,[a*] Robert A. Judkins[a] and David R. Witty[b]

[a]Department of Chemistry, University of Exeter, Stocker Road, Exeter UK EX4 4QD

[b]SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex UK CM19 5AW

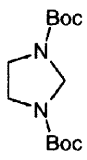
Received 13 August 1998; revised 4 September 1998; accepted 17 September 1998

Abstract: Imidazolidines bearing *tert*-butoxycarbonyl groups on both nitrogen atoms have been prepared in order to test their ability to act as acyl anion equivalents. Proton abstraction was achieved successfully at C-2, between the two nitrogen atoms, using the base *sec*-butyllithium. The resulting organolithium was trapped with a variety of electrophiles. The imidazolidine can be cleaved with acid to generate the desired carbonyl compound. Using chiral imidazolidines and aldehyde electrophiles, the carbon-carbon bond formation occurred with low diastereoselectivities. © 1998 Elsevier Science Ltd. All rights reserved.

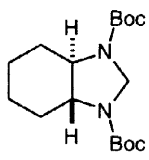
It is now well-known that an α-amino-organolithium species is stabilised by the presence of a carbonyl group attached to the nitrogen atom.[1] The concept of dipole-stabilised organolithium species is continuing to find varied use for the preparation of many novel compounds.[2] Of particular merit is the ability of the *N*-*tert*-butoxycarbonyl group to allow proton abstraction α- to the nitrogen atom.[3] We have recently studied the ability to form α-amino-organolithium species between two such anion-stabilising *N*-Boc groups in imidazolidines.[4] Herein we report full details of our procedure for the deprotonation at C-2 of imidazolidines and their reaction with a variety of electrophiles. The subsequent cleavage of the imidazolidine generates a carbonyl group and the imidazolidines therefore constitute formal acyl anion equivalents.

The ability of two *N*-Boc groups to allow cumulative stabilisation of an organolithium species has not been investigated. Katritzky has reported that the most stable conformer of 2-lithio-1,3-diacylhexahydropyrimidines has double O-Li co-ordination.[5] However, the presence of the additional stabilising group does not cause a substantial increase in the stability of the organolithium species. Proton abstraction studies with 1,3-dibenzoyl- or 1,3-dipivaloyl-imidazolidine resulted in self-condensation or mixtures of products.[5]

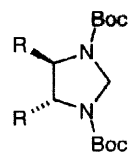
We wished to test the ability of imidazolidines bearing *N*-Boc groups to form an organolithium at C-2, to condense with a variety of electrophiles and to cleave to the carbonyl product. In addition, the use of the saturated imidazolidine ring system, as opposed to the unsaturated imidazole ring system, allows the investigation, using chiral imidazolidines, of asymmetric induction in the addition to prochiral electrophiles. We therefore prepared the imidazolidines **1**, (±)-**2** and optically-pure **3**-**6**.



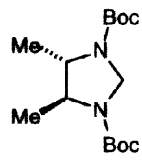
1



2



3, R = Ph
5, R = Pr^n
6, R = CH_2OMe

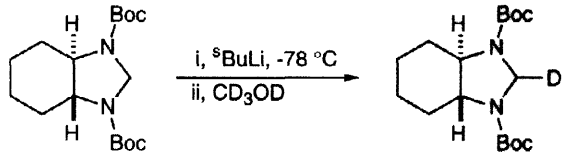


4

E-Mail: I. Coldham@exeter.ac.uk; Fax: +44 (0) 1392 263434

PII: S0040-4020(98)00877-1

We have reported the preparation of the imidazolidines **1-6** using a one-pot condensation reaction of the appropriate 1,2-diamine with paraformaldehyde, followed by addition of di-*tert*-butyl dicarbonate.[6] Using this procedure the imidazolidines **1-6** were prepared in good yield (54-75%). An effective base for proton abstraction at C-2 of *N*-Boc pyrrolidine is *sec*-butyllithium[3] and, of a number of bases tested for the deprotonation of the imidazolidine **2**, *sec*-butyllithium was found to give the best results. No proton abstraction was observed using ^{t}BuOK, KHMDS, NaHMDS, ^{n}BuLi, ^{t}BuMgCl or Bu_2Mg. The extent of deprotonation was determined by quenching the reaction with deuterated methanol to give the imidazolidine **7**. The results of this study are given in Table 1.



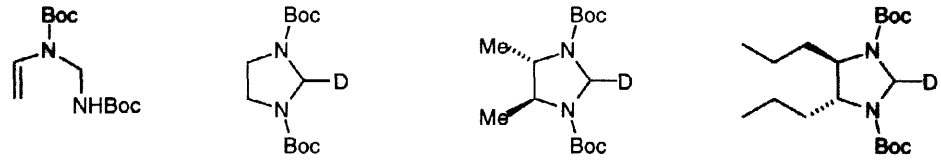
2 **7**

Table 1. Deprotonation of imidazolidine **2**

Entry	^{s}BuLi	solvent	additive	time (h)	Yield **7** (%)	D (%)
1	2.2	THF	—	0.25	79	90
2	2.2	THF	—	0.5	77	>95
3	2.2	THF	—	1	75	>95
4	2.2	Et_2O	—	1	58	>95
5	2.2	THF	—	2.5	65	>95
6	1.2	THF	—	1	83	65
7	1.2	Et_2O	—	1	69	75
8	1.2	THF	TMEDA	6	74	10
9	2.2	THF	TMEDA	1	84	0

It was possible to determine the extent of deuteration of the imidazolidine from the ^{1}H NMR spectrum. The proton at C-2 in the product **7** appears as a 1H singlet at δ 4.61 ppm ($CDCl_3$), whereas the starting material **2** has a 2H singlet at δ 4.63 ppm ($CDCl_3$). Optimum conditions involved the use of 2.2 equivalents of *sec*-butyllithium in THF for about 30 minutes (Entry 2). Some decomposition occurs even over short reaction times and this is accentuated in diethyl ether (Entries 4, 7). However, no products resulting from self-condensation or other reaction pathways could be isolated or detected. Incomplete deuteration occurs using only one equivalent of *sec*-butyllithium or in the presence of TMEDA (Entries 6-9). The organolithium maintains considerable stability at -78 °C in THF, as judged by quenching the reaction after 2.5 hours (Entry 5).

In the same way, the imidazolidines **1** and **3-6** were treated with two equivalents of *sec*-butyllithium in THF, followed by quenching with deuterated methanol. From the imidazolidine **1**, the major product **8** (68%) is a result of ring-opening of the imidazolidine after proton abstraction at C-4. This suggests that the partial decomposition using imidazolidine **2** is probably a result of proton abstraction at C-4. The use of only one equivalent of *sec*-butyllithium also gave the ring-opened product **8**, together with a low yield of the imidazolidine **9** (21%, >95% D) after 15-30 minutes. Problems were also encountered on attempted deprotonation of the imidazolidine **3**. In all cases, numerous compounds were formed, probably due to competing proton abstraction at C-4 (benzylic).

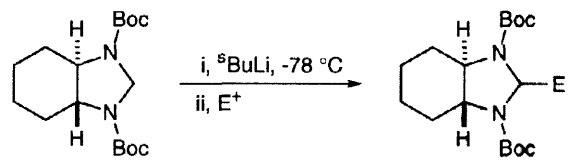


8 9 10 11

Deprotonation of the imidazolidine **4** resulted in a high yield of a mixture of imidazolidines with deuterium incorporation at C-2 (>95% D) and at C-4 (50% D). Reducing the amount of *sec*-butyllithium to one equivalent prevented proton abstraction at C-4 and the imidazolidine **10** was formed in good yield (79%, 95% D). Deprotonation of the imidazolidine **5** with two equivalents of *sec*-butyllithium was successful and resulted in the formation of the imidazolidine **11** in excellent yield (89%, 95% D). Unfortunately, the imidazolidine **6** was prone to proton abstraction at C-4 and gave a low yield of a mixture of products, containing the imidazolidine **6** with up to 35% D at C-2 and 15% D at C-4. It is likely that in this case elimination of methoxide (and ring-opening of the imidazolidine) is taking place.

These deprotonation and deuterium quench studies indicate that the *N*-Boc derivatives are better able to promote proton abstraction and electrophilic quench at C-2, than the corresponding *N*-benzoyl or *N*-pivaloyl derivatives. In addition, high yields of products resulting from quenching the desired organolithium can be obtained, provided that the substituents at C-4 and C-5 are chosen carefully. In agreement with other studies, the additional stabilisation afforded by the second *N*-Boc group does not appear to be substantial. This is illustrated by the competing proton abstraction at C-4, in which only one carbonyl group can stabilise the resulting organolithium species by dipole stabilisation.

Having determined that the best substrates for proton abstraction at C-2 were the imidazolidines **2**, **4** and **5**, we investigated the quench of imidazolidine (±)-**2** with a variety of different electrophiles. These are illustrated in Table 2. It was possible to form different C-2-substituted imidazolidines **12** by quenching the organolithium with alkyl or acyl halides (or phenyl isocyanate). With ketone electrophiles, cyclohexanone gave only recovered starting material, possibly due to enolization, and benzophenone resulted in the blue radical anion but none of the desired product.

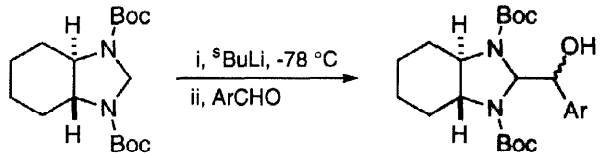


2 12

Table 2. Deprotonation and electrophilic quench of imidazolidine **2**

Entry	E^+	E	Product	Yield **12** (%)
1	MeI	CH_3	**12a**	42
2	$PhCH_2Br$	CH_2Ph	**12b**	40
3	PhNCO	CONHPh	**12c**	50
4	$H_2C{=}CHCH_2Br$	$CH_2CH{=}CH_2$	**12d**	48
5	MeOCOCl	CO_2Me	**12e**	63
6	PhCOCl	COPh	**12f**	58

Of particular significance is the ability to quench the organolithium with prochiral electrophiles. Addition of pivaldehyde or 2-methylpropanal to the organolithium generated from the imidazolidine **2** gave only a low yield of recovered starting material. However, using aromatic aldehydes, good yields of the desired products **13-15** were obtained. In all cases an inseparable mixture of diastereomers were isolated. The ratio of diastereomers was poor (up to 2:1, as determined by ^{1}H NMR spectroscopy) and this may reflect the relatively long distance from the chiral centres of the imidazolidine **2** to the incoming prochiral centre of the electrophile. This result is similar to that obtained for the corresponding dioxolanes, the organolithium of which has been prepared by tin-lithium exchange.[7]



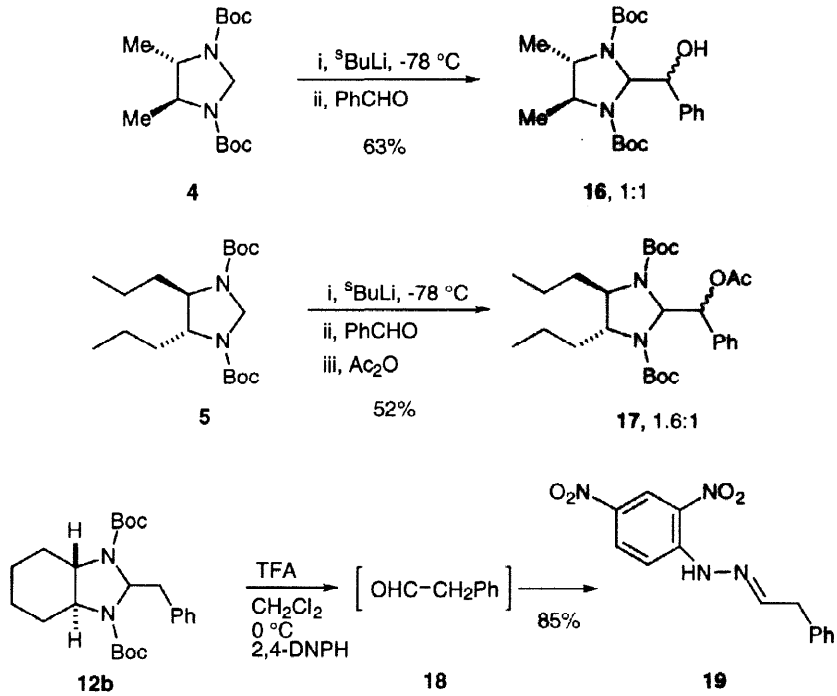
2

Ar	Yield (%)	Ratio	Product
Ph	52	2:1	**13**
p-MeOC$_6$H$_4$	56	2:1	**14**
p-ClC$_6$H$_4$	55	1.5:1	**15**

The highly diastereoselective alkylation or reduction of 2-acyl-imidazolidines, bearing *N*-alkyl groups[8] or of chiral *N*-Boc oxazolidines,[7,9] is known and could provide a solution to the poor selectivities achieved in the carbon-carbon bond formation to **13-15**. Reduction of the imidazolidine **12f**, E = COPh, with sodium borohydride-lithium iodide, according to the literature method, gave the product **13** with a disappointingly poor selectivity (87%, 2:1).

In an attempt to increase the stereoselectivity of the anion addition to aldehyde electrophiles, the imidazolidines **4** and **5** were treated with *sec*-butyllithium in THF, followed by addition of benzaldehyde. In each case the desired imidazolidines, **16** and **17** respectively, were obtained. However, in each case, the stereoselectivity was poor. It appears, therefore that *N,N'*-bisBoc-imidazolidines, bearing alkyl substituents at C-4 and C-5 are capable of proton abstraction at C-2 and electrophilic quench, although the stereoselectivity on addition to prochiral aldehyde electrophiles is low. The reasons for the lack of diastereoselectivity (in contrast with the related oxazolidines or *N*-alkyl imidazolidines) presumably lie with the two planar sp^2 hybridised nitrogen atoms, which cannot relay the stereochemical information. The imidazolidine **17** was isolated as the mixture of stereoisomeric acetates in order to ease purification from the byproduct resulting from attack of *sec*-butyllithium onto benzaldehyde.

Finally, in order to demonstrate that the *N,N'*-bisBoc-imidazolidine can act as an acyl anion equivalent, the imidazolidine needs to be cleaved to generate the new acyl group. The imidazolidine **12b** was treated with trifluoroacetic acid in dichloromethane in order to hydrolyse the imidazolidine ring and give the aldehyde **18**. The chiral 1,2-diaminocyclohexane was recovered from this reaction as its bistrifluoroacetate salt in high yield (90%). Phenyl acetaldehyde **18** was isolated in low yield, due to its propensity to undergo aldol self condensation under acidic conditions, unless the hydrolysis was performed in the presence of 2,4-dinitrophenylhydrazine (2,4-DNPH). This *in situ* trapping of the aldehyde **18** gave the hydrazone **19** in good isolated yield (85%).



In summary, we have demonstrated that *N,N'*-bisBoc-imidazolidines are capable of acting as acyl anion equivalents. Proton abstraction at C-2 gives the organolithium which can be quenched with a variety of electrophiles to give 2-substituted imidazolidines. The use of chiral imidazolidines and aldehydes as electrophiles results in products with low stereoselectivity at the new hydroxyl-bearing chiral centre. Hydrolysis of the imidazolidine ring allows isolation of the carbonyl compound with recovery of the 1,2-diamine.

EXPERIMENTAL

All experiments involving organolithiums were carried out under an inert atmosphere of argon or nitrogen. Diethyl ether and THF were distilled from sodium benzophenone ketyl. Hexane was distilled from sodium hydride. Infrared spectra were recorded on a Perkin Elmer 881 spectrophotometer, using a polystyrene reference (1602 cm^{-1}). ^1H nuclear magnetic resonance (NMR) spectra were run on a Brucker AM250 (250 MHz), AM300 (300 MHz) or AM400 (400 MHz) instrument. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as the reference and *J* values are given in Hz. ^{13}C NMR were run on a Brucker AM250 (62.9 MHz) or AM300 (75.5 MHz) instrument, with $CDCl_3$ (δ 77.2 ppm) as the reference. Mass spectra were run on a Kratos Profile instrument. Elemental analyses were carried out by Butterworth Microanalytical Consultancy Ltd., Teddington, Middlesex, UK.

The preparation of the imidazolidines **12a** and **12b** has been reported in full elsewhere.[6]

Proton abstraction of the imidazolidine 1

N,N'-*Bis*-tert-*butoxycarbonyl-1-amino-2-aza-but-3-ene* **8**

sec-Butyllithium (0.32 cm^3, 0.40 mmol) was added to the imidazolidine **1** (100 mg, 0.37 mmol) in THF (2 cm^3) under nitrogen at -78 °C. After 15 min d^4-methanol (0.4 cm^3) was added and the mixture was allowed to warm to room temperature. The solvent was evaporated and the residue was purified by column chromatography on

silica gel, eluting with light petroleum (b.p. 40-60 °C)-EtOAc (7:1) to give the *carbamate* **8** (68 mg, 68%) as an oil; R_f 0.42 [light petroleum (b.p. 40-60 °C)-EtOAc (7:1)]; $\nu_{max.}$ ($CHCl_3$) cm^{-1} 1710 (C=O) and 1630 (C=C); δ_H (300 MHz, $CDCl_3$) 6.88 (1H, bs, NCH=C), 5.26 (1H, s, NH), 4.90 (1H, s, C*H*$_2$=CH), 4.89 (1H, C*H*$_2$=CH), 4.86-4.73 (1H, bm, NCHN), 4.35-4.24 (1H, bm, NCHN), 1.50 [9H, s, $C(CH_3)_3$] and 1.45 [9H, s, $C(CH_3)_3$]; δ_C (75 MHz, $CDCl_3$) 155.0 (C=O), 131.8 (CH_2=*C*H), 93.1 (*C*H_2=CH), 81.9 [O*C*$(CH_3)_3$], 50.0 (CH_2), 28.3, 28.2 [C(*C*$H_3)_3$] (Found : M^+, 272.1745. $C_{13}H_{24}N_2O_4$ requires M, 272.1736); *m/z* 273 (7%, MH), 272 (4, M), 215 [57, M - $C(CH_3)_3$], 144 [13, M - CH_2CH - $CO_2C(CH_3)_3$], 87 [40, M - CH_2CH - $C(CH_3)_3$ - $CO_2C(CH_3)_3$], 70 [19, M - 2 x $CO_2C(CH_3)_3$], 57 [100, $C(CH_3)_3$].

Proton abstraction of the imidazolidine 2

N,N'-*Bis*-tert-*butoxycarbonyl-2-deutero-1,3-diazabicyclo[4.3.0]nonane* **7**

sec-Butyllithium (0.76 cm^3, 0.98 mmol) was added to the imidazolidine **2** (146 mg, 0.45 mmol) in THF (2 cm^3) under nitrogen at -78 °C. After 30 min d^4-methanol (0.4 cm^3) was added and the mixture was allowed to warm to room temperature. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with light petroleum (b.p. 40-60 °C)-EtOAc (10:1) to give the *imidazolidine* **7** (109 mg, 75%) as needles, m.p. 118-120 °C; R_f 0.40 [light petroleum (b.p. 40-60 °C)-EtOAc (10:1)]; $\nu_{max.}$ (KBr) cm^{-1} 1690 (C=O); δ_H (300 MHz, $CDCl_3$) 4.61 (1H, s, NCHDN), 3.05-2.92 (2H, m, NCHCHN), 2.75-2.63 (2H, m, CH_2), 1.82-1.71 (2H, m, CH_2), 1.45 [18H, s, 2 x $C(CH_3)_3$] and 1.42-1.24 (4H, m, CH_2CH_2); δ_C (75 MHz, $CDCl_3$) 154.3, 80.3, 63.7, 62.6 (t, *J* 22.6 Hz, NCHDN), 29.9, 28.4 and 24.2 (Found : M^+, 327.2272. $C_{17}H_{29}DN_2O_4$ requires M, 327.2268); *m/z* 327 (0.1%, M), 270 [30, M - $C(CH_3)_3$], 213 [23, M - H - 2 x $C(CH_3)_3$], 57 [100, $C(CH_3)_3$]; (Found: C, 62.04; H, 9.37; N, 8.45. $C_{17}H_{29}DN_2O_4$ requires C, 62.35; H, 9.56; N, 8.56%).

N,N'-*Bis*-tert-*butoxycarbonyl-2-(N''-phenylcarboxamidyl)-1,3-diazabicyclo[4.3.0]nonane* **12c**

In the same way as the imidazolidine **7**, the imidazolidine **2** (200 mg, 0.61 mmol), *sec*-butyllithium (1.03 cm^3, 1.29 mmol) and phenyl isocyanate (0.15 cm^3, 1.35 mmol) gave, after purification by column chromatography on silica gel, eluting with light petroleum (b.p. 40-60 °C)-EtOAc (5:1), the *imidazolidine* **12c** (137 mg, 50%) as needles, m.p. 155-156 °C; R_f 0.44 [light petroleum (b.p. 40-60 °C)-EtOAc (5:1)]; $\nu_{max.}$ (KBr) cm^{-1} 1710, 1685 and 1530 (C=O); δ_H (300 MHz, $CDCl_3$) 9.28 (1H, bs, NH), 7.56 (2H, d, *J* 7.5, Ph), 7.31 (2H, t, *J* 7.5, Ph), 7.09 (1H, d, *J* 7.5, Ph), 5.57 (1H, bs, NCHN), 3.37 (1H, td, *J* 10 and 3, NCH), 3.07 (1H, td, *J* 10 and 3, NCH), 2.93 (1H, bs, CH), 2.42 (1H, bs, CH), 1.87-1.72 (2H, m, CH_2), 1.51 [9H, s, $C(CH_3)_3$], 1.45 [9H, s, $C(CH_3)_3$] and 1.38-1.22 (4H, s, CH_2CH_2); δ_C (75 MHz, $CDCl_3$) 166.6 (NHC=O), 154.1 (NC=O), 138.3 (Aryl C), 128.9, 123.9, 119.5 (Aryl CH), 82.1, 80.8 [O*C*$(CH_3)_3$], 73.3, 65.0, 63.4 (CH), 30.3, 29.5 (CH_2), 28.4, 28.2 [C(*C*$H_3)_3$], 24.2 (CH_2) (Found : MH^+, 446.2665. $C_{24}H_{36}N_3O_5$ requires MH, 446.2655); *m/z* 445 (0.1%, MH), 325 (50, M - PhNHCO), 268 [4, M - PhNHCO - $C(CH_3)_3$], 224 [10, M - PhNHCO - $CO_2C(CH_3)_3$], 123 [26, M - PhNHCO - 2 x $CO_2C(CH_3)_3$], 119 (34, PhNCO), 91 (31, PhN), 77 (42, Ph), 57 [100, $C(CH_3)_3$].

N,N'-*Bis*-tert-*butoxycarbonyl-2-prop-2'-enyl-1,3-diazabicyclo[4.3.0]nonane* **12d**

In the same way as the imidazolidine **7**, the imidazolidine **2** (200 mg, 0.61 mmol), *sec*-butyllithium (1.0 cm^3, 1.29 mmol) and allyl bromide (0.12 cm^3, 1.35 mmol) gave, after purification by column chromatography on silica gel, eluting with light petroleum (b.p. 40-60 °C)-EtOAc (10:1), the *imidazolidine* **12d** (101 mg, 45%) as a

wax, m.p. 65-67 °C; R_f 0.42 [light petroleum (b.p. 40-60 °C)-EtOAc (10:1)]; $\nu_{max.}$ (KBr) cm^{-1} 1700 and 1675 (C=O); δ_H (300 MHz, $CDCl_3$) 5.91-5.76 (1H, m, C*H*=CH_2), 5.32 (1H, t, *J* 4, NCHN), 5.11-5.06 (1H, m, CH=C*H*$_2$), 5.05-5.02 (1H, m, CH=C*H*$_2$), 3.09 (1H, td, *J* 11 and 3, NCH), 2.96 (1H, td, *J* 11 and 3, NCH), 2.74 (1H, bd, *J* 14, CH), 2.67-2.53 (3H, m, CH and CH_2), 1.85-1.69 (2H, m, CH_2), 1.46 [18H, s, 2 x $C(CH_3)_3$] and 1.38-1.17 (4H, m, CH_2CH_2); δ_C (75 MHz, $CDCl_3$) 155.5, 152.6 (C=O), 133.5 (*C*H=CH_2), 118.2 (CH=*C*H$_2$), 80.3, 80.1 [O*C*$(CH_3)_3$], 73.0, 64.6, 62.0 (CH), 38.6, 30.8, 29.7 (CH_2), 28.4 [C(*C*H$_3$)$_3$], 24.8, 24.1 (CH_2) (Found : M^+, 366.2520. $C_{20}H_{34}N_2O_4$ requires M, 366.2518); *m/z* 367 (35%, MH), 366 (13, M), 325 (48, M - CH_2CH=CH_2), 268 [19, M - CH_2CH=CH_2 - $C(CH_3)_3$], 224 [18, M - CH_2CH=CH_2 - $CO_2C(CH_3)_3$], 211 [39, M - CH_2CH=CH_2 - 2 x $C(CH_3)_3$], 167 [37, M - CH_2CH=CH_2 - $C(CH_3)_3$ - $CO_2C(CH_3)_3$], 123 [100, M - CH_2CH=CH_2 - 2 x $CO_2C(CH_3)_3$], 57 [58, $C(CH_3)_3$].

N,N'-*Bis*-tert-*butoxycarbonyl-2-(methoxycarbonyl)-1,3-diazabicyclo[4.3.0]nonane* **12e**

In the same way as the imidazolidine **7**, the imidazolidine **2** (500 mg, 1.53 mmol), *sec*-butyllithium (2.59 cm^3, 3.37 mmol) and methyl chloroformate (0.30 cm^3, 3.83 mmol) gave, after purification by column chromatography on silica gel, eluting with light petroleum (b.p. 40-60 °C)-EtOAc (10:1), the *imidazolidine* **12e** (373 mg, 63%) as needles, m.p. 70-72 °C; R_f 0.27 [light petroleum (b.p. 40-60 °C)-EtOAc (10:1)]; $\nu_{max.}$ (KBr) cm^{-1} 1740 and 1710 (C=O); δ_H (300 MHz, $CDCl_3$) 5.40 (1H, s, NCHN), 3.76 (3H, s, OCH_3), 3.45 (1H, td, *J* 10 and 3, NCH), 3.05 (1H, td, *J* 10 and 3, NCH), 2.78 (1H, bd, *J* 11, CH), 2.61 (H, bd, *J* 11, CH), 1.88-1.71 (2H, m, 2 x CH), 1.45 [9H, s, $C(CH_3)_3$], 1.42 [9H, s, $C(CH_3)_3$] and 1.38-1.27 (4H, m, CH_2CH_2); δ_C (75 MHz, $CDCl_3$) 170.9 (CH_3OC=O), 154.7, 153.5 (NC=O), 81.2, 81.1 [O*C*$(CH_3)_3$], 72.2, 64.7, 63.1 (CH), 52.2 (CH_3O), 30.3, 29.8 (CH_2), 28.4, 28.2 [C(*C*H$_3$)$_3$], 24.3, 24.2 (CH_2) (Found : MH^+, 385.2334. $C_{19}H_{33}N_2O_6$ requires MH, 385.2339); *m/z* 385 (6%, MH), 325 (46, M - CO_2CH_3), 224 [10, M - CO_2CH_3 - $CO_2C(CH_3)_3$], 211 [39, M - CO_2CH_3 - 2 x $C(CH_3)_3$], 123 [29, M - CO_2CH_3 - 2 x $CO_2C(CH_3)_3$], 57 [100, $C(CH_3)_3$].

N,N'-*Bis*-tert-*butoxycarbonyl-2-(benzoyl)-1,3-diazabicyclo[4.3.0]nonane* **12f**

In the same way as the imidazolidine **7**, the imidazolidine **2** (200 mg, 0.61 mmol), *sec*-butyllithium (0.86 cm^3, 1.29 mmol) and benzoyl chloride (0.16 cm^3, 1.35 mmol) gave, after purification by column chromatography on silica gel, eluting with light petroleum (b.p. 40-60 °C)-EtOAc (10:1), the *imidazolidine* **12f** (155 mg, 58%) as needles, m.p. 113-115 °C; R_f 0.25 [light petroleum (b.p. 40-60 °C)-EtOAc (10:1)]; $\nu_{max.}$ (KBr) cm^{-1} 1710 and 1680 (C=O); δ_H (300 MHz, $CDCl_3$) 8.21-8.13 (2H, m, Ph), 7.58-7.50 (1H, m, Ph), 7.47-7.41 (2H, m, Ph), 6.43 (1H, s, NCHN), 3.63 (1H, td, *J* 10.5 and 3, NCH), 3.01 (1H, td, *J* 10.5 and 3, NCH), 2.75 (1H, bd, *J* 11, CH), 2.69 (1H, bd, *J* 11, CH), 1.84-1.75 (2H, m, CH_2), 1.58-1.34 (4H, m, CH_2CH_2) and 1.26 [18H, s, 2 x $C(CH_3)_3$]; δ_C (75 MHz, $CDCl_3$) 198.4 (Ph*C*=O), 153.3 (NC=O), 136.6 (Aryl C), 133.2, 129.2, 128.3 (Aryl CH), 81.2, 81.1 [O*C*$(CH_3)_3$], 70.1, 64.7, 63.6 (CH), 30.4, 29.9 (CH_2), 28.4, 28.2 [C(*C*H$_3$)$_3$], 24.6, 24.3 (CH_2) (Found : M^+, 430.2450. $C_{24}H_{34}N_2O_6$ requires M, 430.2468); *m/z* 430 (2%, M), 325 (8, M - PhCO), 269 [50, M - PhCO - $CO_2C(CH_3)_3$], 213 [100, M - PhCO - 2 x $C(CH_3)_3$], 123 [20, M - PhCO - 2 x $CO_2C(CH_3)_3$], 105 (44, PhCO), 57 [65, $C(CH_3)_3$].

N,N'-*Bis*-tert-*butoxycarbonyl-2-(1'-hydroxy-1'-phenyl)methyl-1,3-diazabicyclo[4.3.0]nonane* **13**

In the same way as the imidazolidine **7**, the imidazolidine **2** (199 mg, 0.61 mmol), *sec*-butyllithium (0.97 cm^3, 1.21 mmol) and benzaldehyde (0.16 cm^3, 1.52 mmol) gave, after purification by column chromatography on

silica gel, eluting with light petroleum (b.p. 40-60 °C)-EtOAc (10:1), the *imidazolidine* **13** (136 mg, 52%) as a 2:1 mixture of diastereomers, as a powder, m.p. 99-101 °C; R_f 0.27 [light petroleum (b.p. 40-60 °C)-EtOAc (10:1)]; $\nu_{max.}$ (KBr) cm^{-1} 3350 (OH), 1690 and 1660 (C=O); δ_H (300 MHz, $CDCl_3$) 7.37-7.22 (5H, m, Ph), 5.66-5.63 (1H, m, C*H*OH), 5.29 (0.35H, bs, OH), 5.10-5.04 (1H, m, NCHN), 2.89-2.79 (1H, m, NCH), 2.57-2.43 (1H, m, NCH), 2.36 (0.35H, d, *J* 11, CH), 2.27 (0.65H, d, *J* 11, CH), 1.87 (0.65H, bs, OH), 1.72-1.65 (3H, m, CH and CH_2), 1.52 [3H, s, $C(CH_3)_3$], 1.50 [12H, s, $C(CH_3)_3$], 1.39 [3H, s, $C(CH_3)_3$], 1.36-1.05 (2H, m, CH_2) and 0.95-0.55 (2H, m, CH_2); δ_C (75 MHz, $CDCl_3$) 158.2, 152.3 (C=O), 140.5, 140.2 (Aryl C), 127.9, 127.85, 127.8, 127.7, 127.6, 127.2 (Aryl CH), 82.1, 81.4, 81.2, 80.6 [O*C*$(CH_3)_3$], 77.3, 77.0, 76.9, 75.0 (NCHN and CHOH), 64.7, 64.5, 62.1, 61.7 (NCH), 30.5, 30.1, 29.7, 29.4 (CH_2), 28.5, 28.4, 28.3 [C(*C*$H_3)_3$], 24.9, 24.6, 23.9, 23.8 (CH_2) (Found : MH^+, 433.2711. $C_{24}H_{36}N_2O_5$ requires MH, 433.2703); *m/z* 433 (0.1%, M), 325 [37, M - CH(OH)Ph], 269 [35, MH - CH(OH)Ph - $C(CH_3)_3$], 168 [14, M - CH(OH)Ph - $C(CH_3)_3$ - $CO_2C(CH_3)_3$], 107 [29, CH(OH)Ph], 57 [100, $C(CH_3)_3$].

N,N'-*Bis*-tert-*butoxycarbonyl-2-(1'-hydroxy-1'*-para-*methoxyphenyl)methyl-1,3-diazabicyclo[4.3.0]nonane* **14**

In the same way as the imidazolidine **7**, the imidazolidine **2** (200 mg, 0.61 mmol), *sec*-butyllithium (1.02 cm^3, 1.29 mmol) and *p*-methoxybenzaldehyde (0.13 cm^3, 1.53 mmol) gave, after purification by column chromatography on silica gel, eluting with light petroleum (b.p. 40-60 °C)-EtOAc (7:1), the *imidazolidine* **14** (157 mg, 56%) as a 2:1 mixture of diastereomers, as a powder, m.p. 110-112 °C; R_f 0.13 [light petroleum (b.p. 40-60 °C)-EtOAc (7:1)]; $\nu_{max.}$ (KBr) cm^{-1} 3340 (OH), 1690 and 1660 (C=O); δ_H (300 MHz, $CDCl_3$) 7.17 (2H, d, *J* 8.5, Ar), 6.86 (2H, d, *J* 8.5, Ar), 5.64-5.57 (1H, m, C*H*OH), 5.25 (0.35H, bs, OH), 5.06-4.96 (1H, m, NCHN), 3.81 (3H, s, OCH_3), 2.92-2.78 (1H, m, NCH), 2.58-2.43 (1H, m, NCH), 2.45-2.33 (0.35H, m, CH), 2.28 (0.65H, bd, *J* 12, CH), 1.85 (0.65H, bs, OH), 1.72-1.55 (3H, m, CH and CH_2), 1.52 [3H, s, $C(CH_3)_3$], 1.50 [12H, s, $C(CH_3)_3$], 1.39 [3H, s, $C(CH_3)_3$], 1.35-1.02 (2H, m, CH_2) and 0.98-0.59 (2H, m, CH_2); δ_C (75 MHz, $CDCl_3$) 159.5, 159.3 (C=O), 132.6, 132.5 (Aryl C), 128.8, 128.3, 127.8, 113.6, 113.4, 113.3 (Aryl CH), 82.0, 81.4, 81.2, 80.6 [O*C*$(CH_3)_3$], 77.2, 76.9, 76.8, 74.5 (NCHN and CHOH), 64.8, 64.5, 62.1, 61.7 (NCH), 55.3, 55.2 (OCH_3), 30.6, 30.2, 29.7, 29.4 (CH_2), 28.5, 28.4, 28.3 [C(*C*$H_3)_3$], 24.9, 24.6, 23.9, 23.8 (CH_2) (Found : MH^+, 463.2828. $C_{25}H_{38}N_2O_6$ requires MH, 463.2808); *m/z* 463 (0.3%, MH), 325 [13, M - CH(OH)C_6H_4OMe], 137 [33, CH(OH)C_6H_4OMe], 123 [10, M - CH(OH)C_6H_4OMe - 2 x $CO_2C(CH_3)_3$], 57 [100, $C(CH_3)_3$].

N,N'-*Bis*-tert-*butoxycarbonyl-2-(1'-hydroxy-1'*-para-*chlorophenyl)methyl-1,3-diazabicyclo[4.3.0]nonane* **15**

In the same way as the imidazolidine **7**, the imidazolidine **2** (200 mg, 0.61 mmol), *sec*-butyllithium (1.02 cm^3, 1.29 mmol) and *p*-chlorobenzaldehyde (0.22 g, 1.53 mmol) gave, after purification by column chromatography on silica gel, eluting with light petroleum (b.p. 40-60 °C)-EtOAc (7:1), the *imidazolidine* **15** (158 mg, 55%) as a 1.5:1 mixture of diastereomers, as needles, m.p. 115-117 °C; R_f 0.36 [light petroleum (b.p. 40-60 °C)-EtOAc (7:1)]; $\nu_{max.}$ (KBr) cm^{-1} 3355 (OH), 1695 and 1660 (C=O); δ_H (300 MHz, $CDCl_3$) 7.34-7.16 (4H, m, Ar), 5.65-5.57 (1H, m, C*H*OH), 5.45 (0.4H, bs, OH), 5.09-4.98 (1H, m, NCHN), 2.93-2.79 (1H, m, NCH), 2.60-2.46 (1H, m, NCH), 2.40 (0.4H, bd, *J* 10, CH), 2.30 (0.6H, bd, *J* 10, CH), 1.93 (0.6H, bs, OH), 1.62-1.55 (3H, m, CH and CH_2), 1.52 [3.5H, s, $C(CH_3)_3$], 1.49 [11H, s, $C(CH_3)_3$], 1.38 [3.5H, s, $C(CH_3)_3$], 1.37-1.06 (2H, m, CH_2) and 1.02-0.60 (2H, m, CH_2); δ_C (75 MHz, $CDCl_3$) 156.4, 152.3 (C=O), 139.1,

138.9 (Aryl C), 133.6, 133.4 (Aryl C), 129.1, 128.6, 128.0, 127.9 (Aryl CH), 82.6, 81.7, 81.4, 80.8 [O*C*$(CH_3)_3$], 77.2, 76.8, 76.5, 74.5 (NCHN and CHOH), 64.8, 64.5, 62.1, 61.7 (NCH), 30.6, 30.3, 29.7, 29.4 (CH_2), 28.4, 28.3, 28.2 [C(*C*$H_3)_3$], 24.9, 24.6, 23.9, 23.8 (CH_2) (Found : MH$^+$, 467.2304. $C_{24}H_{35}ClN_2O_6$ requires MH, 467.2313); *m/z* 467 (7%, MH), 325 [17, M - CH(OH)C_6H_4Cl], 141 [32, CH(OH)C_6H_4Cl], 124 (29, CHC_6H_4Cl), 111 (32, C_6H_4Cl), 57 [100, C$(CH_3)_3$].

Proton abstraction of the imidazolidine 4

N,N'-***Bis***-tert-*butoxycarbonyl-2-(1'-hydroxy-1'-phenyl)methyl-4,5-dimethyl-imidazolidine* **16**

In the same way as the imidazolidine **7**, the imidazolidine **4** (134 mg, 0.47 mmol), *sec*-butyllithium (0.37 cm^3, 0.47 mmol) and benzaldehyde (0.06 cm^3, 0.6 mmol) gave, after purification by column chromatography on silica gel, eluting with light petroleum (b.p. 40-60 °C)-acetone (7:1), the *imidazolidine* **16a** (62 mg, 33%) as an oil; R_f 0.44 [light petroleum (b.p. 40-60 °C)-acetone (7:1)]; $\nu_{max.}$ ($CHCl_3$) cm^{-1} 3350 (OH), 1690 and 1660 (C=O); δ_H [300 MHz, $(CD_3)_2SO$] 7.34-7.16 (5H, m, Ph), 5.73 (1H, bs, C*H*OH), 5.45 (1H, d, *J* 3, NCHN), 4.93 (1H, bs, OH), 3.33 (2H, bs, NCHCHN), 1.35 [9H, s, C$(CH_3)_3$], 1.28 [9H, s, C$(CH_3)_3$], 1.24 (6H, bs, 2 x CH_3); δ_C [75 MHz, $(CD_3)_2SO$] 152.7 (C=O), 142.4 (Aryl C), 128.2, 127.5, 127.3 (Aryl CH), 80.5, 79.8 [O*C*$(CH_3)_3$], 77.1, 74.8 (CHOH and NCHN), 60.7, 59.4 (CH), 28.3, 28.2 [C(*C*$H_3)_3$], 18.8 (CH_3) (Found : MH$^+$, 407.2555. $C_{22}H_{34}N_2O_5$ requires MH, 407.2546); *m/z* 407 (3%, MH$^+$), 299 [7, M - CH(OH)Ph], 107 [100, CH(OH)Ph], 77 (82, Ph), 57 [38, C$(CH_3)_3$], and the *imidazolidine* **16b** (60 mg, 30%) as an oil, R_f 0.14 [light petroleum (b.p. 40-60 °C)-acetone (7:1)]; $\nu_{max.}$ ($CHCl_3$) cm^{-1} 3345 (OH), 1690 (C=O); δ_H (300 MHz, $CDCl_3$) 7.35-7.18 (5H, m, Ph), 5.61-5.55 (1H, m, C*H*OH), 5.20-5.12 (1H, m, NCHN), 3.57 (1H, bs, NCH), 3.23 (1H, bs, NCH), 1.51 [9H, s, C$(CH_3)_3$], 1.43 [9H, s, C$(CH_3)_3$], 1.21 (3H, d, *J* 6.5, CH_3) and 0.70 (3H, bs, CH_3); δ_C (75 MHz, $CDCl_3$) 153.8 (C=O), 140.0 (Aryl C), 128.0, 127.8, 127.6 (Aryl CH), 81.5, 80.8 [O*C*$(CH_3)_3$], 76.8, 75.7 (CHOH and NCHN), 59.7 (CH), 28.3, 28.2 [C(*C*$H_3)_3$], 19.3, 19.2 (CH_3) (Found : MH$^+$, 407.2542. $C_{22}H_{34}N_2O_5$ requires MH, 407.2546); *m/z* 407 (4%, MH$^+$), 299 [21, M - CH(OH)Ph], 107 [10, CH(OH)Ph], 77 (12, Ph), 57 [100, C$(CH_3)_3$].

Proton abstraction of the imidazolidine 5

N,N'-*Bis*-tert-*butoxycarbonyl-2-(1'-hydroxy*-O-*ethanoyl-1'-phenyl)methyl-4,5-dipropyl-imidazolidine* **17**

In the same way as the imidazolidine **7**, the imidazolidine **5** (200 mg, 0.56 mmol), *sec*-butyllithium (1.42 cm^3, 1.52 mmol) and benzaldehyde (0.20 cm^3, 1.97 mmol) gave, after purification by column chromatography on silica gel, eluting with light petroleum (b.p. 40-60 °C)-acetone (10:1), the *alcohol* (222 mg) as a mixture of diastereomers, R_f 0.25 [light petroleum (b.p. 40-60 °C)-acetone (10:1)], which was treated with acetic anhydride (0.23 cm^3, 2.44 mmol) in pyridine (4.0 cm^3) at 70 °C for 2 d. The mixture was evaporated, added to sat. NaCl (12 cm^3) and washed with CH_2Cl_2 (3 x 6 cm^3). The combined extracts were dried (Na_2SO_4), filtered and purified by flash chromatography on silica gel, eluting with light petroleum (b.p. 40-60 °C)-acetone (10:1), to give the *imidazolidine* **17** (148 mg, 52%) as a 2:1 mixture of diastereomers as an oil; R_f 0.24 [light petroleum (b.p. 40-60 °C)-acetone (10:1)]; $\nu_{max.}$ ($CHCl_3$) cm^{-1} 1750 and 1700 (C=O); δ_H (300 MHz, CD_3OD) 7.39-7.21 (5H, m, Ph), 6.47 (0.6H, s, PhCH), 6.12 (0.4H, bs, PhCH), 5.75 (0.6H, d, *J* 4, NCHN), 5.57 (0.4H, m, NCHN), 3.96 (0.4H, bs, NCH), 3.85 (0.4H, bs, NCH), 3.71 (0.6H, bs, NCH), 3.36 (0.6H, bs, NCH), 2.11 (3H, s, CH_3), 1.55 [7H, s, C$(CH_3)_3$], 1.52 [5.5H, s, C$(CH_3)_3$], 1.40 [5.5H, s, C$(CH_3)_3$], 1.30-0.96 (8H, m, 2 x CH_2CH_2) and 0.96-0.68 (6H, m, 2 x CH_3); δ_C (75 MHz, CD_3OD) 170.3, 169.5 (OC=O), 155.2, 153.4 (NC=O), 137.1 (Aryl C), 128.0, 127.9, 127.7 (Aryl CH), 81.0, 80.7 [O*C*$(CH_3)_3$], 74.9, 74.2, 73.6 (NCHN

and PhCH), 62.2, 62.0 (NCH), 37.3, 36.8 34.6 (CH_2), 27.3, 27.2, 27.1, 26.6 [$C(CH_3)_3$], 19.9, 19.8 (CO_2CH_3), 19.7, 19.6 (CH_2), 13.2, 13.0, 12.9, 12.7 (CH_3) (Found : MH^+, 505.3282. $C_{29}H_{44}N_2O_6$ requires MH, 505.3278); *m/z* 505 (6%, MH^+), 355 [49, M - CH_3 - Ph - $C(CH_3)_3$], 332 [14, M - CH_3 - $C(CH_3)_3$ - $CO_2C(CH_3)_3$], 255 [25, M - CH_3CO_2 - Ph - 2 x $C(CH_3)_3$], 243 [99, M - CH_3CO_2 - 2 x $CO_2C(CH_3)_3$], 57 [100, $C(CH_3)_3$].

Hydrolysis of the imidazolidine 12b

Phenylacetaldehyde 2,4-Dinitrophenylhydrazone **19**

The imidazolidine **12b** (291 mg, 0.7 mmol), 2,4-dinitrophenylhydrazine (191 mg, 0.96 mmol) in CH_2Cl_2 (60 cm^3) and TFA (12 cm^3) was stirred at 0 °C for 2 h. The mixture was added to water (60 cm^3) and washed with CH_2Cl_2 (4 x 20 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered, evaporated and purified by flash chromatography on silica gel, eluting with light petroleum (b.p. 40-60 °C)-EtOAc (10:1), to give the hydrazone **19** (172 mg, 85%) as needles; m.p. 124-126 °C (lit.[10] 124-126 °C); δ_H (300 MHz, CD_3OD) 11.05 (1H, s, NH), 9.11 (1H, d, *J* 2.5, Ar), 8.33 (1H, dd, *J* 9.5 and 2.5, Ar), 7.98 (1H, d, *J* 9.5, Ar), 7.59 (1H, t, *J* 6, CH=N), 7.44-7.19 (5H, m, Ph), 3.76 (2H, d, *J* 6, $PhCH_2$) and, after freeze drying the aqueous layer, the bis-trifluoroacetate salt of 1,2-diaminocyclohexane as needles (163 mg, 68 %), m.p. (dec.) 191-192 °C.

Acknowledgements

We thank the E.P.S.R.C. for a studentship (to R.A.J.) and SmithKline Beecham Pharmaceuticals for a CASE award (to R.A.J.).

REFERENCES AND NOTES

1. Seebach, D. *Angew. Chem., Int. Ed. Engl.*, **1979**, *18*, 239; Beak, P.; Zajdel, W.J.; Reitz, D.B. *Chem. Rev.*, **1984**, *84*, 471; Meyers, A.I.; Beak, P. *Acc. Chem. Res.*, **1986**, *19*, 356; Gawley, R.E.; Rein, K. in *Comprehensive Organic Synthesis*, ed. Trost, B.M.; Fleming, I. **1991**, *3*, 65.
2. For some recent examples, see Hoppe, D.; *Angew. Chem., Int. Ed. Engl.*, **1997**, *36*, 2283; Lautens, M.; *J. Org. Chem.*, **1997**, *62*, 7080; Dieter, R.K.; *Tetrahedron Lett.*, **1997**, *38*, 5937;
3. Beak, P.; Basu, A.; Gallagher, D.J.; Park, Y.S.; Thayumanavan, S. *Acc. Chem. Res.*, **1996**, *29*, 552.
4. Coldham, I.; Houdayer, P.M.A.; Judkins, R.A.; Witty, D.R. *Synlett*, **1996**, 1109.
5. Katritzky, A.R.; Murugan, R.; Luce, H.; Zerner, M.; Ford, G.P. *J. Chem. Soc., Perkin Trans. 2*, **1987**, 1695.
6. Coldham, I.; Houdayer, P.M.A.; Judkins, R.A.; Witty, D.R. *Synthesis*, **1998**, 1463.
7. Colombo, L.; Di Giacomo, M.; Brusotti, G.; Delogu, G. *Tetrahedron Lett.*, **1994**, *35*, 2063.
8. Alexakis, A.; Tranchier, J.-P.; Lensen, N.; Mangeney, P. *J. Am. Chem. Soc.*, **1995**, *117*, 10767.
9. Colombo, L.; Di Giacomo, M.; Brusotti, G.; Milano, E. *Tetrahedron Lett.*, **1995**, *36*, 2863; P. O'Brien and S. Warren, *Tetrahedron: Asym.*, 1996, **7**, 3431.
10. Moskal, J.; van Leusen, A.M. *Recl. Trav. Chim. Pays-Bas*, **1987**, *106*, 137.