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Synthesis of Chiral 1,2-Diamines by Asymmetric Lithiation–Substitution

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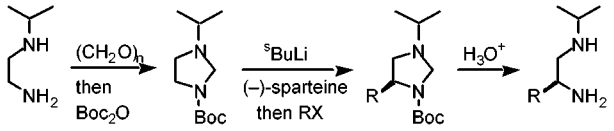
ABSTRACT



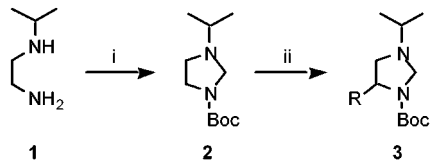
The imidazolidine (tetrahydroimidazole) 2, prepared in one step from *N-iso*-propylethylenediamine, was subjected to asymmetric lithiation and substitution using *sec*-butyllithium, (–)-sparteine and a range of electrophiles. Substituted imidazolidines were formed with high optical purity and could be hydrolyzed under acidic conditions to chiral, substituted ethylenediamines. Kinetic data indicate that the conformation of the carbonyl group is crucial to the extent of deprotonation, and this has implications for the lithiation of unsymmetrical carbamates and carboxylic amides.

Asymmetric deprotonation-substitution, typically with a 1:1 complex of *sec*-butyllithium and (−)-sparteine, has been exploited widely over the past decade for the formation of highly enantiomerically enriched products.[1] A typical example is the asymmetric deprotonation of *N*-Boc-pyrrolidine (Boc = *tert*-butoxycarbonyl), described by Beak and coworkers.[2] This reaction proceeds with very high selectivity for abstraction of the *pro-S* hydrogen atom at C-2 and leads, after electrophilic quench, to a variety of *N*-Boc-2-substituted pyrrolidines with very high optical purity.

Despite the widespread interest and usefulness of this procedure, there are very few extensions of this asymmetric lithiation−substitution protocol to other nitrogen-containing heterocycles.[3] Our studies[4] of the lithiation−substitution of symmetrical imidazolidines (tetrahydroimidazoles) led to the realization that this ring system would be amenable to an asymmetric deprotonation using an external chiral ligand such as (−)-sparteine. This paper reports the regio- and stereoselective lithiation and substitution of unsymmetrical imidazolidines, leading after acidic hydrolysis to chiral, substituted 1,2-diamines.[5]

The imidazolidine **2** was prepared in one pot from *N-iso*-propylethylenediamine **1**, paraformaldehyde, $MgSO_4$ and K_2CO_3, followed by addition of Boc_2O (Scheme 1).[6] It was anticipated that on addition of *sec*-butyllithium to the

Scheme 1. Preparation, Lithiation and Substitution of **2**[a]



[a] Reagents: (i) CH_2O, $CHCl_3$, $MgSO_4$, K_2CO_3, 95%; (ii) *s*-BuLi, THF, −78 °C, 1 h then Me_3SiCl, 50%; or *s*-BuLi, Et_2O, (−)-sparteine, −78 °C, 1 h then RX; see Table 1.

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(1) (a) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552. (b) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282.

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imidazolidine **2**, complexation to the carbonyl group would occur, leading to subsequent proton abstraction α- to the *N*-Boc group.[7] In contrast to the proton abstraction of the *N*,*N*′-bis-Boc analogue, which occurs at C-2, between the two nitrogen atoms,[4] addition of *sec*-BuLi to the imidazolidine **2** promoted exclusive deprotonation at C-5 to give, after electrophilic quench, the 5-substituted imidazolidine **3**. No products derived from proton abstraction at C-2 were isolated.

Using the standard conditions for asymmetric deprotonation, as described by Beak and co-workers,[2] with *sec*-BuLi in Et_2O and (−)-sparteine, the products **3** were formed with high optical purity (Table 1). A range of electrophiles could

Table 1. Asymmetric Lithiation−Substitution of **2**

entry	RX	yield **3** (%)[a]	er
1	Bu_3SnCl	40 (66)	94:6
2	Me_3SiCl	40 (67)	93:7
3	$Ph_2MeSiCl$	44 (86)	94:6
4	$Ph_2C{=}O$	50 (86)	92:8
5	MeI	44 (76)	92:8
6	$CH_2{=}CHCH_2Br$	40 (66)	50:50

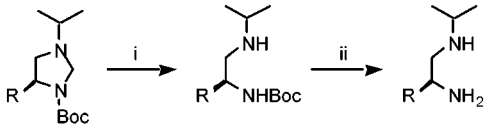
[a] Yields in brackets refer to yields based on recovered **2**.

be used to trap the organolithium species, with results similar to those for the related *N*-Boc-pyrrolidine substrate. Thus, no evidence for single electron-transfer processes were apparent using the electrophile benzophenone (entry 4), which provided the quenched product with high optical purity; however the electrophile allyl bromide produced racemic product (entry 6).

The enantiomeric ratios of the products **3** were determined either by chiral HPLC (Gilson 231 XL column, type AD) or by NMR of the ring-opened Mosher amide derivatives.

Hydrolysis of the imidazolidine **3** (carried out for R = $SiMe_3$, $SiMePh_2$, Me, allyl) using malonic acid resulted in the selective formation of the amino-carbamate **4**, without loss of the *N*-Boc group (Scheme 2). Subsequent treatment

Scheme 2. Hydrolysis of 3[a]



3 **4** **5**

[a] Reagents: (i) $CH_2(CO_2H)_2$, pyridine, EtOH, heat; (ii) CF_3CO_2H, CH_2Cl_2, rt.

with trifluoroacetic acid (TFA) promoted further hydrolysis to the diamine **5**. The diamine **5** can alternatively be prepared in one step by treatment of the imidazolidine **3** with TFA. The yields of the products **4** and **5** (yield of **5** from **4**) are shown in Table 2.

Table 2. Yields for the Hydrolysis of Imidazolidines **3**

entry	R	yield **4** (%)	yield **5** (%)
1	Me_3Si	84	90
2	Ph_2MeSi	80	99
3	Me	99	82
4	$CH_2{=}CHCH_2$	96	87

The mechanism of asymmetric induction follows an asymmetric lithiation rather than an asymmetric substitution reaction, since treating the racemic stannane **3**, R = $SnBu_3$ with *n*-BuLi and (−)-sparteine in Et_2O, followed by quenching with Me_3SiCl, gave the silane **3**, R = $SiMe_3$ as a racemic mixture. In addition, the enantiomerically enriched stannane **3** could be transmetalated in the absence of (−)-sparteine and quenched with Me_3SiCl to give the silane **3**, R = $SiMe_3$ with good optical purity, thus illustrating that the chiral organolithium species derived from the imidazolidine **2** can maintain its optical purity. These results are consistent with those using *N*-Boc-pyrrolidine, and we anticipate therefore that the major enantiomer of the imidazolidine **3** has the absolute configuration with the (*S*)-stereochemistry at C-5 [(*R*)-stereochemistry by definition for **3**, R = $C(OH)Ph_2$]. This was confirmed by a single-crystal X-ray diffraction study of the product **3**, R = $C(OH)Ph_2$ (Figure 1).[8] Recrys-

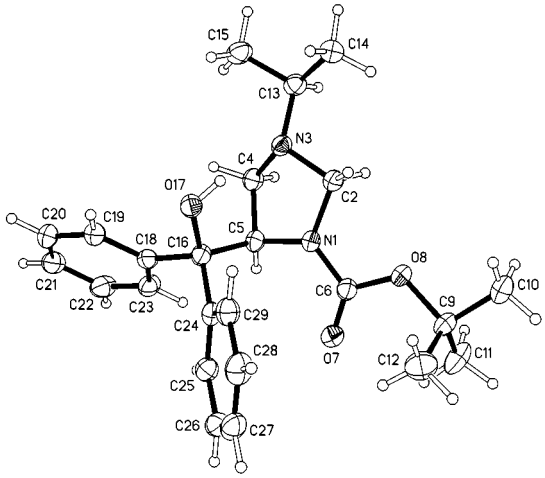


Figure 1. X-ray Structure of **3**, R = $C(OH)Ph_2$. Anisotropic atomic displacement ellipsoids for the non-hydrogen atoms are shown at the 50% probability level.

tallization of the product **3**, R = $C(OH)Ph_2$ gave crystals suitable for X-ray analysis which were determined (HPLC)

(4) Coldham, I.; Judkins, R. A.; Witty, D. R. *Tetrahedron* **1998**, *54*, 14255.

(5) For a review on 1,2-diamines, see Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.

(6) Coldham, I.; Houdayer, P. M. A.; Judkins, R. A.; Witty, D. R. *Synthesis* **1998**, 1463.

(7) For deprotonation and diastereoselective quench of a related imidazolidine, see: Pfammatter, E.; Seebach, D. *Liebigs Ann. Chem.* **1991**, 1323.

to be essentially enantiopure (>99.8% ee). On the basis of the refined absolute structure parameter,[9] the chiral center at C-5 was assigned the expected (*R*)-configuration. The X-ray structure shows an intramolecular hydrogen bond between the OH group and N-3.

In each deprotonation reaction to give the imidazolidine **3**, a substantial quantity of the starting material **2** was recovered, and this could be separated from the product **3** by conventional column chromatography. Experiments with excess *sec*-BuLi, longer reaction times, or inverse addition of the electrophile did not improve this result, which contrasts with the significantly higher yields obtained from the asymmetric lithiation and substitution of *N*-Boc-pyrrolidine. To gain further insight into the reasons for the low yields, we carried out the deprotonation at low temperature in d_8-THF and obtained the resulting ^{1}H and ^{13}C NMR spectra. Before addition of *s*-BuLi, as a result of slow rotation of the carbamate group, both conformers of the imidazolidine **2** are present in a 1:1 ratio.[10] On addition of 1 equiv of the base at −78 °C, the signals for one of the two conformers disappeared and were replaced by broad signals typical of an organolithium species. The other conformer remained unchanged, even on warming to about −40 °C, above which temperature or after more than about 1 h, marked decomposition occurred. These results indicate that only one conformer is deprotonated and support the hypothesis that initial complex formation precedes proton abstraction.[11] Presumably only the conformer in which the carbonyl oxygen atom is *cis* to C-5 of the imidazolidine ring undergoes deprotonation. This result contrasts with the few reported deprotonations of unsymmetrical, cyclic *N*-Boc compounds, in which yields over 50% have been reported.[3a−c] In these cases, some rotation about the carbamate C−N bond must be possible under the reaction conditions, or there must be a thermodynamic preference for one of the two conformers.

To probe the rate of isomerization of the two conformers, the imidazolidine **2** was warmed in d_6-DMSO and studied by ^{13}C NMR spectroscopy.[12] Coalescence of a number of signals was observed; for example, coalescence of C-5 (δ 44.78 and 45.18 ppm)[10] occurred at approximately 60 °C (333 K), which corresponded to a rate constant $k = 88.6\ s^{-1}$ and therefore a half-life $t_{1/2} \approx 7.8 \times 10^{-3}$ s at this temperature. This corresponds to a barrier to rotation $\Delta G^{\ddagger} \approx 69.4\ kJ\ mol^{-1}$ at 333 K. Assuming that the change in entropy is close to zero, then this value of $\Delta G^{\ddagger}$ gives a half-life for rotation $t_{1/2} > 100$ h at −78 °C. This large half-life explains why only one conformer undergoes proton abstraction at this temperature and therefore the observed limitation in the yield. On warming, however, rotation becomes increasingly faster, and at −40 °C, the half-life can be calculated to decrease to approximately $t_{1/2} \approx 10$ min. This value would suggest that higher yields could be obtained on warming; however no enhancement of the yield of the products **3** was obtained at this temperature (e.g., −40 °C, 1 h, **3**, R = $SiMe_3$ 40% + recovered **2**, 34%). On warming above −40 °C, decomposition of the imidazolidine **2** in the presence of *s*-BuLi occurs. It seems that the organolithium species derived from the imidazolidine **2** is at the limit of stability prior to significant rotation of the *N*-Boc group and that the half-life for rotation of the carbamate in THF or Et_2O/(−)-sparteine may be slightly longer than that calculated above.

In summary, we have shown that it is possible to obtain chiral 1,2-diamines with high optical purity using asymmetric deprotonation and electrophilic quench. With the imidazolidine **2**, the extent of deprotonation is restricted to about 50% as a result of slow rotation of the *N*-Boc group. The rate of rotation about the *N*-CO bond is clearly of crucial importance in deprotonation chemistry and may influence the outcome of other examples involving unsymmetrical carbamates or carboxylic amides.

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Supporting Information Available: X-ray coordinates for imidazolidine **3**, R = $C(OH)Ph_2$; NMR spectra for imidazolidine **2** in the absence and presence of *s*-BuLi in d_8-THF and on warming in d_6-DMSO; experimental procedure for the asymmetric deprotonation and quench and for the hydrolysis; spectroscopic data for compounds **3**, **4** and **5**, R = $SiMe_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Crystal structure determination for **3**, R = $C(OH)Ph_2$: $C_{24}H_{32}N_2O_3$; $M = 396.52$; colorless block, 0.28 × 0.22 × 0.08 mm^3; monoclinic, space group $P2_1$ (No. 4); $a = 6.0081(2)$ Å, $b = 20.5769(9)$ Å, $c = 9.1980(4)$ Å, $\beta = 103.3930(10)°$, $V = 1106.20(13)$ Å$_3$; $Z = 2$; $T = 150(2)$ K.; $d_{calc} = 1.190$ g cm^{-3}; F(000) = 428; μ(Cu Kα, $\lambda = 1.54178$ Å) = 0.621 mm^{-1}; 10583 reflections collected; absorption correction by integration; 3843 unique reflections; $R_{int} = 0.0205$; $R_1 = 0.0261$; $wR_2 = 0.0699$; absolute structure parameter = 0.10(13).

(9) Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876.

(10) For plots of the NMR spectra, see Supporting Information.

(11) Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1995**, *60*, 7092.

(12) The barrier to rotation in carbamates is similarly little by the solvent: Cox, C.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 2426.