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An Asymmetric Synthesis of (1*S*,4*R*)-4-Amino-2-cyclopentenol Derivatives

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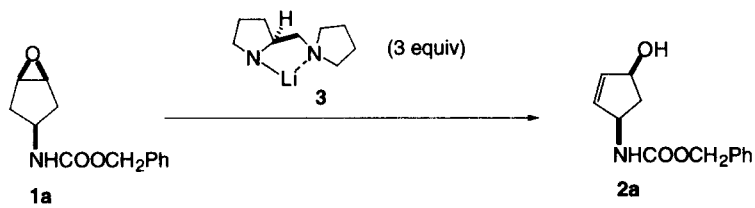
Abstract: A highly enantioselective deprotonation of *cis*-4-aminocyclopentene oxide derivatives **1** was achieved by using a chiral lithium amide, prepared from (2*S*,3a*S*,7a*S*)-2-(pyrrolidin-1-ylmethyl)-octahydroindole. (1*S*,4*R*)-4-Amino-2-cyclopentenol derivative **2** was obtained in up to 90% ee.

Keywords: deprotonation; enantioselection; epoxides; rearrangement

Asymmetric reaction using chiral lithium amide is emerging for the preparation of non-racemic compounds from prochiral compounds.[1] We have been studying the enantioselective deprotonation of *meso*-epoxides using chiral lithium pyrrolidide derivatives[2,3] and found that high selectivity was achieved for 4-alkoxy or 4-alkoxymethylcyclopentene oxide derivatives.[3] Then we began to investigate the reaction of 4-amino-cyclopentene oxide derivative **1** with chiral lithium amide,[4] because the product, 4-amino-2-cyclopentenol derivative **2**, is employed as a useful intermediate for syntheses of carbocyclic nucleosides and their analogues.[5] Here we wish to report a facile method for the synthesis of (1*S*,4*R*)-4-benzyloxycarbonylamino-2-cyclopentenol (**2a**) and (1*S*,4*R*)-4-benzoylamino-2-cyclopentenol (**2b**), and their transformation to the corresponding cyclopentenone derivatives **5a,b**.[6]

4-Benzyloxycarbonylaminocyclopentene oxide and 4-benzoylaminocyclopentene oxide were obtained in 76% (*cis*:*trans*=86:14) and 67% (*cis*:*trans*=98:2), respectively, in two steps from 4-aminocyclopentene hydrochloride according to a reported method.[7] The *cis*-isomers **1a**[8] (65%, mp 46.8-48.4 ℃) and **1b**[7,8] (66%, mp 89.1-90.9 ℃ (lit.[7] mp 84 ℃)) were then separated from the corresponding *trans*-isomers by silica-gel column chromatography.

In our previous work, high yield and selectivity were obtained using non polar solvent in the reaction of



Toluene, 20 °C, 7.5 h	19%, 41%ee
THF, 20 °C, 4 h	61%, 74%ee
THF, 3.3 equiv DBU, 20 °C, 4 h	59%, 83%ee

Scheme 1

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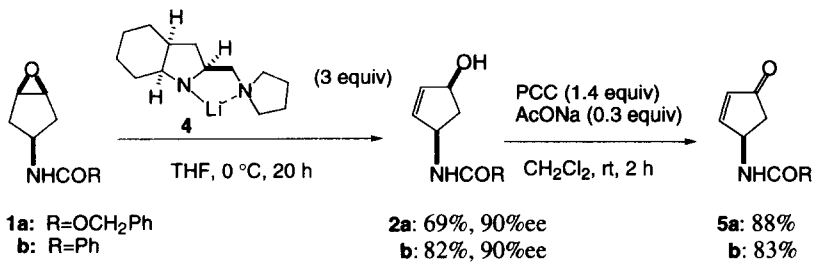
cis-4-alkoxycyclopentene oxide and lithium (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidide (**3**).[3a] Therefore we firstly examined the reaction of **1a** using **3** (3.0 equiv) in toluene at 20 ℃. (1*S*,4*R*)-4-Benzyloxycarbonylamino-2-cyclopentenol (**2a**)[5c,8] (mp 82.2-83.5 ℃) was obtained after 7.5 h at 20 ℃, but, the yield and selectivity were low (19%, 41%ee).[9] Both the yield and selectivity were improved by carrying out the reaction in THF (20 ℃, 4 h, 61%, 74%ee), and good selectivity was obtained when 1,8-diazabicycloundec-7-ene (DBU) (3.3 equiv) was used as an additive (20 ℃, 4 h, 59%, 83%ee) (Scheme 1).

Another chiral lithium amide **4**, derived from (2*S*,3a*S*,7a*S*)-2-(pyrrolidin-1-ylmethyl)octahydroindole,[2b] was also examined in the reaction in order to enhance the selectivity. Alcohol **2a** was obtained in 83% yield with high selectivity (89%ee) without using DBU (20 ℃, 4 h). The selectivity was slightly improved (90%ee, $[\alpha]_D^{20}$ +55.8 (*c* 0.2, $CHCl_3$)) when the reaction was conducted at 0 ℃ (20 h). (1*S*,4*R*)-4-Benzoylamino-2-cyclopentenol (**2b**)[4,8,9] (mp 95.8-97.2 ℃, $[\alpha]_D^{20}$ +144.9 (*c* 1.0, $CHCl_3$)) was also obtained in good yield with high ee by the reaction of the corresponding epoxide **1b** and **4** (0 ℃, 20 h, 82%, 90%ee). We next examined the transformation of **2** into 4-amino-2-cyclopentenone derivative **5**, which was used in carbapenem synthesis in racemic form.[10,11] (*R*)-4-Benzyloxycarbonylamino-2-cyclopentenone (**5a**)[8] (mp 72.3-73.5 ℃, $[\alpha]_D^{20}$ +65.8 (*c* 1.0, $CHCl_3$)) and (*R*)-4-benzoylamino-2-cyclopentenone (**5b**)[8] (mp 149.8-150.8 ℃, $[\alpha]_D^{20}$ +175.6 (*c* 0.5, $CHCl_3$)) were obtained in good yield by the oxidation of (1*S*,4*R*)-**2a** or **2b** with pyridinium chlorochromate (PCC) (Scheme 2).



Scheme 2

In summary, a convenient method for the preparation of useful chiral synthetic blocks **2** and **5** in high ee was developed by the enantioselective deprotonation of *meso*-epoxide **1** by chiral lithium amide **4**.

References and Notes

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