Synthesis of a New Chiral Auxiliary, (1*R*,2*R*,3*R*,6*R*)-3,6-Dimethylcyclohexane-1,2-diamine

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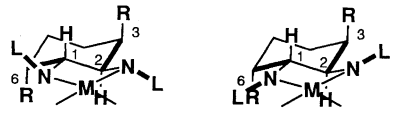
(1*R*,2*R*,3*R*,6*R*)-3,6-Dimethylcyclohexane-1,2-diamine which was expected to serve as an effective chiral auxiliary, was synthesized from (*R*)-(+)-3-methylcyclohexanone enantiospecifically in a straightforward manner.

N-Arylsulfonyl, *N*-alkyl, and Schiff base derivatives of cyclohexane-1,2-diamine have been used as effective chiral auxiliaries in various types of reactions including asymmetric cyclopropanation, epoxidation, dihydroxylation, aziridination, and oxidation of sulfides.[1] These diamine derivatives form complexes with various metal ions, the coordination atmospheres of which are regulated by the substituents on the nitrogen atoms.

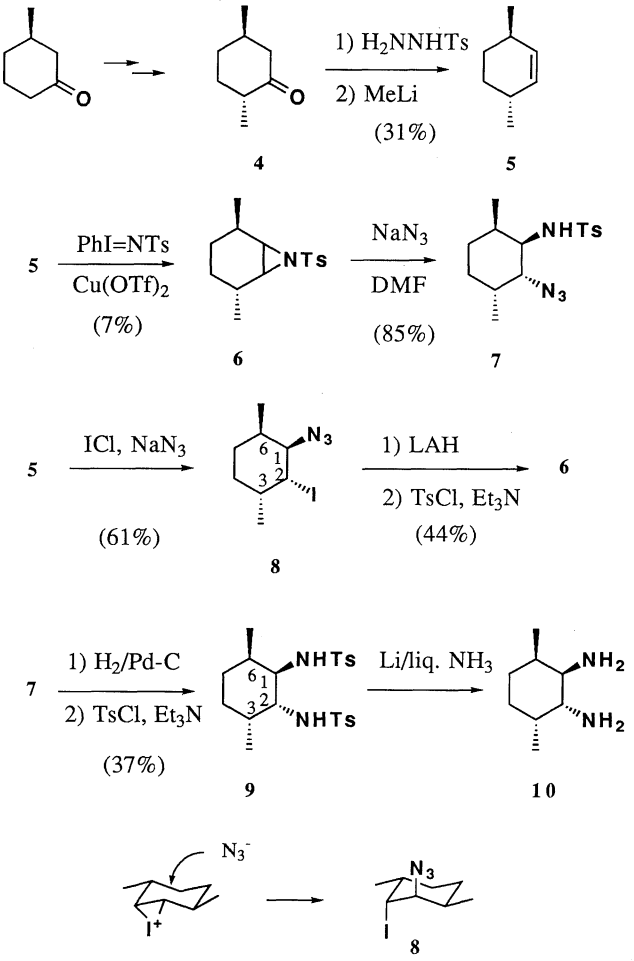
Although the *N*-substituents of the metalated cyclohexanediamine derivatives are oriented to minimize the tortional strain between the *N*-substituent and the cyclohexane ring, we expected that the desired conformation of the *N*-substituents would be further favored by steric effect, if some substituents are properly introduced onto the cyclohexane ring. As shown in Figure 1, the orientation of the *N*-substituents disfavored by the tortional strain between N-L bond (e.g., L= SO_2Ar) and C1-C6 bond (or C2-C3 bond) was considered to be further destabilized by the introduction of bulky C3- and C6-axial substituents. Thus, 3,6-diaxially substituted cyclohexanediamine was expected to serve as a more effective chiral auxiliary. Based on this analysis, we planned to synthesize (1*R*,2*R*,3*R*,6*R*)-3,6-dimethylcyclohexane-1,2-diamine as a new chiral auxiliary.



favorable orientation unfavorable orientation

Figure 1. The view of the cyclohexanediamine derivatives complexed with metal ion

The synthesis of (1*R*,2*R*,3*R*,6*R*)-3,6-dimethylcylohexane-1,2-diamine started from commercial (*R*)-(+)-3-methylcyclohexanone that was converted into (2*R*,5*R*)-2,5-dimethylcyclohexanone (**4**) according to the literature procedure (Scheme 1).[2] Although compound **4** was contaminated by its (2*S*,5*R*)-isomer (20%), it was used for the next reaction without purification. Compound **4** was then converted into the corresponding tosylhydrazone which was purified by silica gel chromatography and subsequent recrystallization from ethanol, and subjected to Shapiro reaction to give (3*R*,6*R*)-3,6-dimethylcyclohexene (**5**). Compound **5** was first subjected to copper-catalyzed aziridination under Evans' conditions,[3] but the reaction gave a complex mixture and the desired aziridine (**6**)[4] was obtained only in 7% yield after tedious chromatographic separation. Compound **5** was then treated with iodo chloride in the presence of sodium azide to give iodo azide **8**[4] as a single isomer. Although the stereochemistry of **8** has not been determined, it was considered to be 1*R*,2*R*,3*R*,6*R*, since an azide anion attack the intermediary iodonium ion to give the diaxial iodo azide for stereoelectronic reason. LAH reduction of **8** followed by tosylation gave tosylaziridine **6**. Treatment of **6** with sodium azide gave azide **7**[4] together with a small amount of diastereomer (7%) which was separated from **7** by silica gel chromatography. Azide **7** was reduced by catalytic hydrogenation in ethyl acetate to the corresponding amine and then tosylated to ditosylamine **9**.[4] The stereochemistry of **9** was confirmed to be 1,2-*trans*, 2,3-*cis*, 1,6-*cis* by NMR analysis.[5] Compound **9** should serve as an effective chiral auxiliary. Compound **9** was further reduced by treatment with lithium in liquid ammonia to give diamine **10** which could be in situ derivatized.[6] For example, subsequent treatment of an alcoholic solution of **10** with (a*S*)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthyl[7] and manganese acetate gave a new Mn-salen catalysts which was found to be an effective catalyst for the



Scheme 1.

asymmetric epoxidation of conjugated *cis*-olefins.[8]

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References and Notes

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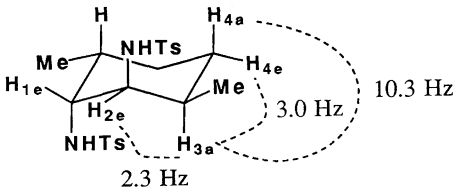
4 **6**: IR (KBr) 2928, 1599, 1157, 934, 849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, 2H, J= 8.1 Hz), 7.32 (d, 2H, J= 8.1 Hz), 2.84 (dd, 1H, J= 7.3, 2.9 Hz), 2.77 (d, 1H, J= 7.3 Hz), 2.44 (s, 3H), 1.85–1.72 (m, 2H), 1.61–1.58 (m, 1H), 1.33–1.29 (m, 1H), 1.06 (d, 3H, J= 6.8 Hz), 1.02–0.92 (m, 1H), 0.84–0.74 (m, 1H), 0.72 (d, 3H, J= 6.8 Hz); $[\alpha]_D^{24}$ +3.6° (c 0.6, $CHCl_3$)
7: IR (KBr) 3292, 2963, 2100, 1599, 816, 667, 590, 552 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, 2H, J= 8.1 Hz), 7.32 (d, 2H, J= 8.1 Hz), 4.62 (d, 1H, J= 7.6 Hz), 3.58 (dd, 1H, J= 2.9, 2.4 Hz), 3.27 (ddd, 1H, J= 7.6, 3.4, 2.4 Hz), 2.44 (s, 3H), 1.89–1.80 (m, 2H), 1.45–1.33 (m, 2H), 1.26–1.16 (m, 1H), 0.94 (d, 3H, J= 6.8 Hz), 0.97–0.85 (m, 1H), 0.53 (d, 3H, J= 6.8 Hz); $[\alpha]_D^{24}$ +88.8° (c 1.0, $CHCl_3$)
8: IR (KBr) 2097, 1654, 1259 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.77 (dd, 1H, J= 2.6, 2.0 Hz), 4.54 (dd, 1H, J= 3.0, 2.0 Hz), 2.73–2.64 (m, 1H), 1.61–1.18 (m, 5H), 1.00 (d, 3H, J= 6.6 Hz), 0.92 (d, 3H, J= 5.9 Hz); $[\alpha]_D^{24}$ +12.8° (c 1.0, $CHCl_3$)
9: IR (KBr) 3294, 2962, 1597, 937, 814, 669, 592, 553 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.75 (d, 4H, J= 8.1 Hz), 7.34 (d, 4H, J= 8.1 Hz), 4.42 (d, 2H, J= 6.3 Hz), 3.30 (dd, 2H, J= 6.3, 2.3 Hz), 2.45 (s, 6H), 1.89–1.82 (m, 2H), 1.42–1.39 (m, 2H), 0.96–0.90 (m, 2H), 0.44 (d, 6H, J= 6.8 Hz); $[\alpha]_D^{24}$ +194.1° (c 0.17, $CHCl_3$); MS(EI) m/z 450 (M^+).

5 ^1H NMR decoupling revealed the coupling constants described below, demonstrating to be 1,2-*trans*, 2,3-*cis*, 1,6-*cis*.



6 Since compound **10** is hygroscopic, it was usually used for the next reaction without isolation. However, **10** was isolated as the salt of trifluoroacetic acid by the following procedure: The reaction mixture of **9** and lithium in liquid ammonia was evaporated and diluted with THF. The THF solution was treated with $(t\text{-BuOCO})_2O$ at room temperature for 2 h and chromatographed on silica gel to give the corresponding di-*t*-butoxycarbonylated **10** (di-BOC **10**). Di-BOC **10** was exposed to trifluoroacetic acid at room temperature for 1 h and concentrated *in vacuo* to give the ditrifluoroacetate of **10** as a syrup: IR (neat) 2940, 1681, 1205, 1140, 843, 800, 725 cm^{-1}; ^1H NMR (270 MHz, D_2O) δ 3.37-3.27 (m, 2H), 1.84-1.72 (m, 2H), 1.56-1.39 (m, 2H), 1.17-1.05 (m, 2H), 0.79 (d, 6 H, J= 6.9 Hz).

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8 See the succeeding paper.