[2.2]Paracyclophane-Derived *N*-Acyloxazol-2(3*H*)-one as a Suitable Planar Chiral Auxiliary for the Enantioselective Synthesis of β-Hydroxy Acids

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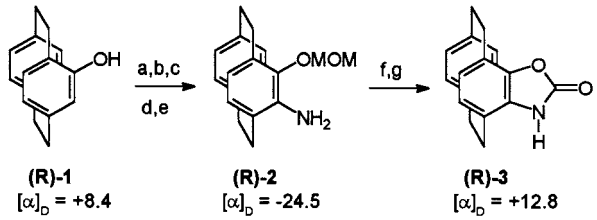
The synthesis of optically active (+)-(*R*)-[2.2]paracyclophano[4,5-*d*]-oxazol-2(3*H*)-one is described. The aldol reaction of *N*-acyl derivatives of this planar chiral auxiliary with beazaldehyde occurs with good diastereo- and enantioselectivity.

Chiral 1,3-oxazolidinones are versatile auxiliaries for many asymmetric transformations. Only chiral oxazolidinones with central chirality are known.[1]

Recently[2] we reported an efficient route to both enantiomers of 4-hydroxy[2.2]paracyclophane and noted their absolute configuration.[2,3] We were attracted by the idea that these compounds could be suitable precursors for preparing oxazolones with planar chirality.

Here we report the preliminary results of the synthesis of the first planar chiral oxazol-2(3*H*)-one derived from (+)-(*R*)-4-hydroxy[2.2]paracyclophane **1**, as well as examples of its application as chiral auxiliary for the enantioselective synthesis of β-hydroxy acids.

Ortho-directed metallation of MOM-protected **1** with *n*-butyllithium (Scheme 1) followed by the nucleophilic attack of lithio-derivative with *p*-TsN_3 gives the corresponding azido-derivative which was reduced by $LiAlH_4$ to give (-)-(*R*)-4-OMOM-5-amino[2.2]paracyclophane (**2**). Deprotection of **2** followed by the reaction of the resulting hydroxyamino-derivative with ethyl chloroformate produces (+)-(*R*)-[2.2]paracyclophano[4,5-*d*]-oxazol-2(3*H*)-one (**3**) as a stable and optically pure compound in ca. 30% overall yield.



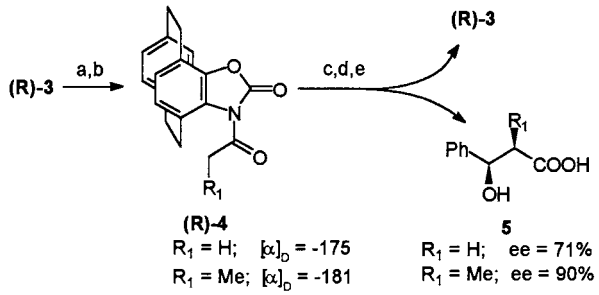
(R)-1 $[\alpha]_D$ = +8.4 **(R)-2** $[\alpha]_D$ = -24.5 **(R)-3** $[\alpha]_D$ = +12.8

a. NaH; b. CH_2ClOMe; c. BuLi; d. *p*-TsN_3; e. $LiAlH_4$; f. HCl; g. $ClCO_2Et$. Spectroscopic data (^{1}H-, ^{13}C-NMR, IR) and elemental analyses support the assigned structures.

Scheme 1.

The aldol reaction of *N*-acyloxazol-2(3*H*)-ones **4** with benzaldehyde was chosen to test the effectiveness of the [2.2]paracyclophane moiety as chiral auxiliary.

Optically active acetyl- and propionyl-oxazol-2(3*H*)-ones **4**, prepared according to the standard procedure[1b] (Scheme 2), were first treated with Bu_2BOTf/Et_3N to give boron enolates which were allowed to react with benzaldehyde at 0 °C. Oxidative workup allowed as to isolate (+)-(*R*)-3-phenyl-3-hydroxypropionic acid (**5**, R_1 = H; ee 71%) and (+)-(*2R, 3R*)-*syn*-2-methyl-3-phenyl-3-hydroxypropionic acid (**5**, R_1 = Me; ee 90%; *syn/anti* = 80/20) respectively, in good yield (70-75%).[4,5]

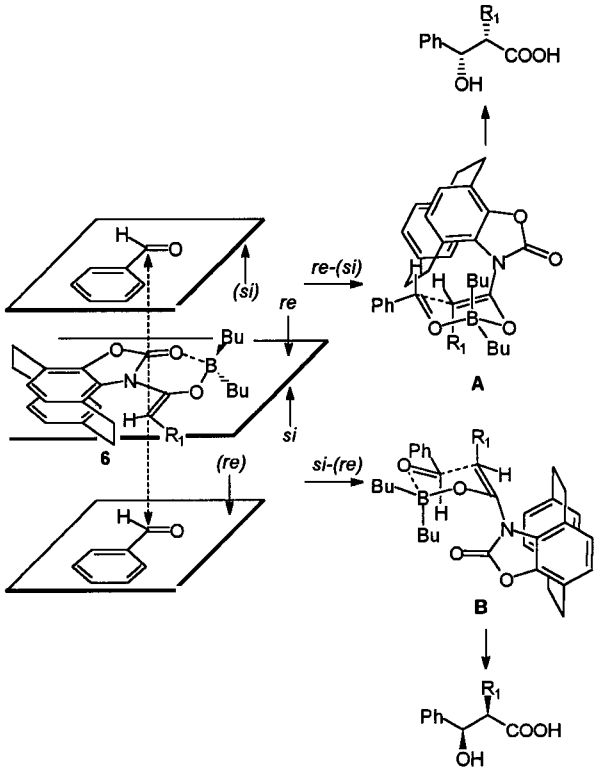


(R)-4 R_1 = H; $[\alpha]_D$ = -175 R_1 = Me; $[\alpha]_D$ = -181

5 R_1 = H; ee = 71% R_1 = Me; ee = 90%

a. BuLi; b. R_1CH_2COCl; c. Bu_2BOTf/Et_3N; d. PhCHO; e. H_2O_2. Spectroscopic data (^{1}H-, ^{13}C-NMR, IR) and elemental analyses support the structure of **4**.

Scheme 2.



Scheme 3.

The cleavage of the auxiliary is quantitative, very easy, occurs in a completely exocyclic way and does not require a specific treatment. The oxazolone **3**, separated during the oxidative workup, is recycled.

The enantioselectivity of the reaction can be explained by considering that the the double bond of boron enolates **6**[6] reacts preferentially with its *si*-face on the *re*-face of benzaldehyde (Scheme 3) via the closed transition state **B** as proposed by Evans et al.[7] The addition of the *re*-face of enolate on the *si*-face of benzaldehyde is obstructed by steric interaction of the phenyl ring with the C_7-C_8 ethylene bridge of the [2.2]paracyclophane moiety and the transition state **A** is less preferred than **B**. The strong steric interactions of the phenyl ring with the ethylene bridge of the [2.2]paracyclophane moiety and Bu-Ph 1,3-diaxial interactions are an obstacle to the formation of *anti* aldols.

The (+)-(*R*)-[2.2]paracyclophano[4,5-*d*]-oxazol-2(3*H*)-one (**3**) is a promising chiral auxiliary for many asymmetric reactions via the corresponding chiral imide enolate. Both enantiomers of **3** are available and the removal of the auxiliary is easy and quantitative. Studies on synthetic applications are in progress.

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References and Notes

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4 The configuration of **5** was proven by comparison with authentic specimens.[5]

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6 The boron enolate **6** (R_1 = Me) has been assumed to have *Z*-configuration because this is the stereochemistry of boron enolates of 5-substituted acyloxazolidinones.[1] The C7-C8 ethylene bridge of [2.2]paracyclophane moiety favours this configuration.

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