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Enhanced enantiostability of BINOL dimethyl ether under moderate acidic conditions

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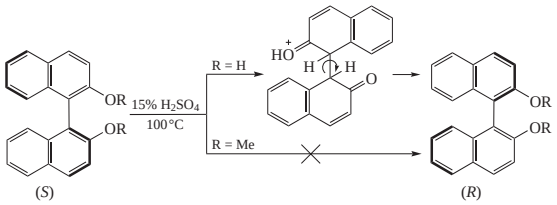
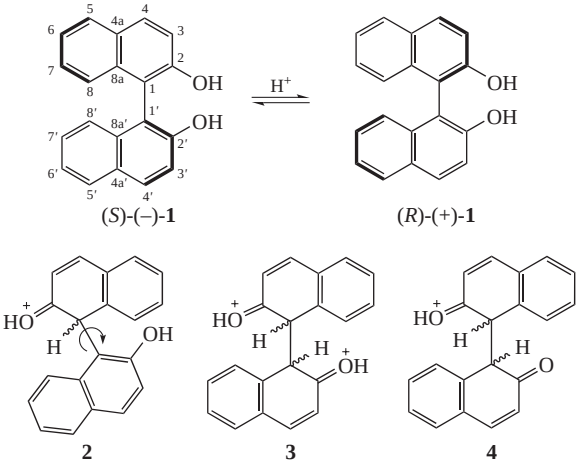
Compared with the parent 1,1′-bi-2-naphthol (BINOL), its dimethyl ether is highly resistant towards racemization under moderate acidic conditions. This finding confirms the hypothetical mechanism of BINOL atropisomerization including internal rotation around the $C^{1}_{sp^3}$–$C^{1'}_{sp^3}$ bond in its protonated forms.



1,1′-Bi-2-naphthol (BINOL) **1** and its derivatives are the well known axially chiral molecules of high practical importance.[1] Sufficient resistance toward atropisomerization is the key feature for their application in asymmetric synthesis and catalysis. In spite of considerable stability under neutral conditions, enantiomers (*R*)-**1** and (*S*)-**1** are known to readily racemize in both acidic and basic solutions.[1,2] For instance, (*S*)-**1** is 72% racemized in 1.2 N HCl / 1,4-dioxane at 100 °C for 24 h.[2(a)] Similarly, refluxing of (*S*)-**1** with 15% D_2SO_4–D_2O / 1,4-dioxane gives 11% of (*R*)-**1** within 15 h.[3] Up to now, mechanistic aspects of atropisomerization of **1** had many unclear points.[2(c)] Generally accepted mechanism for the acid-catalyzed atropisomerization of **1** involves the intermediacy of the C^1-protonated form **2**, which is deemed to ensure the naphthyl ring rotation around the C_{sp^2}–C_{sp^3} bond (Scheme 1).[1,2] However, on the basis of the protonation behavior of **1** in variety of (super)acid media, we have recently demonstrated that atropisomerization of **1** really proceeds *via* rotation around the C_{sp^3}–C_{sp^3} bond either in the C^1,$C^{1'}$-diprotonated form **3** or in the C^1-monoprotonated keto form **4**.[3] At that, it has been argued that dication **3** can emerge in superacids only, while monocationic keto form **4** is the key intermediate in aqueous mineral acids. If this supposition is true, a simple but quite logical consequence follows. Those derivatives of **1** should be resistant towards racemization, which are unable to undergo tautomerization (to form intermediates like structure **4**).

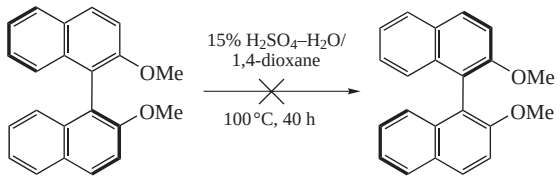


Scheme 1

In order to confirm (or discard) this hypothesis experimentally and to verify the practical possibility of controlling the atropisomerization stability of simple BINOLs, here we have investigated behavior of (*S*)-BINOL dimethyl ether (*S*)-**5** in H_2SO_4–H_2O / 1,4-dioxane medium. Similar conditions previously[3] caused racemization of (*S*)-**1**.

Notably, in contrast to BINOL **1** and its polar derivatives,[3–5] determination of the enantiomeric composition of diether **5** by chiral HPLC is problematic.[6] Also, we did not succeed in the ^{1}H and ^{13}C NMR chiral discrimination of **5** using quinine (6 equiv.), a typical chiral solvating agent (CSA) for some derivatives of **1**.[7] Here, therefore, racemization of (*S*)-**5** was initially quantified by ^{13}C NMR using (–)-isopulegol as CSA. However, the use of (–)-isopulegol–$CDCl_3$ (1 : 1, v/v) appeared to provide discrimination only between signals of C^1, C^3 and *C*(OMe) in (*S*)-**5** and (*R*)-**5**. Moreover, due to negligible solubility of **5** in (–)-isopulegol and because of weak splitting of the signals (about 0.01 ppm) the detection limit for the enantiomeric impurity is at the level of 2%, which is insufficient for the validity of the method. Fortunately, the use of chiral lanthanide shift reagent, $Eu(hfc)_3$ (0.1 equiv.), combined with the ^{1}H NMR, turned out to be a much more fruitful approach. All the ^{1}H NMR signals of racemic **5** have shown splitting, except those of atoms H^3 and H^4. The detection limit of the enantiomeric purity was at least 0.5% in that case. Nevertheless, despite the increased sensitivity of detection, no traces of (*R*)-**5** was observed in the sample of (*S*)-**5** after treatment with H_2SO_4–H_2O / 1,4-dioxane (Scheme 2).[†]

[†] For the synthesis of (*S*)-**5** and NMR determination of enantiomeric composition of the product obtained by its treatment with H_2SO_4–H_2O / 1,4-dioxane, see Online Supplementary Materials.



(*S*)-**5** (*R*)-**5**

Scheme 2

Thus, in contrast to parent (*S*)-**1**, its dimethyl ether (*S*)-**5** is highly resistant to racemization under the same moderate acidic conditions. Unlike compound **1**, its derivative **5** cannot produce tautomeric keto form analogous to **4**. Generation of the C^1,$C^{1'}$-diprotonated form of **5** (analogous to dication **3**) is also impossible under employed reaction conditions due to insufficient acidity[3] and taking into account that protonation behavior of naphthols and their methyl ethers is normally comparable.[8] Therefore, it can be concluded that the observed dramatic difference in the atropisomerization of **1** and **5** provides indirect confirmation for the hypothesis that atropisomerization of **1** proceeds *via* rotation around the $C^1_{sp^3}$–$C^{1'}_{sp^3}$ bond in its protonated forms **3** and **4**.

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Diether (*S*)-**5** (20 mg, 0.07 mmol) was added to a solution of H_2SO_4 (700 mg, 7 mmol) in H_2O (4 ml) and 1,4-dioxane (7 ml). The solution was stirred under reflux (~100 °C) for 40 h, then poured onto ice and extracted with Et_2O. The ethereal extract was washed with aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to recover back enantiomerically pure compound (*S*)-**5**.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.01.007.

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