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A chiral ketone for enantioselective recognition of 1,2-amino alcohols

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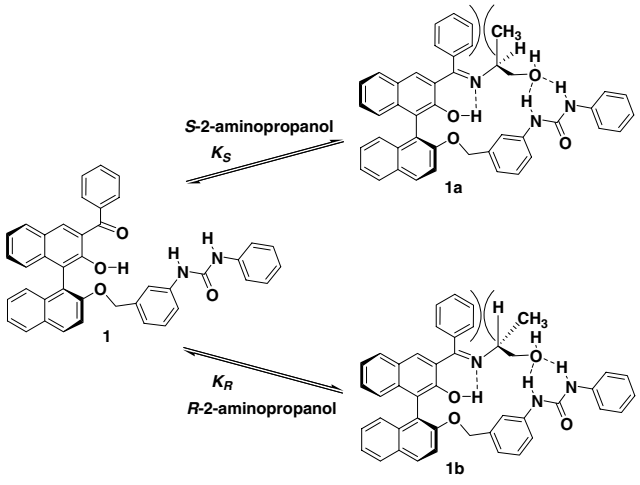
Abstract—A novel auxillary chiral ketone has been designed, synthesized, and used to enantioselectively recognize 1,2-amino alcohols. This work proves that the keto group can serve as a chiral recognition center by imine formation supported by resonance assisted hydrogen bonding (RAHB).

The development of synthetic molecular receptors as chiral hosts capable of exhibiting enantiomeric differentiation towards racemic guests has become an important and rapidly growing field of chemistry. Recent work has led to the design and synthesis of chiral hosts for alkaloids,[1] peptides,[2] amino acids,[3] amino alcohols[4–6] and other neutral guests.[7] In particular, chiral discrimination of amino alcohols by molecular receptors needs much attention because of their importance as vital intermediates for establishing a wide spectrum of biologically active molecules[8] and also as ligands for stereoselective catalysts.[9]

Many molecular recognition studies are based on non-covalent interactions such as hydrogen bonding, metal coordination, etc. Our recent works[10] proved that an aldehyde can be a good stereoselective recognition center for 1,2-amino alcohols via reversible imine formation with resonance assisted hydrogen bonding.[11] Although keto compound acetone was known to racemize amino acids,[12] no keto compound has been studied as a receptor for chiral recognition through imine formation. In interest of the above, we designed a novel chiral keto receptor **1** for the stereoselective recognition of 1,2-amino alcohols. Receptor **1**, after the imine formation, **1a** and **1b** with (*S*)- and (*R*)-2-aminopropanol, respectively, experience a different steric hindrance around the imine bond as shown in Scheme 1. Hence, the imine formation constants K_R and K_S are ideally not the same.[10a] Herein, we report the synthesis of **1** and its stereoselective recognition property.

Receptor **1** was conveniently synthesized from (*S*)-2,2′-binol via ortho lithiation through a five step protocol (Scheme 2).[13] The reaction of (*S*)-2,2′-binol **2** with sodium hydride and chloromethylmethylether in dimethyl-formamide yielded the MOM protected binol **3**. Ortho lithiation of compound **3** and subsequent



Scheme 1.

Keywords: Chiral ketone; Enantioselective recognition; 1,2-Amino alcohols; Imine bond.
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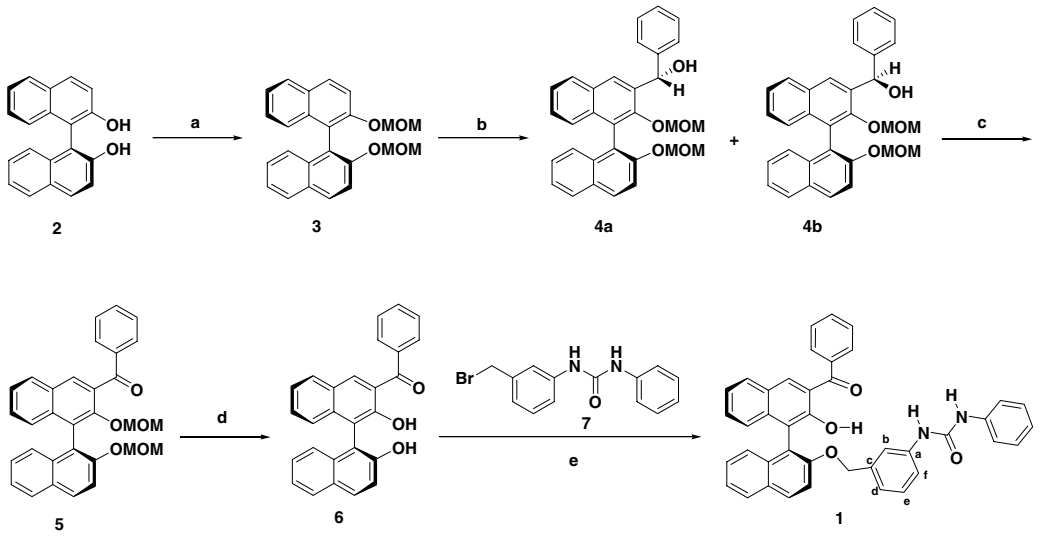

Scheme 2. Reagents and conditions: (a) NaH/DMF, MOMCl, rt, 2 h, 98%; (b) *n*-Bu–Li, C_6H_5CHO, THF, −78 °C, 3 h, 70%; (c) PCC, CH_2Cl_2, 4 h, 74%; (d) conc. HCl, EtOH, reflux, 2 h, (Quant.); (e) NaH, DMF, rt, 5 h, 33%.

treatment with benzaldehyde afforded epimers **4a** and **4b** with considerable stereoselectivity. Oxidation of both epimers using pyridinium chlorochromate (PCC) in methylene chloride followed by deprotection with an acid provided the keto binol **6**. Finally, ketone **6** and phenylurylbenzyl bromide[12a] were reacted in the presence of sodium hydride in dimethyl-formamide silica gel column chromatography afforded the designed receptor **1** in moderate yield. Compound **1** is freely soluble in solvents such as DMSO, $CHCl_3$, benzene, etc.

Figure 1 shows the partial ^{1}H NMR spectra of the receptor **1** and the imines formed. Figure 1a indicates the ^{1}H NMR spectrum for **1** in benzene-d_6. Addition of (*S*)-2-aminopropanol to **1** results in a steady formation of the imine over a period of 24 h. This can be clearly noted by the downfield chemical shift of H_d (doublet) in receptor **1** from 6.60 ppm to 6.65 ppm. Similarly, there is a significant chemical shift from 6.60 ppm to 6.53 ppm by the addition of (*R*)-2-aminopropanol to **1**. Besides, H_d proton chemical shifts, the benzylic CH_2 signals exhibit prominent splitting pattern thereby providing some vital informations for distinguishing **1a** and **1b**. The benzylic hydrogens are diastereotopic and appear as an AB quartet. Figure 1d shows the ^{1}H NMR spectrum for a mixture of **1a** and **1b** formed by the addition of two equivalents of racemic 2-aminopropanol to **1**. The ratio of **1a** and **1b** are obtained from the signals of the benzylic hydrogen and H_d. Integration of the two peaks provides the ratio of **1a**/**1b** is 1.5:1 at equilibirium. This indicates that the imine formation constant for **1b** (K_R) is larger than that for **1a** (K_S) by a factor of about 2.25 (1.5^2).[14]

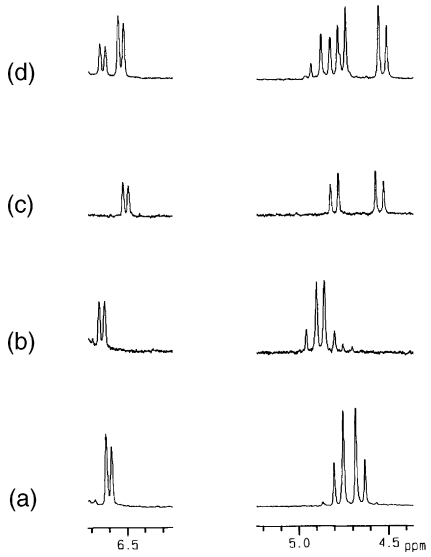

Figure 1. Partial ^{1}H NMR spectra (benzene-d_6) of (a) **1**, (b) **1a**, (c) **1b** and (d) mixture of **1a** and **1b** formed from addition of 2 equiv of racemic 2-aminopropanol to **1**.

Table 1 lists the values of K_R/K_S for four amino alcohols, which shows that the keto binol receptor **1** compares favourably with previously reported receptors for enantioselective recognition of 1,2-amino alcohols. The origin of the stereoselectivity of **1** is the steric hindrance around imine bond as shown in Scheme 1. More steric energy is assumed in the imine of (*S*)-aminopropanol (**1a**) due to the repulsion between phenyl ring and methyl group than in the imine of (*R*)-aminopropanol (**1b**) where repulsion between phenyl ring and proton is less. The molecular mechanics computation[15] corroborates the same sense of stereoselectivity for all four amino alcohols in Table 1.

The stereoselectivity K_R/K_S, depends on the degree of the difference of steric energies around imine bonds between **1a** and **1b**. This will be maximized in the condition that the whole imine complex is rigid by hydrogen bonds (resonance assisted hydrogen bond between imine nitrogen and phenolic –OH, and the hydrogen bond between uryl –NH and alcoholic –OH). Experiments with

Table 1. Enantioselective imine formation (K_R/K_S) between **1** and chiral amines as determined by ^{1}H NMR

Amines	δ, ppm				K_R/K_S
	H_d		Benzylic CH_2		
	R	*S*	*R*	*S*	
Methylbenzylamine	6.72	6.72	4.79 4.85	4.80 4.87	1.0
2-Amino-1-propanol	6.53	6.65	4.79 4.54	4.91 4.82	2.3
2-Amino-1-butanol	6.57	6.66	4.90 4.65	4.97 4.84	2.4
2-Amino-3-phenyl-1-propanol	6.58	6.69	4.98 4.67	5.06 4.94	2.3
2-Amino-2-phenylethanol	6.55	6.70	4.93 4.58	4.98 4.89	2.1

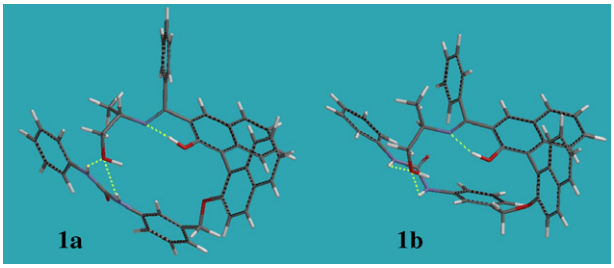

Figure 2. Energy minimized structures of **1a** and **1b** calculated by semi empirical computation.

methylbenzylamine for imine formation, compound **1** does not bind with noticeable stereoselectivity explaining that the hydrogen bonds perform an important role in stereoselective recognition of amino alcohols. The complete loss of stereoselectivity of the receptor **1** in DMSO is also explicable by the hydrogen bond effect.

The energy differences between **1a** and **1b** were calculated to be ~3 kcal/mol by molecular mechanics computation and to be ~0.3 kcal/mol by semi empirical computation using the Spartan program. The semi empirical calculation better corresponds to the experimental results in Table 1. The energy minimized structures of **1a** and **1b** are shown in Figure 2.

In conclusion, we have developed a novel keto receptor recognizing the chirality in amino alcohols, whose origin is supported through the semi empirical computation. This work proves that the keto group can serve as a chiral recognition center by imine formation and it extends the scope of chiral ketones which were viewed mainly as asymmetric catalyst in epoxidation.[16]

Acknowledgements

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13. *Data for compound* **4a** and **4b**: Compound **4a**: mp: 185 °C. ^{1}H NMR (DMSO-d_6, 250 MHz) δ 8.17 (s, 1H), 8.05 (d, 1H), 7.94 (t, 2H), 7.68 (d, 1H), 7.21–7.44 (m, 10H), 7.05 (d, 1H), 6.80 (d, 1H), 6.25 (d, 1H, –CH), 6.05 (d, 1H, –OH), 5.19 (dd, 2H, –O–CH_2–OCH_3), 4.75 (dd, 2H, –O–CH_2–OCH_3), 3.13 (s, 3H, –O–CH_2–OCH_3) 2.86 (s, 3H, –O–CH_2–OCH_3). Anal. Calcd for $C_{31}H_{28}O_5$: C, 77.48; H, 5.87. Found: C, 77.55; H, 5.98. Compound **4b**: mp: 156 °C. ^{1}H

NMR (DMSO-d_6, 250 MHz) δ 8.17 (s, 1H), 8.07 (d, 1H), 7.97 (t, 2H), 7.59 (d, 1H), 7.20–7.44 (m, 10H), 6.96–7.02 (m, 2H), 6.20 (d, 1H, –CH), 6.03 (d, 1H, –OH), 4.96–5.11 (dd, 2H, –O–CH_2–OCH_3), 4.27–4.48 (dd, 2H, –O–CH_2–OCH_3), 2.98 (s, 3H, –O–CH_2–OCH_3), 2.69 (s, 3H, –O–CH_2–OCH_3). Anal. Calcd for $C_{31}H_{28}O_5$: C, 77.48; H, 5.87. Found: C, 77.63; H, 6.02.

Data for compound **5** and **6**: Compound **5**: mp: 94 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.17 (s, 1H), 8.10 (d, 2H), 7.98 (d, 1H), 7.87 (d, 2H), 7.08–7.68 (m, 8H), 7.09 (d, 2H), 5.22 (s, 2H, –O–CH_2–OCH_3), 4.32–4.45 (dd, 2H, –O–CH_2–OCH_3), 3.34 (s, 3H, –O–CH_2–OCH_3), 3.12 (s, 3H, –O–CH_2–OCH_3). ^{13}C NMR ($CDCl_3$, 63 MHz) 196.200, 152.912, 150.741, 137.684, 134.926, 134.202, 133.887, 133.244, 130.240, 130.188, 130.044, 129.879, 129.599, 128.713, 128.344, 127.991, 127.611, 126.795, 126.575, 126.031, 125.671, 125.421, 124.174, 119.714, 116.287, 99.628, 94.842, 56.435, 56.045. Anal. Calcd for $C_{31}H_{26}O_5$: C, 77.81; H, 5.48. Found: C, 77.72; H, 5.32. Compound **6**: mp: 132 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 11.57 (s, 1H, –OH), 8.43 (s, 1H), 6.85–7.98 (m, 15H), 5.06 (s, 1H, –OH). ^{13}C NMR ($CDCl_3$, 63 MHz) 201.787, 155.920, 151.484, 138.094, 137.763, 137.443, 133.478, 132.633, 130.787, 130.370, 130.247, 129.703, 129.336, 128.654, 128.381, 127.046, 126.706, 124.826, 124.662, 124.608, 123.501, 120.966, 117.817, 115.276, 113.915. Anal. Calcd for $C_{27}H_{18}O_3$: C, 83.06; H, 4.65. Found: C, 83.23; H, 4.81.

Data for compound **1**: mp: 108 °C. ^{1}H NMR (C_6D_6, 250 MHz) δ 8.08 (s, 1H), 7.94 (d, 1H), 7.82 (d, 2H), 6.96–7.61 (m, 20H), 6.84 (d, 1H), 6.60 (d, 2H), 4.61–4.82 (dd, 2H, –O–CH_2). ^{13}C NMR ($CDCl_3$, 63 MHz), 201.933, 154.058, 153.753, 153.296, 138.409, 138.292,138.025, 137.800, 137.315, 136.417, 133.673, 132.740, 130.267, 129.895, 129.849, 129.477, 128.938, 128.573, 128.311, 126.950, 126.893, 125.127, 124.814, 124.206, 124.031, 123.280, 121.736, 121.598, 119.971, 119.354, 118.831, 118.484, 118.127, 115.252. HRMS [EI] Calcd for $C_{41}H_{30}N_2O_4$: 614.2206. Found: 614.2210.

14. $K_R = [\mathbf{1b}]/([\mathbf{1}][R])$ and $K_S = [\mathbf{1a}]/([\mathbf{1}][S])$ where $[R]$ and $[S]$ are concentrations of *R*- and *S*-2-aminopropanol, respectively. Hence, $K_R/K_S = ([\mathbf{1b}]\ [S])/([\mathbf{1a}][R]) = ([\mathbf{1b}]/[\mathbf{1a}])^2$ when $[\mathbf{1}]_0 = [R]_0 = [S]_0$.
15. Molecular mechanics computation was performed using Spartan'04 Windows from Wavefunction, Inc.
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