Organic LETTERS

Letter

pubs.acs.org/OrgLett

2,2′-Dihydroxybenzil: A Stereodynamic Probe for Primary Amines Controlled by Steric Strain

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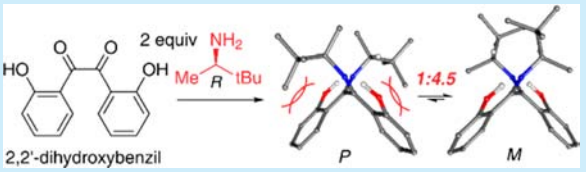
Supporting Information

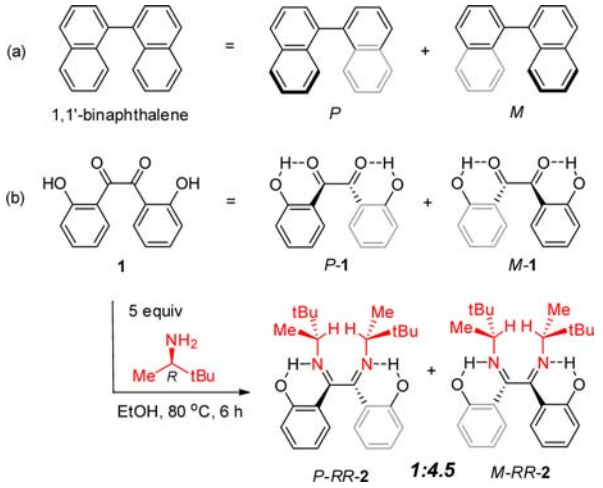
ABSTRACT: A rational approach for generating 1,1′-binaphthalene-like axial chirality of a small organic receptor, 2,2′-dihydroxybenzil is presented. The receptor combines with 2 equiv of monodentate primary amines to form a diimine, of which axial chirality is controlled by steric strain with moderate (1.4:1) to good (4.7:1) stereoselectivity. The observed circular dichroism (CD) spectra have been closely simulated by TD-DFT computations and can be used for determining the absolute chirality and enantiomeric excess of primary amines.



Chirality transfer from central carbons to metals, helices, and molecular self-assemblies has been the topic of much interest in catalysis, supramolecular chemistry, material science, and pharmaceuticals.[1] In particular, such chirality transfer can be the principle of induced circular dichroism (ICD) analysis for signal amplification of UV-silent substrates.[2] The ICD analysis has been used for fast, convenient, sensitive, and accurate determination of the configuration and enantiomeric excess (ee) of chiral analytes such as amines,[3] alcohols,[4] carboxylic acids,[5] and others.[6] One of the remaining challenges is to achieve chiral sensing of monodentate chiral analytes in the absence of any secondary interactions such as hydrogen bonding, which could assist the axial arrangement. The reported stereodynamic probes for sensing chiral monodentate primary amines include arylacetylenes,[7] ethane-bridged bis(zinc porphyrin),[8] *m*-quarterphenyls,[9] and binaphtholate boron and zinc complexes;[10] however, most probes are not readily available due to their lengthy synthetic procedures. Recently, Anslyn and co-workers have reported in situ helical assemblies of Zn^{II} and Fe^{II} complexes for sensing secondary alcohols[11] and primary amines,[12] respectively. These elegant systems showed a strong chiroptical response and broad sensing scope of monodentate chiral analytes; however, it is quite difficult to understand the origin of stereoselectivity owing to the many possible conformers and stereoisomers. We became interested in the rational design of a small organic compound with minimal structural requirements for signal amplification of monodentate chiral analytes. Herein we report a remarkably simple 2,2′-dihydroxybenzil (**1**) that generates axial chirality with monodentate chiral primary amines.

We propose that 2,2′-dihydroxybenzil (**1**) with two internal H-bonds exhibits a 1,1′-binaphthalene-like axial arrangement (Scheme 1). The two axial stereoisomers, *P*-**1** and *M*-**1**, rapidly interconvert and exist as a 1:1 mixture. When an enantiopure primary amine, (*R*)-3,3-dimethyl-2-butylamine, reacts with **1** to form a diimine **2**, two stereoisomers become diastereomers, *P*-*RR*-**2** and *M*-*RR*-**2** (Scheme 1b). We first attempted to determine the thermodynamic ratio between the diastereomeric axial conformers **2**.

Scheme 1. Axial Chirality of (a) 1,1′-Binaphthalene and (b) 2,2′-Dihydroxybenzil (1) and Selective Generation of Axial Stereoisomers of a Diimine (2) Formed from 1 and 2 equiv of (*R*)-3,3-Dimethyl-2-butylamine



When 5 equiv of (*R*)-3,3-dimethyl-2-butylamine were heated with **1** in EtOH at 80 °C for 6 h, a clean product of diimine (**2**) was obtained. ^{1}H NMR spectra of the crude mixture showed that the diastereomeric ratio was 4.5:1 in $CDCl_3$. Interestingly, similar values were obtained in DMSO-d_6 (4.5:1), CD_3CN (4.3:1), and CD_3OD (4.7:1), indicating that the solvent effects are not significant to the stereoselectivity of axial stereoisomers **2**. Since the solvent effects are relatively small, it appears that

Received: April 15, 2014
Published: May 12, 2014

   dx.doi.org/10.1021/ol501088v | *Org. Lett.* 2014, 16, 2950−2953

the intramolecular steric interactions play a major role in favoring the formation of one axial stereoisomer of **2**.

In order to understand the origin of stereoselectivity, we performed DFT computations to calculate the energetics of the two diastereomers, *P*-*RR*-**2** and *M*-*RR*-**2**.[13] The global energy minimum structures showed that two internal hydrogen bonds are maintained between the phenolic hydrogen and the imine nitrogen; at the same time, the hydrogens on the chiral carbons are facing each other, as depicted in Scheme 1b. Such hydrogen bonding, also called the resonance-assisted hydrogen bonding (RAHB),[14] is a class of strong hydrogen bonding reinforced by delocalization of π-bonds. According to the DFT computation for *RR*-**2**, the *M*-form is more stable than the *P*-form by about 0.9 kcal/mol. This calculated energy difference translates to an equilibrium ratio of 4.5:1 at 25 °C, which is in excellent agreement with the experimental value of 4.5:1. Moreover, the calculation indicates potential steric interactions in *P*-*RR*-**2** and *M*-*RR*-**2**. First, the hydrogens on the chiral carbons are facing each other, thereby reducing the steric repulsion between the two chiral amines in **2** (Figure 1a). With this fixed arrangement

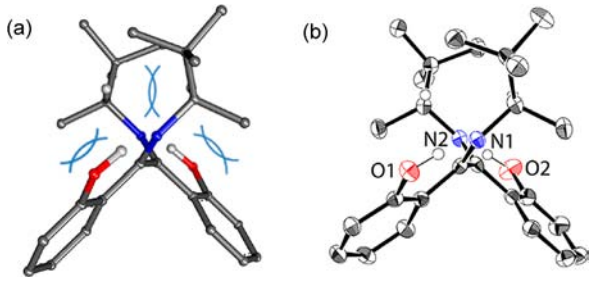


Figure 1. (a) Calculated global energy minimum of *M*-*RR*-**2** (DFT B3LYP/6-31G(d,p)) and (b) crystal structure (50% ellipsoid probability) of *RR*-**2**. All hydrogens except for phenols and chirality carbon centers are omitted for clarity.

of chiral amines, additional steric repulsion appears between the substituents (Me or *tert*-Bu groups) on the chiral carbons and the phenol rings (Figure 1a). In the case of *RR*-**2**, the Me groups are placed near the phenol rings in the *M* form while the *tert*-Bu groups are placed near the phenol rings in the *P* form. Thus, *M*-*RR*-**2** is more stable than *P*-*RR*-**2**, allowing it to reduce the steric repulsion. Indeed, the crystal structure of *RR*-**2** showed an *M*-configuration, with two internal H-bonds as well as a fixed orientation of amines (Figure 1b). Therefore, there is excellent agreement between the DFT computations and the experimental results, such as ^{1}H NMR and X-ray analysis.

Consistent with the X-ray data (Figure 1b), *RR*-**2** was selectively crystallized to *M*-*RR*-**2**. The ^{1}H NMR spectra of *M*-*RR*-**2** showed that equilibrium was established within hours at ambient temperature. Then, we carried out kinetic studies by monitoring the reaction by ^{1}H NMR spectroscopy ($CDCl_3$, 10 mM) at various temperatures (40 to 55 °C, Supporting Information). The resulting linear Eyring plot gave us values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the forward reaction from *P*-*RR*-**2** to *M*-*RR*-**2** of 14.2 kcal/mol and −29.2 cal/mol, respectively. Similarly, the values of the activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, of the backward reaction from *M*-*RR*-**2** to *P*-*RR*-**2** were found to be 15.0 kcal/mol and −29.3 cal/mol, respectively. Thus, we were able to determine the rotation barriers ($\Delta G^{\ddagger}$ = 22.9 and 23.8 kcal/mol) and the free energy change (ΔG = 0.9 kcal/mol) at 25 °C.

The axial arrangement of *RR*-**2** can be verified using circular dichroism (CD) spectroscopy. As shown in Figure 2, there are

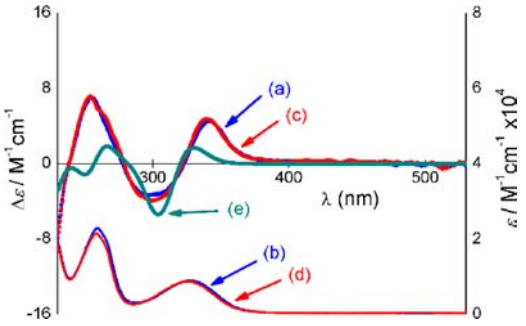


Figure 2. (a) Measured CD spectrum and (b) UV−vis spectrum of *RR*-**2** (75 μM in ethanol, 10 mm cell, at 20 °C), (c) measured CD spectrum, and (d) UV−vis spectrum of *RR*-**2** (75 μM in acetonitrile, 10 mm cell, at 20 °C) and (e) simulated CD spectrum of *M*-*RR*-**2** (TD-SCF, CAM-B3LYP/6-31G(d,p)).

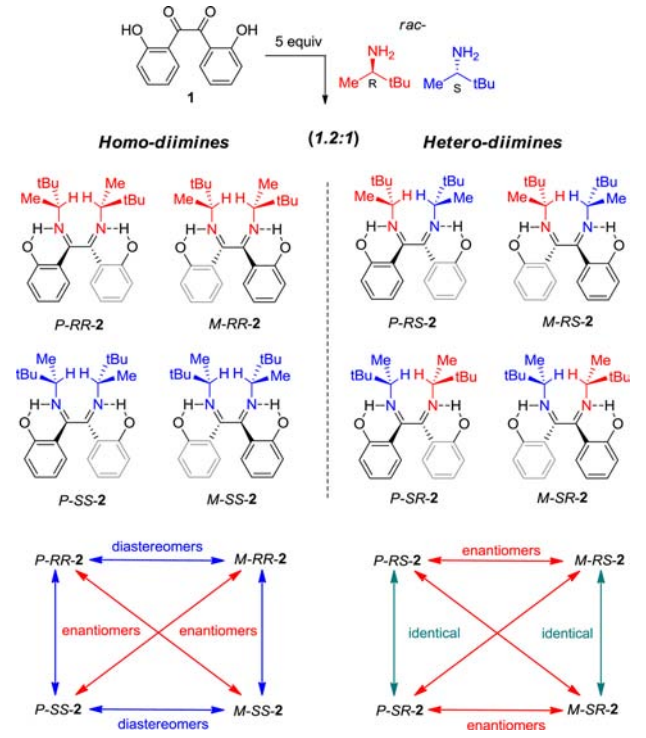
strong Cotton effects in the CD spectra of *RR*-**2**. Again, the solvent effect is negligible to provide the closely overlapped CD spectra in ethanol and acetonitrile (Figure 2a and 2c). The 1,1′-binaphthalene-like axial structure of 2,2′-dihydroxybenzil is crucial for the chiroptical signals because neither salicylaldehyde nor 2,2′-dihydroxybenzophenone yielded any active CD signals during the formation of imines with (*R*)-3,3-dimethyl-2-butylamine (Supporting Information). It is known that the exciton coupling of chromophores can be used to assign the absolute chirality. However, the bisignate CD curves at 340 nm predict a *P*-configuration of *RR*-**2** that is opposite to that of the calculation and X-ray results. The failure of the exciton chirality analysis is due to the dihedral angles of the imines. The imine dihedral angles of the calculated and crystal structure of *RR*-**2** are 88.5° and 90.3°, respectively. According to the theory of exciton coupling, when dihedral angles are 0° and 90°, the CD coupling of two degenerate electric dipole moments is zero.[15] Instead, we simulated the CD spectra by performing TD-DFT calculations (Figure 2e).[13] When the bisignate CD curves overlap at 340 nm, the simulated CD signals are well-matched with the experimental CD signals for the first positive and the second negative Cotton effects.

In principle, a racemic amine reacted with **1** to form eight possible stereoisomers (Scheme 2). In our experiment, the 1.2:1 ratio of homo- and heterodiimine was obtained when an excess amount of *rac*-3,3-dimethyl-2-butylamine was used. The homodiimine is slightly more stable than the heterodiimine, and the equilibrium is established by a statistical distribution. Interestingly, the stereochemical analysis indicates that optical signals of heterodiimines become zero because they are all identical or racemic (Scheme 2). Thus, the observed optical response could be in a linear relationship with the enantiomeric excess of the chiral amines, as found in other studies of chiroptical probes. Indeed, there is an excellent linear relationship between the enantiopurities of 3,3-dimethyl-2-butylamine and the observed CD signals (Figure 3).

Since we have shown that the axial arrangement of **1** can be controlled by the steric effect of chiral amines, we have determined the stereoselectivities of a variety of chiral amines (Table 1). When monodentate chiral amines were used, moderate (1.4:1) to good (4.7:1) stereoselectivities were obtained. It appears that the steric difference between two substrates of chiral amines correlates with the stereoselectivity

dx.doi.org/10.1021/ol501088v | *Org. Lett.* 2014, 16, 2950−2953

Scheme 2. Eight Possible Stereoisomers and Their Relationship in the Formation of Diimine between 1 and *rac*-3,3-Dimethyl-2-butylamine



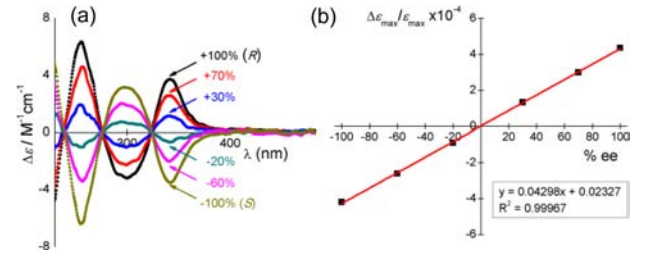
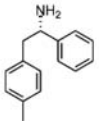


Figure 3. (a) Circular dichroism spectra of **2** with varied enantiopurities of 3,3-dimethyl-2-butylamine and (b) a linear plot between CD/UV−vis ratios and enantiopurities of 3,3-dimethyl-2-butylamine (75 μM in ethanol, 10 mm cell, at 20 °C).

of axial conformers. Remarkably, a subtle difference between methyl and ethyl groups in 2-aminobutane also gave a meaningful diastereoselectivity of 1.4:1, as well as strong CD signals (Table 1, entry 1). Although exciton chirality is not applicable for determining absolute chirality, our CD spectra indicate that the signal of the first Cotton effect at 320−340 nm can be used to assign the absolute chirality of primary amines. (*R*)-Amines with alkyl substituents gave positive first Cotton effects (entries 1−3), while (*R*)-amines with aryl-alkyl substituents gave negative first Cotton effects (entries 4−7). The CD spectra for a diimine between **1** and (*R*)-2-methyl benzylamine (entry 4) was also closely simulated by TD-DFT computation (Supporting Information). We reasoned that the electric dipole moments of imines strongly coupled with those of aryl substituents, overriding the possible imine−imine couple. On the basis of the CD and computational data, we can rationalize that all (*R*)-amines selectively form *M*-axial conformers that give negative or positive first Cotton effects with regard to the alkyl or aryl substituents of the amines. Thus,

Table 1. Stereoselective Chirality Transfer from Monodentate Primary Amines to 2,2′-Dihydroxybenzil (1)

entry	amine	abs config	dr[a]	1st Cotton effect		
				λ_{max} (nm)	$\Delta\varepsilon$ ($M^{-1}cm^{-1}$)[b]	predicted CD
1		*R*	1.4	341	+0.679	+
2		*R*	2.1	342	+1.09	+
3		*R*	4.5	340	+3.37	+
4		*R*	1.5	323	-9.70	-
5		*R*	4.7	332	-11.5	-
6		*S*	1.7	325	+3.90	+
7		*S*	2.6	322	+3.86	+

[a]Determined by ^{1}H NMR spectra. [b]75 μM in ethanol, 10 mm cell, at 20 °C.

experimental CD spectra can be used to determine the absolute chirality of primary amines.

In conclusion, using an exceptionally simple 1,1′-binaphthalene-like axial compound, 2,2′-dihydroxybenzil (**1**), we have demonstrated a rational approach for signal amplification of primary amines. The axial chirality of the stereodynamic receptor is controlled by forming diimines with a series of monodentate primary amines that have moderate (1.4:1) to good (4.7:1) stereoselectivity. The origin of stereoselectivity can be unambiguously explained by combining the experimental data, such as that from the ^{1}H NMR and CD spectroscopy and the X-ray crystallography, with computational data from geometry optimization and electronic CD simulation. Furthermore, the stereodynamic receptor can be used for the accurate determination of the value of ee and the absolute configuration of the primary amines.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, and spectroscopic, spectrometric, calculation, and crystallographic details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Research Foundation of Korea (NRF 2011-0014197) and the Institute for Basic Sciences (IBS) for supporting this research. M.-S.S. acknowledges financial support from the Kwanjeong Education Foundation.

We thank Dr. Alan J. Lough (University of Toronto) for X-ray analysis.

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