JOC The Journal of Organic Chemistry

Article

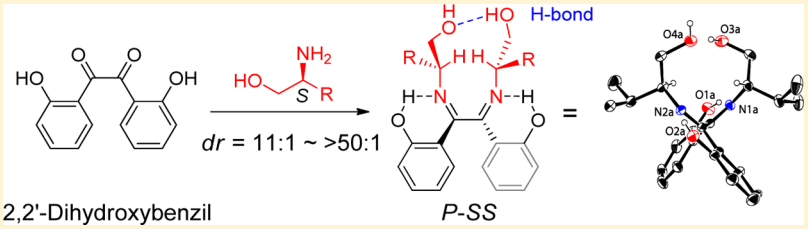
pubs.acs.org/joc

Stereoselective Chiral Recognition of Amino Alcohols with 2,2′-Dihydroxybenzil

Min-Seob Seo, Daeyoung Sun, and Hyunwoo Kim*

Department of Chemistry, KAIST, Daejeon 34141, Korea

Supporting Information



ABSTRACT: 2,2′-Dihydroxybenzil is demonstrated to be a highly diastereoselective stereodynamic receptor for the chiral recognition of amino alcohols. The receptor by forming diimine compounds with amino alcohols showed good (11:1) to excellent (>50:1) diastereoselectivity in chloroform. The existence of intramolecular hydrogen bonding with amino alcohols only in an axial conformer is demonstrated by ^{1}H NMR and CD spectroscopy, X-ray crystallography, and DFT computations. The exciton chirality method can be used with diazo-attached 2,2′-dihydroxybenzil.

INTRODUCTION

Amino alcohols are among the important classes of compounds widely used for the synthesis of bioactive compounds.[1a,b] Moreover, natural or unnatural amino alcohols have been widely applied for the development of chiral ligands, auxiliaries, and catalysts.[1c−f] Due to the importance of amino alcohols, it is highly desirable to develop simple, accurate, and practical methods for the stereochemical analysis of amino alcohols. In recent years, the induced circular dichroism (ICD) analysis[2] has been used for chiral analyses, such as the determination of the configuration and enantiomeric excess (*ee*) of chiral compounds, such as amines,[3] alcohols,[4] carboxylic acids,[5] and others,[6] and tests of high-throughput screening applications.[2b,d] For amino alcohols, several stereodynamic probes have been reported, including diarylnaphthalenes,[7] arylacetylenes,[8] binaphtolate borons,[9] palladium complexes,[10] and others[11] (Figure 1a). Although several types of stereodynamic receptors have been developed, it remains challenging to achieve a high level of diastereoselectivity upon the formation of diastereomeric complexes between a stereodynamic receptor and an amino alcohol. Thus, ICD signals are often weak and variable with regard to the analyte structure due to the low level of diastereoselectivity. To ensure an accurate and sensitive chiral analysis, it is crucial to develop highly diastereoselective stereodynamic receptors.

We recently reported a stereodynamic probe, 2,2′-dihydroxybenzil (**1**), which can be used for the chiral amplification of monodentate primary amines.[3b] Although 2,2′-dihydroxybenzil exhibits minimal structural requirements for the generation of axial chirality, this probe showed low to moderate diastereoselectivity of 1.4 to 4.7 controlled by the steric strain. We demonstrate here that intramolecular hydrogen bonding interaction can improve the diastereoselectivity to achieve a highly stereoselective recognition of amino alcohols.

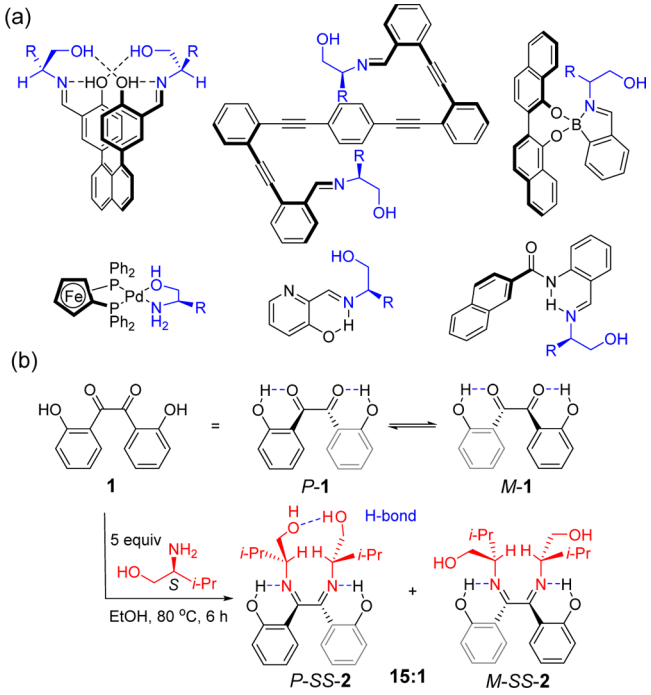


Figure 1. (a) Reported chiroptical probes and (b) 2,2′-dihydroxybenzil (**1**) for the chirality sensing of amino alcohols.

Received: March 13, 2017
Published: June 5, 2017

DOI: 10.1021/acs.joc.7b00600
J. Org. Chem. 2017, 82, 6586−6591

RESULTS AND DISCUSSION

2,2′-Dihydroxybenzil (**1**), readily prepared by coupling between oxalyl chloride and phenol, exhibits a 1,1′-binaphthalene-like axial arrangement with two internal hydrogen bonds and exists as an equal mixture of rapidly interconverting *P* and *M* forms (Figure 1b). The stereodynamic nature of **1** was confirmed in our previous report, which showed that diimines formed from **1** and chiral monodentate amines become diastereomers.[3b] In such cases, low (1.4:1) to moderate (4.7:1) stereoselectivity can be observed. We then questioned whether additional intramolecular interactions, such as hydrogen bonding enhance the diastereoselectivity of diimines. In order to test this idea, we first reacted L-valinol and **1** to form diimine **2**, resulting in two diastereomeric mixtures *P*-*SS*-**2** and *M*-*SS*-**2** (Figure 1b).

When 5 equiv of L-valinol was heated with **1** in EtOH at 80 °C for 6 h, a clean product of diimine (**2**) was obtained. The ^{1}H NMR spectra of the crude mixture showed that the diastereomeric ratio was 15:1 in $CDCl_3$. Indeed, the diastereoselectivity for 3-methyl-2-butylamine (2.1:1)[3b] was significantly improved when a hydroxyl group was attached to the methyl group.

In order to verify the existence of the intramolecular H-bond interactions with the hydroxyl groups of amino alcohols, we initially determined the crystal structure of **2**. Although the diastereoselectivity for *SS*-**2** was found to be 15:1 in $CDCl_3$ as determined by the ^{1}H NMR spectra, the crystal structure indicated that the *SS*-**2** with the *P*-configuration was selectively crystallized (Figure 2). In the crystal structure of *P*-*SS*-**2**, there are three intramolecular H-bonds: two H-bonds between phenolic hydrogens and imine nitrogens as well as one H-bond between the hydroxyl groups of L-valinol. It is remarkable that all hydroxyl groups in *SS*-**2** are involved in the intramolecular H-bonds to establish axial chirality of the *P* form.

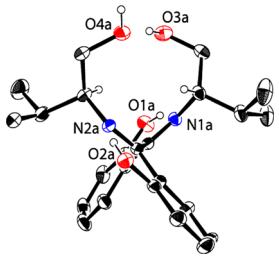


Figure 2. Crystal structure (50% ellipsoid probability) of *P*-*SS*-**2**. All hydrogens except for phenols, alcohols, and chirality carbon centers are omitted for clarity.

The DFT calculation also supports the contention that additional H-bonding between the hydroxyl groups of L-valinol can increase the energy difference between *P*-*SS*-**2** and *M*-*SS*-**2**, resulting in an increase in the diastereoselectivity. The DFT calculation showed that both energy minimum structures of *P*-*SS*-**2** and *M*-*SS*-**2** exhibit two intramolecular H-bonds between the phenolic hydrogens and the imine nitrogens, forming a class of strong resonance-assisted hydrogen bonds (RAHBs).[12] In both the *P*- and *M*-conformers, the hydrogens on the chiral carbons face each other in order to minimize the steric repulsion. However, in *P*-*SS*-**2**, both hydroxymethyl groups are positioned in the same direction, whereas in *M*-SS-**2**, both hydroxymethyl groups are positioned in opposite directions. Accordingly, the third intramolecular H-bond is found not in the *M*-form but in the *P*-form due to the relative arrangement of the isopropyl and hydroxymethyl groups. It is remarkable that the crystal and optimized structures of *P*-*SS*-**2** are in excellent agreement (Figures 2 and 3). As expected, *P*-*SS*-**2** due to the additional H-bond is approximately 4.31 kcal/mol more stable than *M*-*SS*-**2**. In the case of imine **2′** formed from (*R*)-3-methyl-2-butylamine, the *M*-form is more stable than the *P*-form by about 0.64 kcal/mol because the steric repulsion between the isopropyl groups and the phenol groups increases the energy of the *P*-form (Figure 3). Accordingly, the DFT computation indicates that the intramolecular H-bond between the hydroxyl groups provide sufficient stabilization energy of approximately 4.95 kcal/mol, favoring an axial conformer, which is a minor axial conformer with respect to the repulsive steric interactions.

In order to verify the existence of H-bonding not only in the solid state but also in the solution state, we examined the solvent effect on the stereoselectivity of *SS*-**2**. The measured values of the diastereoselectivity for *SS*-**2** were 15:1 in $CDCl_3$, 5.3:1 in CD_3CN, and 3.4:1 in CD_3OD (Scheme 1a). The intramolecular H-bonds are generally reinforced in aprotic solvents, such as $CDCl_3$, but are disrupted in protic solvents,

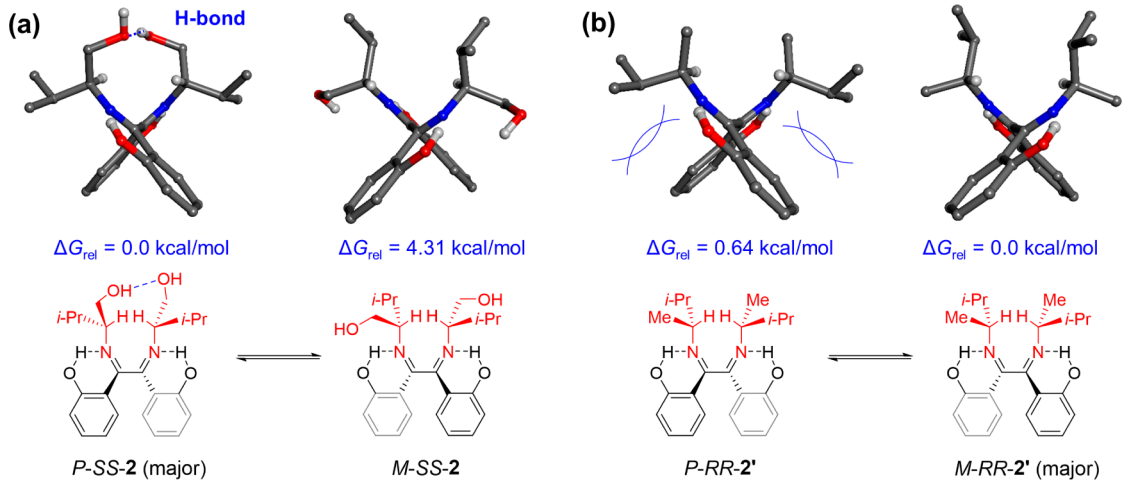
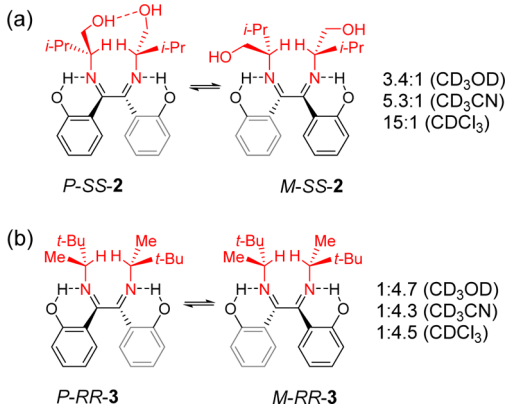


Figure 3. Calculated global energy minimum structures of (a) *P*-*SS*-**2** and *M*-*SS*-**2** as well as (b) *P*-*RR*-**2′** and *M*-*RR*-**2′**, an imine (**2′**) formed between **1** and (*R*)-3-methyl-2-butylamine.

DOI: 10.1021/acs.joc.7b00600
J. Org. Chem. 2017, 82, 6586−6591

Scheme 1. Solvent Effects on the Stereoselectivity of Diimines Formed from (a) L-Valinol and (b) (*R*)-3,3-Dimethyl-2-butylamine



such as CD_3OD. Thus, the decreased stereoselectivity of *SS*-**2** by a polar solvent or protic solvent supports the presence of intramolecular H-bonds. In addition, we measured the ^1H NMR spectra of *SS*-**4** formed from L-phenylglycinol in various concentrations ($CDCl_3$, 38−50 mM). The signal of the phenolic proton at 14.5 ppm was almost constant to the various concentrations because this hydrogen bond is a strong resonance-assisted hydrogen bond. However, the proton signal of the hydroxyl groups around 3.7 ppm was quite variable (Figure 4). We found that an addition of 4 Å molecular sieves

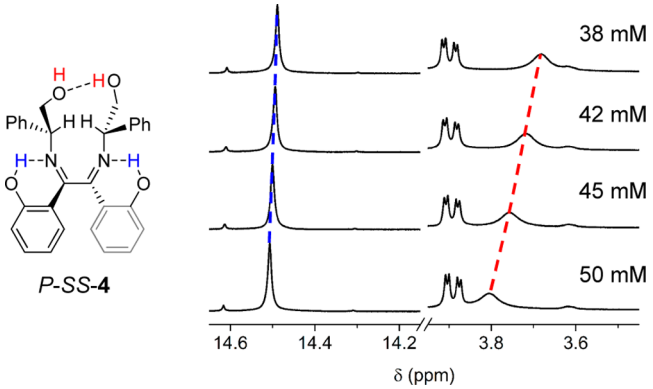


Figure 4. Concentration effect for the chemical shifts of the phenolic OH and the hydroxyl OH of *SS*-**4** in $CDCl_3$.

decreased the peak shift of the hydroxyl OH signal to within 0.1 ppm, suggesting that the hydroxyl groups form a weak intramolecular H-bond and can be partially disrupted by residual water in the $CDCl_3$. On the other hand, in an imine (*RR*-**3**) formed from **1** and (*R*)-3,3-dimethyl-2-butylamine, the stereoselectivity was measured to be 1:4.5, 1:4.3, and 1:4.7 in $CDCl_3$, CD_3CN, and CD_3OD, respectively (Scheme 1b). In *RR*-**3**, the stereoselectivity was maintained independent of the solvent because its stereoselectivity originated from the relative steric bulkiness of the methyl and *tert*-butyl groups.

The axial arrangement of a diimine can be verified by circular dichroism (CD) spectroscopy.[13] The CD spectra of the crude mixtures of *SS*-**2** were measured without any purification procedures. As shown in Figure 5, there are strong Cotton effects in the CD spectra of *SS*-**2**, but the exciton chiral method[2e,13] is not applicable when determining the absolute chirality, as because bisignate CD curves are not clearly

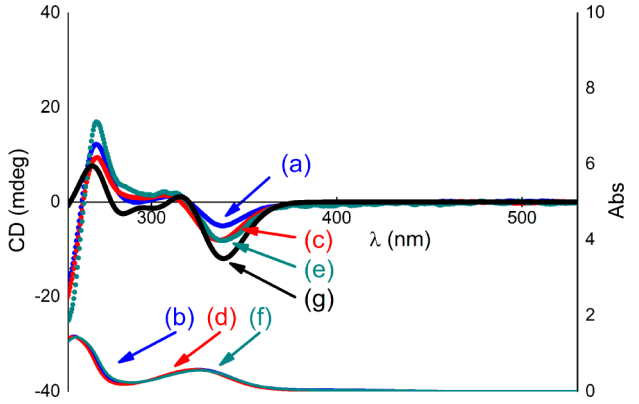


Figure 5. Measured CD spectrum and UV−vis spectrum (75 μM, 10 mm cell, at 20 °C) of *SS*-**2** in EtOH (a and b), CH_3CN (c and d), and $CHCl_3$ (e and f) and simulated CD spectrum of *P-SS*-**2** (g).

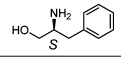
observed. Instead, we simulated the CD spectra by performing a TD-DFT calculation (Figure 5).[14] When the simulated CD curves are overlapped, the CD signals of *P-SS*-**2** are in very good agreement with the experimental CD signals of *SS*-**2**. In addition, the CD signals of *SS*-**2** are stronger in $CHCl_3$ and CH_3CN than in EtOH, in agreeing with the solvent effect. However, the signal intensity in $CHCl_3$ is not significantly greater than that in CH_3CN although the diastereoselectivity in $CHCl_3$ (15:1) is much greater than that in CH_3CN (5.3:1). The observed CD spectra of *SS*-**2** in three solvents also indicate that the major axial conformer is also the *P*-form in a protic solvent because the intramolecular H-bonds still play a crucial role to favor the equilibrium to the *P*-form of *SS*-**2**.

In order to investigate the analytical scope for our stereodynamic probe **1**, we prepared imine compounds by the reaction between **1** and a variety of L-amino alcohols with *i*-Pr (**2**), phenyl (**4**), ethyl (**5**), methyl (**6**), *iso*-butyl (**7**), and benzyl (**8**) substituents (Table 1). We could isolate the desired imines in 67−87% yields and their diastereoselectivity was determined by ^1H NMR spectroscopy in $CDCl_3$, CD_3CN, and CD_3OD. In all cases, good (11:1) to excellent (>50:1) diastereomeric ratios were obtained in $CHCl_3$ but the diastereoselectivity decreased in CD_3CN (3.7:1 ∼ > 50:1) and CD_3OD (2.5:1−26:1). In order to understand the observed diastereoselectivity of various imines, we calculated the equilibrium energies between the *P*-form and the *M*-form of the imines in a range of 3.1 to 7.0 kcal/mol, but there is no linear relationship between the calculated equilibrium energy and the observed diastereoselectivity (Table 1).

Imine compounds **2** and **4**−**8** as a crude mixture showed strong CD signals in EtOH (Table 1). Our analysis by comparing the experimental and simulated CD spectra by TD-DFT calculations indicates that the signal of the first Cotton effect at 330−340 nm can be used for assigning the absolute chirality of amino alcohols. The negative first Cotton effects by (*S*)-amino alcohols can be rationalized to form *P*-axial conformers. Thus, the experimental CD spectra together with a CD simulation can be used to determine the absolute chirality of amino alcohols. In addition to the determination of the absolute chirality, the CD spectra can be used to determine enantiomeric excess (*ee*), as observed optical response may exist in a linear relationship with the *ee* of chiral amino alcohols. Indeed, there is an excellent linear relationship between the enantiopurities of valinol and the observed CD signal (Figure 6).

DOI: 10.1021/acs.joc.7b00600
J. Org. Chem. 2017, 82, 6586−6591

Table 1. Stereoselective Chirality Transfer from Amino Alcohols to 2,2′-Dihydroxybenzil (1)

Entry	Amino alcohol	Major product	ΔG_{calc} (kcal/mol)	*dr*[a]			1st Cotton Effect		
				$CDCl_3$	CD_3CN	CD_3OD	λ_{max} (nm)	$\Delta\varepsilon$ (mdeg)[b]	Predicted CD
1		*P-SS*-**2**	4.3	15:1	5.3:1	3.4:1	338	-5.6	-
2		*P-SS*-**4**	7.0	14:1	8.1	5.4:1	333	-27.8	-
3		*P-SS*-**5**	4.5	11:1	3.7:1	2.5:1	337	-4.8	-
4		*P-SS*-**6**	3.1	21:1	5.9:1	3.7:1	337	-5.4	-
5		*P-SS*-**7**	6.3	> 50:1	> 50:1	26:1	338	-9.2	-
6		*P-SS*-**8**	6.2	> 50:1	16:1	13:1	338	-11.1	-

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

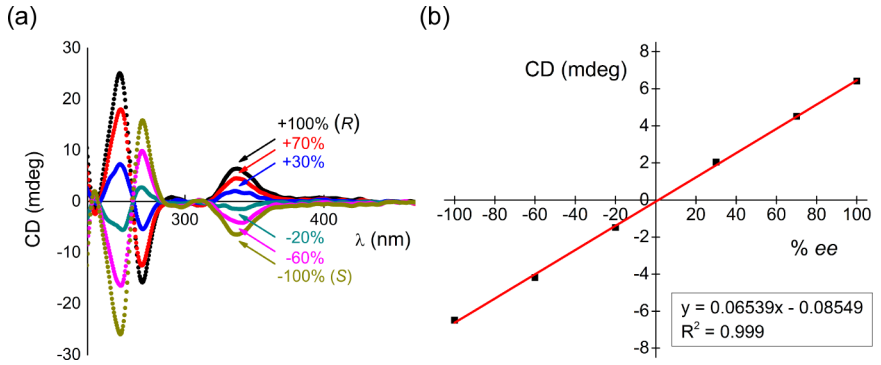


Figure 6. (a) Circular dichroism spectra of **2** with various enantiopurities of valinol and (b) a linear plot between the CD/UV−vis ratios and the enantiopurities of valinol (75 μM in ethanol, 10 mm cell, at 20 °C).

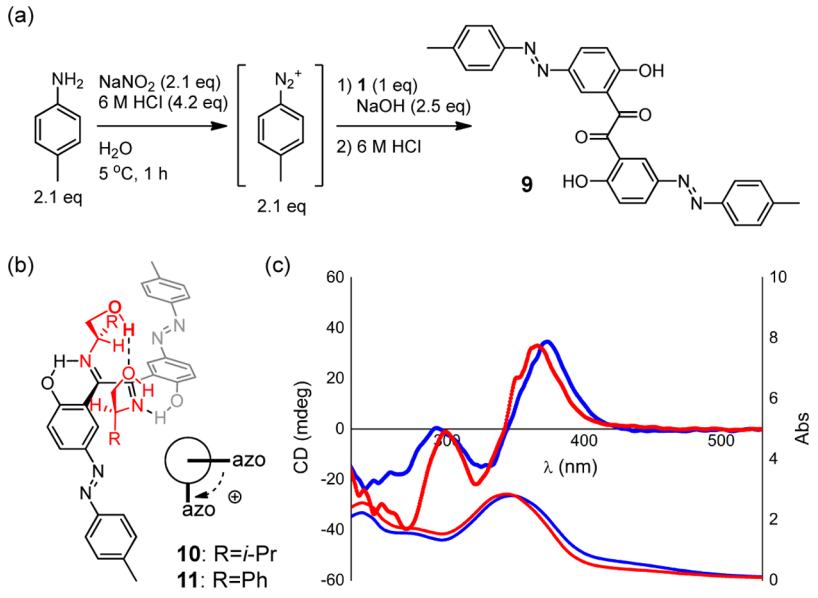


Figure 7. (a) Procedure for the formation of diazo attached 2,2′-dihydroxybenzil (**9**). (b) Structure of the imine complex formed between the new probe and amino alcohol, and (c) measured CD and UV−vis spectra (75 μM in ethanol, 10 mm cell, at 20 °C) of *P-SS*-**10** (blue) and *P-SS*-**11** (red).

Although 2,2′-dihydroxybenzil (**1**) can be used to ascertain the absolute chirality and enantiomeric excess, as previously demonstrated, this stereodynamic probe shows weak CD signals for amino alcohols with alkyl substituents, and a TD-DFT calculation is required to determine the absolute chirality instead of the more intuitively simple exciton chirality method. In order to overcome these challenges, we designed a new probe (**9**) by attaching the diazo group to the 5-position of the

DOI: 10.1021/acs.joc.7b00600
J. Org. Chem. 2017, 82, 6586−6591

phenol group of 2,2′-dihydroxybenzil. Because the UV signals of diazo groups may appear in regions separated from those of other chromophores, a spatial arrangement of two diazo groups can be used for the determination of the absolute chirality by the exciton chirality method. Indeed, when imines **10** and **11** were formed by a reaction between the new probe and L-valinol or L-phenylglycinol, respectively, the UV signals at 370 nm were observed to have similar patterns, indicating that the diazo groups can be an independent signal unit regardless of the functional groups of the analytes. To our surprise, in both cases the first positive and the second negative Cotton effects were observed, and the absolute chirality was determined as the *P*-configuration, in agreement with the crystallographic and DFT calculation data (Figure 7).

CONCLUSION

In summary, we have demonstrated the highly stereoselective recognition of amino alcohols using 2,2′-dihydroxybenzil as a stereodynamic receptor. The axial chirality is controlled via the formation of diimines with a series of amino alcohols that have good (11:1) to excellent (>50:1) stereoselectivity. The origin of the high diastereoselectivity and the existence of H-bond interactions were verified by combining the experimental data of ^{1}H NMR and CD spectroscopy and X-ray crystallography with computational data. The experimental CD spectra can be used to determine the absolute chirality of amino alcohols by comparing simulated CD spectra, and there is an excellent linear relationship between the enantiopurity of amino alcohols and the observed CD signals. In addition, diazo-attached 2,2′-dihydroxybenzil is feasible for use with the exciton chirality method. Thus, 2,2′-dihydroxybenzil is a highly stereoselective stereodynamic probe which can be utilized for the determination of the absolute configurations and *ee* values of amino alcohols.

EXPERIMENTAL SECTION

General Information. Commercially available compounds were used without further purification or drying. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ascend 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) and are reported in ppm, relative to residual protonated solvent peak ($CDCl_3$, CD_3CN, and CD_3OD). The high-resolution mass spectra (HRMS) were obtained on a Bruker Daltonik microTOF-QII spectrometer. Circular dichroism (CD) and UV−vis spectra were performed on a JASCO J-815 spectrometer. All calculations were performed using Gaussian 09. 2,2′-Dihydroxybenzil was prepared according to the reported procedure.[3b]

Procedure for Formation of 2,2′-Dihydroxybenzil.[3b] To a suspension of $AlCl_3$ (11.2 g, 84 mmol) in CH_2Cl_2 (75 mL), a solution of phenol (3.95 g, 42 mmol) in CH_2Cl_2 (12.5 mL) was added dropwise at room temperature and the mixture was stirred for 30 min. A solution of oxalyl chloride (1.72 mL, 20 mmol) in CH_2Cl_2 (12.5 mL) was added dropwise to the reaction mixture at room temperature. After 3 h, the reaction was quenched by the addition of 12 M HCl solution. The layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with water, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by recrystallization from EtOH (10 mL) to afford the product, 2,2′-dihydroxybenzil (**1**).

2,2′-Dihydroxybenzil (**1**). Greenish yellow solid (1.54 g, 32%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.28 (s, 2H), 7.59 (ddd, J = 8.6, 7.4, 1.6 Hz, 2H), 7.47 (dd, J = 8.0, 1.6 Hz, 2H), 7.10 (dd, J = 8.5, 1.0 Hz, 2H), 6.92 (ddd, J = 8.2, 7.3, 1.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 163.7, 138.5, 132.5, 120.0, 119.0, 116.8; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{10}O_4Na$ 265.0471; Found: 265.0453.

General Procedure for the Diimine Formation of 2,2′-Dihydroxybenzil. To a stirred solution of **1** (15.1 mg, 0.0625 mmol) in EtOH (0.125 mL) was added 5 equiv of chiral amino alcohol (0.3125 mmol). The solution was stirred for 6 h at 80 °C, and then all volatile residues were removed in vacuo. The resulting crude mixture was used for CD analysis without further purification. The isolated product was used for NMR analysis.

P-SS-**2**. Yellow solid (21.9 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.89 (br, 2H), 7.31 (ddd, J = 8.7, 7.2, 1.6 Hz, 2H), 7.09 (dd, J = 8.0, 1.6 Hz, 2H), 7.02 (dd, J = 8.4, 1.1 Hz, 2H), 6.71 (ddd, J = 8.2, 7.2, 1.2 Hz, 2H), 3.95−3.82 (m, 4H), 3.82 (br, 2H), 3.63 (dt, J = 8.1, 3.8 Hz, 2H), 1.71−1.63 (m, 2H), 0.91 (d, J = 7.0 Hz, 6H), 0.74 (d, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 162.3, 133.3, 130.9, 118.4, 118.3, 117.8, 68.3, 62.9, 31.6, 19.7, 16.8; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{32}N_2O_4Na$ 435.2254; Found: 435.2265.

P-SS-**4**. Yellow solid (22.0 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.55 (br, 2H), 7.19−7.06 (m, 8H), 7.00−6.99 (m, 6H), 6.41 (dd, J = 8.0, 1.6 Hz, 2H), 6.12 (ddd, J = 8.3, 7.2, 1.2 Hz, 2H), 4.84 (dd, J = 9.9, 3.3 Hz, 2H), 4.17 (t, J = 10.6 Hz, 2H), 4.04 (br, 2H), 3.89 (dd, J = 9.1, 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 161.6, 137.9, 133.3, 131.1, 128.6, 127.8, 127.5, 118.4, 117.8, 116.7, 69.3, 68.9; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{30}H_{28}N_2O_4Na$ 503.1941; Found 503.1962.

P-SS-**5**. Yellow solid (18.1 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.64 (br, 2H), 7.32 (ddd, J = 8.6, 7.2, 1.6 Hz, 2H), 7.09 (dd, J = 8.0, 1.6 Hz, 2H), 7.02 (dd, J = 8.4, 1.2 Hz, 2H), 6.73 (ddd, J = 8.1, 7.2, 1.0 Hz, 2H), 4.00−3.77 (m, 4H), 3.71−3.64 (m, 2H), 3.51 (br, 2H), 1.60−1.26 (m, 4H), 0.74 (t, J = 7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 162.2, 133.4, 130.7, 118.4, 118.4, 117.6, 66.2, 64.7, 25.6, 9.5; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{28}N_2O_4Na$ 407.1941; Found: 407.1940.

P-SS-**6**. Yellow solid (15.0 mg, 67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.55 (br, 2H), 7.32 (ddd, J = 8.3, 7.2, 1.6 Hz, 2H), 7.09 (dd, J = 8.0, 1.6 Hz, 2H), 7.02 (dd, J = 8.4, 1.1 Hz, 2H), 6.74 (ddd, J = 8.2, 7.2, 1.2 Hz, 2H), 4.01−3.57 (m, 8H), 0.94 (d, J = 5.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 162.1, 133.4, 130.7, 118.5, 118.4, 117.4, 68.5, 59.7, 17.4; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{24}N_2O_4Na$ 379.1628; Found: 379.1630.

P-SS-**7**. Yellow solid (20.1 mg, 73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.59 (br, 2H), 7.32 (ddd, J = 8.6, 7.2, 1.6 Hz, 2H), 7.14 (dd, J = 8.0, 1.6 Hz, 2H), 7.01 (dd, J = 8.4, 1.2 Hz, 2H), 6.75 (ddd, J = 8.2, 7.2, 1.2 Hz, 2H), 3.97−3.77 (m, 2H), 3.78−3.65 (m, 4H), 3.68 (br, 2H), 1.60−1.24 (m, 4H), 1.14−0.87 (m, 2H), 0.64 (d, J = 6.5 Hz, 6H), 0.35 (d, J = 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 162.2, 133.3, 130.9, 118.3, 118.3, 117.6, 66.9, 62.6, 41.8, 25.1, 23.8, 21.2; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{36}N_2O_4Na$ 463.2567; Found: 463.2579.

P-SS-**8**. Yellow solid (27.7 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.41 (br, 2H), 7.40 (ddd, J = 8.6, 7.2, 1.6 Hz, 2H), 7.30 (dd, J = 7.9, 1.6 Hz, 2H), 7.15 (dd, J = 8.4. 1.1 Hz, 2H), 7.13−7.08 (m, 6H), 6.81 (ddd, J = 8.2, 7.2, 1.2 Hz, 2H), 6.71−6.57 (m, 4H), 3.85 (tdd, J = 8.3, 5.0, 3.4 Hz, 2H), 3.72 (dd, J = 11.1, 8.9 Hz, 2H), 3.62 (dd, J = 11.1, 3.3 Hz, 2H), 3.13 (br, 2H), 2.76−2.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 162.1, 136.8, 133.7, 130.7, 129.3, 128.6, 126.8, 118.9, 118.5, 117.5, 65.8, 65.5, 39.2; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{32}H_{32}N_2O_4Na$ 531.2254; Found: 531.2281.

Procedure for Formation of Diazo Attached 2,2′-Dihydroxybenzil. A cooled solution containing $NaNO_2$ (145 mg, 2.1 mmol) and water (1.5 mL) was slowly added to a cooled solution of *p*-toluidine (225 mg, 2.1 mmol), 6 M HCl (0.7 mL), and water (0.7 mL) to form the diazonium salt. The diazonium salt solution was then added dropwise to a cooled solution of 2,2′-dihydroxybenzil (242 mg, 1 mmol) dissolved in dilute sodium hydroxide (100 mg in 1.5 mL). The resulting solution was stirred for 2 h. To precipitate the axo-dye, the solution was acidified with 6 M HCl. The precipitate was filtered off and reslurry from MeOH (5 mL) to give the compound **9**.

9. Dark orange solid (234 mg, 49%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.61 (s, 2H), 8.23 (dd, J = 9.1, 2.4 Hz, 2H), 8.14 (dd, J = 2.4, 0.4 Hz, 2H), 7.86−7.55 (m, 4H), 7.31−7.26 (m, 4H), 7.25 (dd, J = 9.1, 0.4 Hz, 2H), 2.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.9, 165.9, 150.5, 145.7, 142.0, 130.4, 130.1, 129.9, 123.0, 120.0, 116.3,

DOI: 10.1021/acs.joc.7b00600
J. Org. Chem. 2017, 82, 6586−6591

21.6; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{28}H_{22}N_4O_4Na^+$ 501.1533; Found: 501.1539.

General Procedure for the Diimine Formation of Diazo Attached 2,2′-Dihydroxybenzil. To a stirred solution of **9** (29.9 mg, 0.0625 mmol) in EtOH (0.125 mL) was added 5 equiv of chiral amino alcohol (0.3125 mmol). The solution was stirred for 6 h at 80 °C, and then all volatile residues were removed in vacuo. The resulting crude mixture was used for CD analysis without further purification.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00600.

Spectroscopic and calculation data and crystallographic details (PDF)

X-ray crystallographic details for *P-SS*-**2** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*hwkim@kaist.edu

ORCID

Hyunwoo Kim: 0000-0001-5030-9610

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful for the financial support provided by Samsung Science and Technology Foundation (SSTF-BA1601-10). The authors thank Dr. Alan J. Lough (University of Toronto) for his X-ray analysis.

■ REFERENCES

(1) (a) Patel, R. N. *Biomolecules* **2013**, *3*, 741. (b) Klingler, F. D. *Acc. Chem. Res.* **2007**, *40*, 1367. (c) Karjalainen, O. K.; Koskinen, A. M. P. *Org. Biomol. Chem.* **2012**, *10*, 4311. (d) Donohoe, T. J.; Callens, C. K. A.; Flores, A.; Lacy, A. R.; Rathi, A. H. *Chem. - Eur. J.* **2011**, *17*, 58. (e) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561. (f) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

(2) For recent reviews, see: (a) You, L.; Zha, D.; Anslyn, E. V. *Chem. Rev.* **2015**, *115*, 7840. (b) Jo, H. H.; Lin, C.-Y.; Anslyn, E. V. *Acc. Chem. Res.* **2014**, *47*, 2212. (c) Wolf, C.; Bentley, K. W. *Chem. Soc. Rev.* **2013**, *42*, 5408. (d) Leung, D.; Kang, S. O.; Anslyn, E. V. *Chem. Soc. Rev.* **2012**, *41*, 448. (e) Berova, N.; Bari, L. D.; Pescitelli, G. *Chem. Soc. Rev.* **2007**, *36*, 914.

(3) (a) De los Santos, Z. A.; Wolf, C. *J. Am. Chem. Soc.* **2016**, *138*, 13517. (b) Seo, M.-S.; Lee, A.; Kim, H. *Org. Lett.* **2014**, *16*, 2950. (c) Kuwahara, S.; Nakamura, M.; Yamaguchi, A.; Ikeda, M.; Habata, Y. *Org. Lett.* **2013**, *15*, 5738. (d) Dragna, J. M.; Pescitelli, G.; Tran, L.; Lynch, V. M.; Anslyn, E. V.; Di Bari, L. *J. Am. Chem. Soc.* **2012**, *134*, 4398. (e) Iwaniuk, D. P.; Wolf, C. *J. Am. Chem. Soc.* **2011**, *133*, 2414. (f) Iwaniuk, D. P.; Wolf, C. *Org. Lett.* **2011**, *13*, 2602. (g) Kim, H.; So, S. M.; Yen, C. P.-H.; Vinhato, E.; Lough, A. J.; Hong, J.-I.; Kim, H.-J.; Chin, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 8657. (h) Borovkov, V. V.; Hembury, G. A.; Inoue, Y. *Acc. Chem. Res.* **2004**, *37*, 449.

(4) (a) Wang, L.; Zhang, T.; Redden, B. K.; Sheppard, C. I.; Clark, R. W.; Smith, M. D.; Wiskur, S. L. *J. Org. Chem.* **2016**, *81*, 8187. (b) Li, X.; Burrell, C. E.; Staples, R. J.; Borhan, B. *J. Am. Chem. Soc.* **2012**, *134*, 9026. (c) You, L.; Berman, J. S.; Lucksanawichien, A.; Anslyn, E. V. *J. Am. Chem. Soc.* **2012**, *134*, 7126. (d) You, L.; Pescitelli, G.; Anslyn, E. V.; Di Bari, L. *J. Am. Chem. Soc.* **2012**, *134*, 7117. (e) You, L.; Berman, J. S.; Anslyn, E. V. *Nat. Chem.* **2011**, *3*, 943. (f) Tartaglia, S.; Padula, D.; Scafato, P.; Chiummiento, L.; Rosini, C. *J. Org. Chem.* **2008**, *73*, 4865.

(5) (a) Tanasova, M.; Anyika, M.; Borhan, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 4274. (b) Wezenberg, S. J.; Salassa, G.; Escudero-Adán, E. C.; Benet-Buchholz, J.; Kleij, A. W. *Angew. Chem., Int. Ed.* **2011**, *50*, 713. (c) Joyce, L. A.; Maynor, M. S.; Dragna, J. M.; da Cruz, G. M.; Lynch, V. M.; Canary, J. W.; Anslyn, E. V. *J. Am. Chem. Soc.* **2011**, *133*, 13746. (d) Superchi, S.; Bisaccia, R.; Casarini, D.; Laurita, A.; Rosini, C. *J. Am. Chem. Soc.* **2006**, *128*, 6893.

(6) (a) Iwaniuk, D. P.; Wolf, C. *Chem. Commun.* **2012**, *48*, 11226. (b) Leung, D.; Anslyn, E. V. *Org. Lett.* **2011**, *13*, 2298. (c) Katoono, R.; Kawai, H.; Fujiwara, K.; Suzuki, T. *J. Am. Chem. Soc.* **2009**, *131*, 16896. (d) Ściebura, J.; Skowronek, P.; Gawronski, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 7069.

(7) (a) Bentley, K. W.; Wolf, C. *J. Org. Chem.* **2014**, *79*, 6517. (b) Bentley, K. W.; Wolf, C. *J. Am. Chem. Soc.* **2013**, *135*, 12200. (c) Ghosn, M. W.; Wolf, C. *J. Org. Chem.* **2011**, *76*, 3888. (d) Ghosn, M. W.; Wolf, C. *J. Am. Chem. Soc.* **2009**, *131*, 16360.

(8) Iwaniuk, D. P.; Bentley, K. W.; Wolf, C. *Chirality* **2012**, *24*, 584.

(9) Bentley, K. W.; Nam, Y. G.; Murphy, J. M.; Wolf, C. *J. Am. Chem. Soc.* **2013**, *135*, 18052.

(10) Zhang, P.; Wolf, C. *Chem. Commun.* **2013**, *49*, 7010.

(11) (a) Hasan, M.; Khose, V. N.; Pandey, A. D.; Borovkov, V.; Karnik, A. V. *Org. Lett.* **2016**, *18*, 440. (b) Ikbal, S. A.; Dhamija, A.; Brahma, S.; Rath, S. P. *J. Org. Chem.* **2016**, *81*, 5440. (c) De los Santos, Z. A.; Ding, R.; Wolf, C. *Org. Biomol. Chem.* **2016**, *14*, 1934. (d) Joyce, L. A.; Sherer, E. C.; Welch, C. J. *Chem. Sci.* **2014**, *5*, 2855. (e) Escárcega-Bobadilla, M. V.; Salassa, G.; Belmonte, M. M.; Escudero-Adán, E. C.; Kleij, A. W. *Chem. - Eur. J.* **2012**, *18*, 6805.

(12) (a) Kim, H.; Nguyen, Y.; Yen, C. P.-H.; Chagal, L.; Lough, A. J.; Kim, B. M.; Chin, J. *J. Am. Chem. Soc.* **2008**, *130*, 12184. (b) Gilli, P.; Bertolasi, V.; Ferretti, V.; Gilli, G. *J. Am. Chem. Soc.* **2000**, *122*, 10405.

(13) *Circular Dichroism: Principles and Applications*, 2nd ed.; Berova, N., Nakanishi, K., Woody, R. W., Eds.; Wiley-VCH: New York, 2000.

(14) The Gaussian 09 was used for all calculations. We used the B3LYP/ 6-31G(d,p) or CAM-B3LYP/ 6-31G(d,p) basis for all atoms. TD-SCF method was used for electronic CD simulation and CD spectra were generated using the program SpecDis v. 1.61.

DOI: 10.1021/acs.joc.7b00600
J. Org. Chem. 2017, 82, 6586−6591