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Reactive Extraction of Enantiomers of 1,2-Amino Alcohols via Stereoselective Thermodynamic and Kinetic Processes

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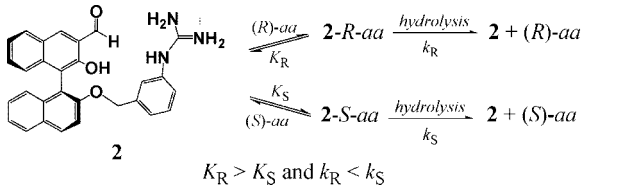
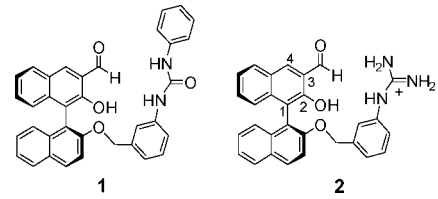


(*R*)-Amino alcohol with an enantiomeric excess of >95% was resolved by reactive extraction processes from 2 equiv of racemic alcohol using a chiral receptor **2** as an enantioselective extractant. One resolution cycle is composed of three extractions: a stereoselective reversible imine formation, a stereoselective irreversible imine hydrolysis, and the recovery of **2** and enantiomeric amino alcohols.

Enantioselective recognition of amino alcohols has been extensively studied[1] because of their importance as a chiral pool in the ligand design for stereoselective catalysts and as biologically active molecules.[2,3] The resolution of enantiomers by solvent extraction has been of interest[4] and currently appears to be a time-saving and cost-effective process. However, industrial scale application of most extractors so far developed is limited due to low enantioselectivity, narrow range of applicable substrates, and sometimes tedious conditions in releasing substrates. Steensma et al. tested several tens of selectors for enantioselective separation of a number of chemically related amino alcohols and amines by solvent extraction.[5] They reported the enantioselectivity of azophenolic crown ether of Hirose[6] to be 5.0 as the highest among those tested and most promising enantioselective extractor.[5]

Recently, we demonstrated[7] that a chiral receptor **1** recognizes the chirality of 1,2-amino alcohols (*aa*) based on reversible imine formation and multiple hydrogen bonding including resonance assisted hydrogen bond (RAHB).[8] Receptor **1** showed moderate stereoselectivity (K_R/K_S) of 3−5. Considering the origin of the stereoselectivity of **1**, strong hydrogen bond donors in the receptor will enhance the stereoselectivity. In this context, we developed a new receptor **2** derivatized with a guanidinium group which provides a charge-reinforced hydrogen bond[9] as a protonated form over a wide pH range.[10]



Scheme 1 describes the synthesis of receptor **2** from (*S*)-2,2′-dihydroxy-1,1′-binaphthyl-3-carboxaldehyde,[7] through selective monoprotection of the hydroxyl group followed by several steps including a PCC oxidation and deprotection. All the compounds were confirmed by spectroscopic data and are in good agreement with the presented structures. It is noteworthy that compound **2** is highly soluble in organic solvents such as chloroform and dichloromethane but not soluble in water even as Cl^- salt form, which is an important requisite as an extractor.

Partial ^{1}H NMR spectra for the enantioselective recognition of 2-amino-1-butanol (*ab*) by receptor **2** in $CDCl_3$ are shown in Figure 1. The aldehyde peak at 9.98 ppm (Figure 1a) disappears on addition of (*S*)-*ab* with a rapid complete formation of an imine (**2**-*S*-*ab*) C−H signal at 8.76 ppm (Figure 1b).

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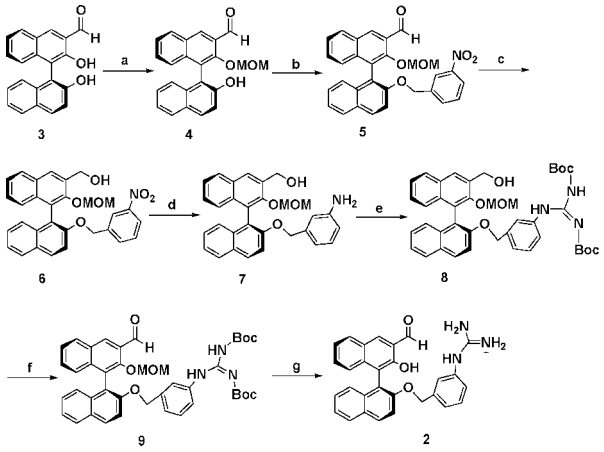
SCHEME 1. Synthesis of 2[a]



[a] Reagents: (a) MOMCl, NaH/DMF; (b) 3-nitrobenzylbromide, NaH/DMF; (c) $NaBH_4/CH_3OH$; (d) Fe, NH_4Cl, C_2H_5OH/dioxane/H_2O, reflux; (e) 1,3-bis-BOC-2-methyl-2-thiopseudourea, TEA, $HgCl_2$/DMF; (f) PCC/CH_2Cl_2; (g) HCl in diethyl ether.

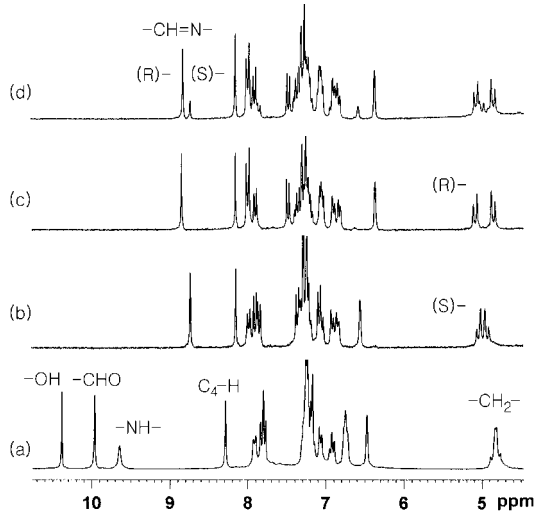


FIGURE 1. Partial ^1H NMR (250 MHz, $CDCl_3$) spectra of (a) **2**, (b) **2**-*S*-*ab*, (c) **2**-*R*-*ab*, and (d) mixture of **2** and 2.0 equiv of racemic 2-amino-1-butanol (*ab*).

Likewise, addition of (*R*)-*ab* to **2** results in the increase of an imine (**2**-*R*-*ab*) C−H signal at 8.88 ppm (Figure 1c). Furthermore, the diastereotopic benzylic CH_2 signals between 4.7 and 5.3 ppm provide prominent information to differentiate **2**-*S*-*ab* and **2**-*R*-*ab*. Figure 2d shows the ^1H NMR spectrum for a mixture of **2**-*S*-*ab* and **2**-*R*-*ab* formed by addition of 2.0 equiv of racemic *ab* to **2**. The integration of imine C−H signals gives the ratio of **2**-*S*-*ab* to **2**-*R*-*ab* to be 3.9:1 at equilibrium, which demonstrates that the imine formation constant for **2**-*R*-*ab* (K_R) is greater than that of **2**-*S*-*ab* (K_S) by a factor of about $3.9^2 = 15$.[11] Although **2**-*S*-*ab* is first formed by the addition of 1 equiv of (*S*)-*ab*, the above equilibrium ratio is obtained within minutes upon addition of 1 equiv of (*R*)-*ab*. The stereoselectivities (K_R/K_S) of **2** for five different amino alcohols are compared with receptor **1** in Table 1. Though both receptors **1** and **2** bind all amino alcohols with the same sense of stereoselectivity, receptor **2** has higher selectivity. Moreover, the selectivity of **2** is 2−3-fold larger than the azophenolic crown ether of Hirose.[5] To the best of our knowledge, **2** represents one of the highly stereoselective small organic receptors for a wide range of underivatized 1,2-amino alcohols.

(11) $K_R = [\mathbf{2}\text{-}R\text{-}aa]/([\mathbf{2}][R\text{-}aa])$ and $K_S = [\mathbf{2}\text{-}S\text{-}aa]/([\mathbf{2}][S\text{-}aa])$, where *aa* = amino alcohol. $K_R/K_S = ([\mathbf{2}\text{-}R\text{-}aa][S\text{-}aa])/([\mathbf{2}\text{-}S\text{-}aa][R\text{-}aa]) = ([\mathbf{2}\text{-}R\text{-}aa]/[\mathbf{2}\text{-}S\text{-}aa])^2$ when $[\mathbf{2}]_0 = [R\text{-}aa]_0 = [S\text{-}aa]_0$.

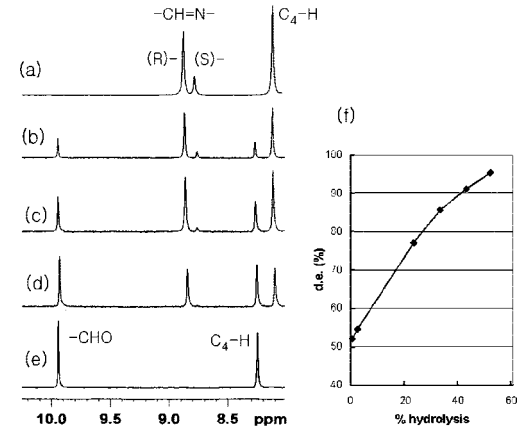


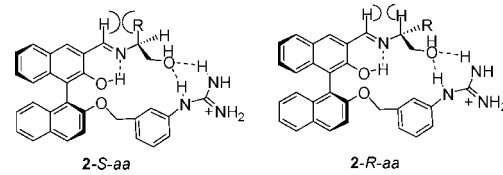
FIGURE 2. The resolution of the (*R*)-enantiomer of *ape* by reactive extraction using **2** as an extractor. (a) ^1H NMR of the $CDCl_3$ layer in equilibrium with the D_2O layer, where **2** and *ape* are in 1:2 ratio. (b−d) Change of ^1H NMR in the $CDCl_3$ layer in contact with 0.1 N DCl/D_2O. (e) ^1H NMR of the $CDCl_3$ layer after hydrolysis of (d) with 1 N DCl/D_2O, which proves complete imine hydrolysis and clean recovery of **2**. (f) Increase of de value upon the hydrolysis.

TABLE 1. Stereoselective Imine Formation (K_R/K_S) of 1 and 2 Measured by ^1H NMR Study[a]

amines	K_R/K_S **1**[7]	K_R/K_S **2**
methylbenzylamine	1.0	1.0
2-amino-1-propanol	3.7	11
2-amino-1-butanol	3.1	15
2-amino-2-phenylethanol	4.8	9.8
phenyl alaninol	3.7	8.3
valinol		12
leucinol		7.4

[a] The solvents used are benzene-d_6 and $CDCl_3$ for **1** and **2**, respectively. The error range is related to NMR integration error.

SCHEME 2. Different Steric Repulsions between 2-*R*-(Amino Alcohol) and 2-*S*-(Amino Alcohol) around The Imine Bond



Scheme 2 illustrates different steric repulsion between the imines **2**-*R*-*aa* and **2**-*S*-*aa*, a key origin of the stereoselective imine formation. The steric energy due to the repulsion between hydrogen and alkyl/aryl around the imine bond in **2**-*S*-*aa* is greater than that in **2**-*R*-*aa* where the interaction is only between the hydrogen atoms. Both the receptors, **1** and **2**, do not bind methylbenzylamine with noticeable stereoselectivity. The stereoselectivity of the receptors toward the amino alcohols is almost completely lost in polar DMSO-d_6. These clearly indicate that the H-bond between the receptor and guest plays an important role in the chiral discrimination. The charge-reinforced stronger H-bonding between the guanidinium motif and OH induces rigidity in the three-dimensional structure of the imine

and thus higher enantioselectivity of **2** compared to that of uryl-based receptor **1**.

We tried reactive extraction of racemic amino alcohol by using **2** as a chiral extractor in the $CDCl_3/D_2O$ bilayer. A 10 mM $CDCl_3$ solution of **2** and a 20 mM D_2O solution of racemic 2-amino-2-phenylethanol (*ape*) were prepared. Ethylene glycol was added to D_2O solution as an integral standard in order to assess the amount of *ape* distribution between aqueous and organic layers. Equal volumes of $CDCl_3$ and D_2O solutions were mixed and shaken for 10 min in a small vial, which was enough for the biphasic system to reach the equilibrium. The pD value of the D_2O layer was adjusted to 7−8 with DCl so that free amino alcohol exists almost exclusively in the aqueous layer. Figure 2a shows the ^{1}H NMR spectrum for the $CDCl_3$ layer, where the aldehyde (**2**) was completely reacted to form imine, and the ratio of **2**-*R*-*ape*/**2**-*S*-*ape* was 3.1. Comparison of peaks of *ape* and ethylene glycol in the ^{1}H NMR spectrum of the D_2O layer represents that the amount of *ape* in the D_2O layer decreased to half of its initial number. Therefore, it is safe to say that the ratio of *R*-*ape*/*S*-*ape* in the D_2O layer is 1/3.1. The thermodynamic equilibrium established between the two layers corresponds to the stereoselectivity of $3.1^2 = 9.6$, which is actually another way to prove the selectivity (K_R/K_S) listed in Table 1. Eventually, the amino alcohol in the D_2O layer is stereoselectively extracted into the $CDCl_3$ layer, giving **2**-*R*-*ape* domination in the organic layer with the diastereomeric excess (de) value of 52%.

Furthermore, the de value in the $CDCl_3$ layer of Figure 2a could be enhanced by second reactive extraction with 0.1 N DCl/D_2O. The hydrolysis is quite slow, irreversible, and stereoselective. The spectra in Figure 2b–d show the changes occurring in the $CDCl_3$ layer according to the imine hydrolysis. As the hydrolysis proceeds, the NMR peaks corresponding to **2** are growing, and the ratio of **2**-*R*-*ape*/**2**-*S*-*ape* is remarkably increasing. The increase of de upon the hydrolysis is displayed in Figure 2f as it approaches >95%. When the hydrolysis obeys first-order rate law, $\ln([\mathbf{2}\text{-}S\text{-}ape]_0/[\mathbf{2}\text{-}S\text{-}ape]) = (k_S/k_R)\ln([\mathbf{2}\text{-}R\text{-}ape]_0/[\mathbf{2}\text{-}R\text{-}ape])$, where k_S and k_R are hydrolysis rate constant for **2**-*S*-*ape* and **2**-*R*-*ape*, respectively. Using this relation, we can obtain $k_S/k_R = 6.4 \pm 0.4$ from the data of Figure 2f.

Finally, acid hydrolysis of the $CDCl_3$ layer of Figure 2d by 1 N DCl/D_2O solution led to fast and clean recovery of receptor **2** in the organic layer as shown in Figure 2e. The amino alcohol released was transferred to the aqueous layer, where the enantiomeric excess (ee) of *ape* must be consistent with the de of the imine form of Figure 2d. In this representative reactive extraction of one cycle with **2**, we could have obtained (*R*)-amino alcohol of >95% ee from 2 equiv of racemic amino alcohol with ∼48% yield.

Figure 3 depicts conceptually the processes of three extractions of this work which are controlled by pH conditions. The first one is a stereoselective reversible imine formation (thermodynamic process); the second one is stereoselective irreversible imine hydrolysis (kinetic and slow process), and the last one is the recovery of **2** and enantiomeric amino alcohol (kinetic and fast process).

In summary, we have developed a highly enantioselective receptor **2** for 1,2-amino alcohols based on charge-reinforced hydrogen bonds between guanidinium motif and alcoholic OH. More interestingly, we have demonstrated that enantiomers of general 1,2-amino alcohols can be resolved by extraction processes, which could be cost-effective and time-saving ones, using **2** as a chiral extractor.

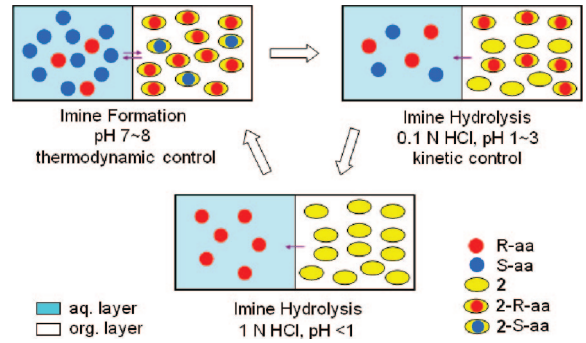


FIGURE 3. Conceptual diagrams representing the (*R*)-*aa* resolution via stereoselective imine formation and hydrolysis in reactive extraction of amino alcohols with a chiral extractor **2**.

Experimental Section

Compound 4. To an ice-cooled solution of (*S*)-1,1′-bi-2-naphtholaldehyde **3** (3.9 g, 12.42 mmol) in DMF was added and stirred NaH (0.447 g, 11.18 mmol) for 1 h. Chloromethyl methyl ether (1.08 mL, 12.42 mmol) in DMF was added to the above mixture (ca. 4 h). After stirring overnight, the reaction mixture was quenched and extracted with ethyl acetate several times. The organic layer was dried, evaporated, and triturated with chloroform/hexane to give a pale yellow solid **4** (2.31 g, 52%): mp 164 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 10.59 (s, 1H), 8.62 (s, 1H), 8.09 (d, 1H, J = 8.0 Hz), 7.99−7.88 (m, 2H), 7.54−7.27 (m, 6H), 7.07 (d, 1H, J = 8.0 Hz), 5.08 (s, 1H), 4.74 (dd, 2H), 3.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 154.4, 151.5, 136.7, 133.6, 132.9, 130.7, 130.4, 130.0, 129.1, 128.9, 128.2, 127.1, 126.6, 125.7, 124.6, 124.1, 123.7, 118.0, 114.5, 100.4, 57.4; HRMS (EI) calcd for $C_{23}H_{18}O_4$ 358.1205; found 358.1201; $[\alpha]_D = -108.17$ (*c* 0.42, $CHCl_3$).

Compound 5. To a stirred ice-cold solution of **4** (0.6 g, 1.67 mmol) in DMF was added NaH (0.081 g, 2.0 mmol). After stirring for 10 min, 3-nitrobenzylbromide (0.434 g, 2.0 mmol) was added and stirred for 4 h. The reaction mixture was quenched and extracted with ethyl acetate several times. The EA layer was dried and evaporated, and column chromatography with EA/hexane (1:3, v/v) gave **5** as pale yellow solids (0.783 g, 95%): mp 71 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 10.65 (s, 1H), 8.64 (s, 1H), 8.07−7.87 (m, 5H), 7.53−7.23 (m, 9H), 5.22 (dd, 2H), 4.77 (dd, 2H), 2.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 139.2, 138.9, 133.9, 132.7, 131.9, 130.6, 130.4, 130.2, 129.5, 129.3, 129.3, 129.1, 128.2, 127.2, 126.8, 126.1, 125.8, 128.3, 124.4, 122.6, 121.7, 119.3, 114.8, 100.4, 69.7, 57.1; HRMS (EI) calcd for $C_{30}H_{23}NO_6$ 493.1525; found 493.1520; $[\alpha]_D = -16.03$ (*c* 1.69, $CHCl_3$).

Compound 6. Sodium borohydride (60 mg, 1.56 mmol) was added to a stirred solution of **5** (0.643 g, 1.3 mmol) in methanol at rt. After being stirred overnight, the mixture was quenched and extracted with EA, dried, and evaporated to give compound **6** quantitatively as an amorphous solid: mp 155 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.09−7.78 (m, 6H), 7.42−7.12 (m, 9H), 5.13 (dd, 2H), 4.96 (s, 2H), 4.55 (dd, 2H), 3.63 (br, 1H), 3.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 153.5, 153.1, 148.1, 139.2, 134.6, 134.0, 133.6, 132.8, 131.2, 130.3, 129.5, 129.2, 129.1, 128.3, 128.2, 127.2, 126.4, 125.5, 125.3, 125.2, 124.4, 122.6, 121.7, 120.4, 115.1, 99.4, 69.8, 61.9, 57.1; HRMS (EI) calcd for $C_{30}H_{25}NO_6$ 495.1682; found 495.1678; $[\alpha]_D = +10.53$ (*c* 0.95, $CHCl_3$).

Compound 7. Nitro compound **6** (0.646 g, 1.3 mmol) was dissolved in a cosolvent of ethanol/dioxane/water with 1/1/1 volume ratio, and iron powder (0.504 g, 9.1 mmol) and ammonium chloride (0.126 g, 2.34 mmol) were added and refluxed overnight. The mixture was filtered and extracted with methylene chloride, and column chromatography with EA/hexane 1:1 mixture gave **7** (0.575

g, 95%) as pale yellow solids: mp 79 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.95−7.79 (m, 4H), 7.40−7.16 (m, 7H), 6.87 (m, 1H), 6.37 (m, 2H), 6.06 (s, 1H), 4.98−4.86 (m, 4H), 4.66 (dd, 2H), 3.52 (br, 3H), 3.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 154.3, 153.1, 146.6, 138.4, 134.7, 134.0, 133.9, 131.2, 130.1, 129.3, 129.1, 128.8, 128.2, 128.1, 127.0, 126.3, 126.0, 125.7, 125.4, 125.2, 124.1, 119.8, 116.6, 115.4, 114.4, 113.5, 99.3, 70.8, 62.0, 57.1; HRMS (EI) calcd for $C_{30}H_{27}NO_4$ 465.1940; found 465.1935; $[\alpha]_D = -3.88$ (*c* 1.80, $CHCl_3$).

Compound 8. To a stirred solution of **7** (0.454 g, 0.98 mmol) and 1,3-bis-BOC-2-methyl-2-thiopseudourea (0.298 g, 1.03 mmol in dry DMF at 0 °C under nitrogen) were added triethylamine (0.54 mL, 3.92 mmol) and $HgCl_2$ (0.291 g, 1.08 mmol). The resulting suspension was stirred at 0 °C for 3 h and at rt overnight. The mixture was diluted with EA and filtered through Celite. Evaporation of the solvent followed by silica column chromatography (EA/hexane, 1:3) gave **8** (0.586 g, 85%) as white solids: mp 118 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 11.68 (s, 1H), 10.12 (s, 1H), 8.01−7.86 (m, 4H), 7.60 (d, 1H, J = 7.9 Hz), 7.46−7.06 (m, 8H), 6.80 (d, 1H, J = 7.6 Hz), 5.09 (dd, 2H), 4.94 (s, 2H), 4.57 (dd, 2H), 3.53 (br s, 1H), 3.18 (s, 3H), 1.59 (s, 9H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 163.5, 153.9, 153.5, 153.1, 137.9, 136.6, 134.3, 133.9, 133.7, 131.0, 129.9, 129.2, 129.1, 128.9, 128.0, 127.9, 126.9, 126.3, 125.7, 125.4, 125.3, 125.1, 124.0, 123.3, 122.0, 120.5, 119.9, 115.4, 99.3, 83.7, 79.7, 70.7, 62.1, 57.1, 28.1, 27.9; HRMS (EI) calcd for $C_{41}H_{45}N_3O_8$ 707.3207; found 707.3204; $[\alpha]_D = +6.26$ (*c* 0.96, $CHCl_3$).

Compound 9. PCC (0.305 g, 1.42 mmol) was added to compound **8** (0.5 g, 0.71 mmol) in methylene chloride at rt. After 12 h, the mixture was passed through a short pad of Celite. The filtrate was concentrated and purified by column chromatography with EA/hexane 1:3 mixture to give **11** (0.46 g, 92%) as white solids: mp 158 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 11.66 (s, 1H), 10.62 (s, 1H), 10.14 (s, 1H), 8.59 (s, 1H), 8.06−7.85 (m, 3H), 7.60 (d, 1H, J = 8.2 Hz), 7.48−7.09 (m, 9H), 6.79 (d, 1H, J = 7.6 Hz), 5.10 (dd, 2H), 4.71 (dd, 2H), 2.93 (s, 3H), 1.58 (s, 9H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 137.8, 137.0, 136.8, 133.8, 131.1, 130.2, 130.2, 129.2, 129.1, 129.0, 128.9, 128.1, 127.0, 128.8, 126.0, 125.9, 125.1, 124.0, 123.2, 121.9, 120.4, 118.8, 115.0, 100.3, 83.8, 79.7, 70.6, 57.1, 28.2, 28.1; HRMS (EI) calcd for $C_{41}H_{43}N_3O_8$ 705.3050; found 705.3045; $[\alpha]_D = -21.79$ (*c* 0.78, $CHCl_3$).

Compound 2. A solution of **9** in methylene chloride was treated with trifluoroacetic acid (2.0 mL) at 0 °C and stirred for 12 h at rt. After neutralization with aqueous NaOH, the organic layer was acidified with dry HCl. The whole evaporation of the solvent afforded **2** quantitatively as yellow solids: mp 170 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 10.38 (s, 1H), 10.10 (s, 1H), 9.64 (s, 1H), 8.29 (s, 1H), 7.77−7.92 (m, 4H), 7.31−6.72 (m, 9H), 6.47 (s, 2H), 6.28 (s, 1H), 4.83 (s, 2H); ^{13}C NMR (DMSO-d_6, 63 MHz) δ 155.6, 153.7, 152.8, 139.0, 136.8, 134.9, 133.2, 130.2, 129.8, 129.4, 128.9, 128,1, 127.2, 126.7, 124.7, 124.3, 124.2, 123.8, 122.8, 122.6, 117.5, 117.4, 115.3, 69.1; HRMS (FAB) calcd for $C_{29}H_{24}N_3O_3$ 462.1818; found 462.1812; $[\alpha]_D = -65.81$ (*c* 0.94, $CHCl_3$).

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for **2**−**9**, and details of the data analysis on the rate constants. This material is available free of charge via the Internet at http://pubs.acs.org.

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