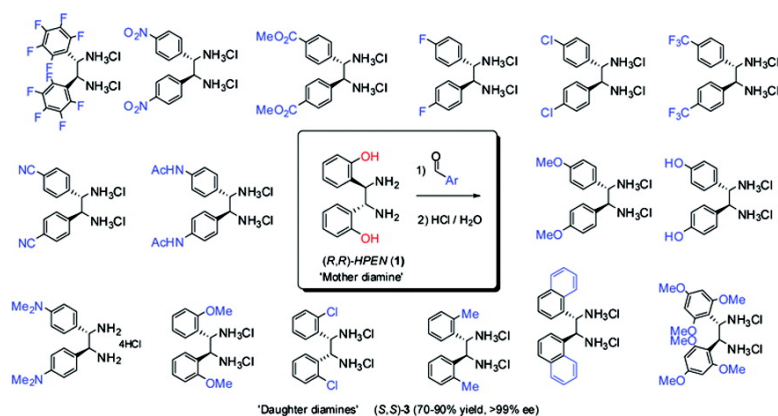


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Stereospecific Synthesis of C_2 Symmetric Diamines from the Mother Diamine by Resonance-Assisted Hydrogen-Bond Directed Diaza-Cope Rearrangement

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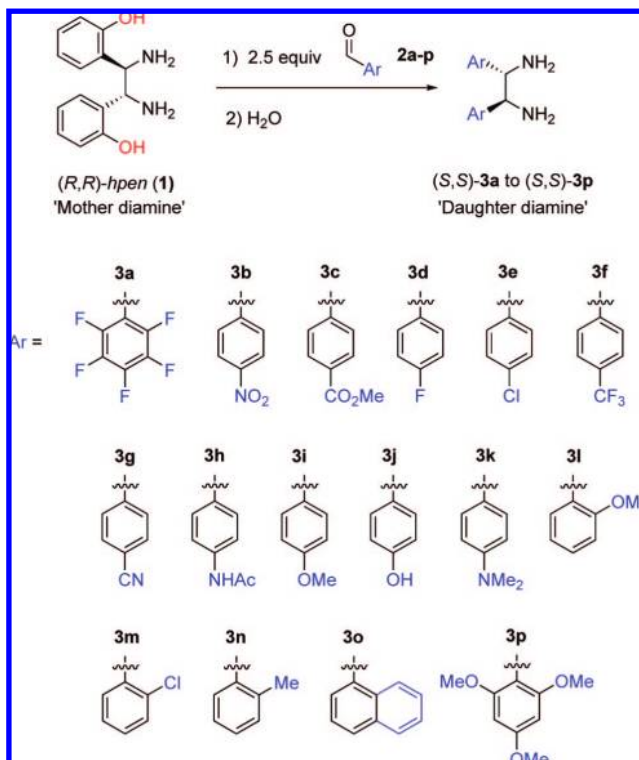
Received June 3, 2008; E-mail: jchin@chem.utoronto.ca

Abstract: Sixteen diphenylethylenediamine analogues including those with electron donating, electron withdrawing, and sterically bulky substituents have been prepared in good overall yields (70~90%) and in enantiomerically pure form (>99% ee) by diaza-Cope rearrangement reaction. A single chiral mother diamine, ((*R,R*)-1,2-bis-(2-hydroxyphenyl)-1,2-diaminoethane), is reacted with appropriate aldehydes to form the initial diimines that rearrange to give all the product diimines in the (*S,S*) form. The daughter diamines are obtained by hydrolysis of the product diimines. Density functional theory computation shows that resonance-assisted hydrogen-bond is the main driving force behind all the rearrangement reactions. Chiral high performance liquid chromatography and circular dichroism spectroscopy show that the highly stereospecific rearrangement reactions take place with apparent inversion of stereochemistry.

Introduction

Chiral diamines may be regarded as privileged structures for making stereoselective catalysts and drugs.^{1,2} Some of the most interesting and effective chiral catalysts developed to date (Chart 1) are based on C_2 symmetric chiral diamines like 1,2-diaminocyclohexane (dach) and 1,2-diphenylethylenediamine (dpn).² These include oxidation³ and reduction⁴ catalysts as well as hydrolysis⁵ and C–C bond forming catalysts⁶ (Chart 1). Diamines are useful not only for making metal-based catalysts but also for making organocatalysts.⁷ While dach and dpn are popular diamine ligands, there is no particular reason why they should be the best for making all diamine-based catalysts. Steric and electronic tuning of chiral catalysts in general can give higher reactivity and stereoselectivity.⁸ Tuning of chiral diamine ligands has been shown to provide interesting mechanistic insights⁹ as well as to yield more effective catalysts.¹⁰ There is much current interest in developing synthetic methods² for building chiral diamine libraries. Such libraries would be useful for the tuning of known catalysts (Chart 1) and receptors as well as for generating new ones.¹¹ In addition, chiral diamine libraries are of considerable interest for developing bioactive compounds.^{1b,12} It is generally difficult to synthesize a wide variety of dpn analogues with electron

Scheme 1

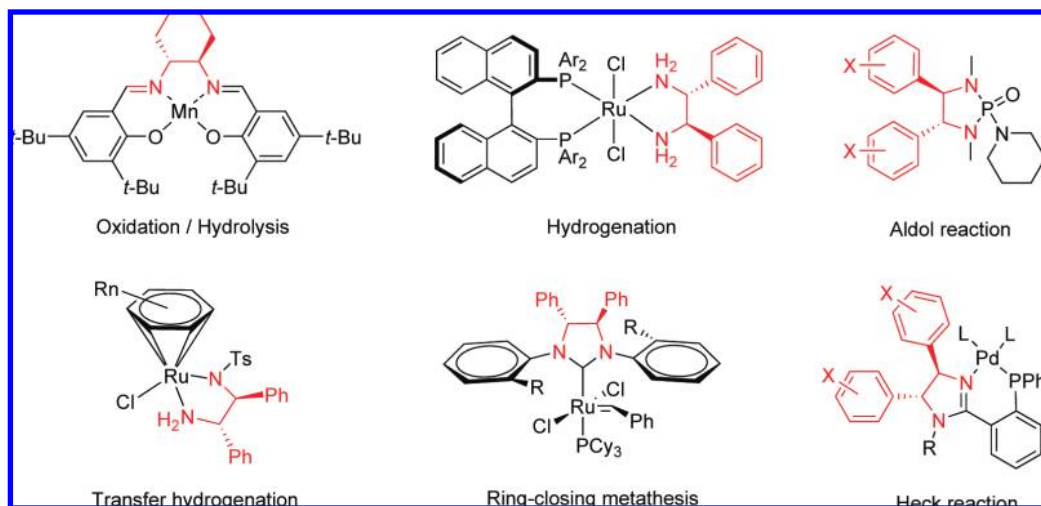


donating, electron withdrawing, or sterically hindered substituents. Resolution of each new chiral diamine often requires tedious optimization.^{13,14} Over thirty years ago Vögtle and

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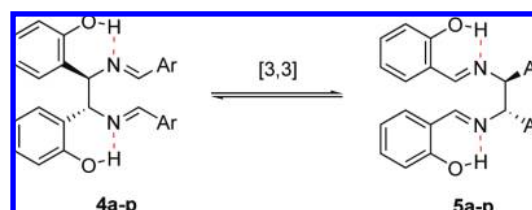
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Chart 1. Diamine Based Catalysts



Goldschmitt showed that a diaza-Cope rearrangement reaction can be used to synthesize meso-vincinal diamines by a unified approach.¹⁵ This elegant reaction has since been widely used to synthesize bioactive compounds based on meso-vincinal diamines.¹⁶ More recently we showed in a preliminary communication that the chiral version of the rearrangement reaction goes even faster and with excellent stereospecificity.¹⁷ Here we examine the scope of this resonance assisted hydrogen bond (RAHB)^{17–19} directed diaza-Cope rearrangement (DCR) reaction for making enantiopure “daughter” diamines from a single “mother” diamine (Scheme 1).

Scheme 2



Results and Discussion

NMR Scale Reactions. To test the scope of the rearrangement reaction for making chiral vicinal diamines, we studied the reaction of 1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (**1**) with a wide variety of aryl aldehydes including those with electron withdrawing (**2a–g**) and donating (**2h–k**) groups at the para position. In addition, we also studied the reaction of **1** with sterically bulky aryl aldehydes (**2l–p**). In all cases, the progress of the rearrangement reaction in DMSO-*d*₆ can be conveniently monitored by ¹H NMR. In a typical reaction, 2.5 equiv of an aldehyde is added to a solution of **1** (50 mM) dissolved in DMSO-*d*₆. The mother diamine (**1**) reacts with the aldehydes (**2a–p**) to form the initial diimines (**4a–p** Scheme 2).²⁰ In general the initial diimines are not isolated since they rearrange to the product diimines (**5**) at ambient temperature. The rearrangement reaction is considerably slower when aldehydes with strongly electron donating groups (**2k**) are used. In

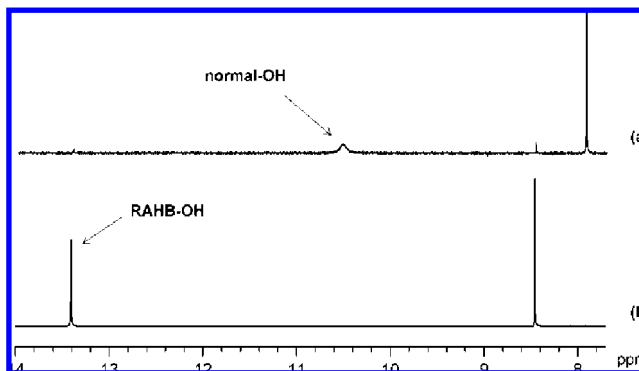


Figure 1. Partial ¹H NMR spectra for conversion of (a) **4k** to (b) **5k** taken in DMSO-*d*₆.

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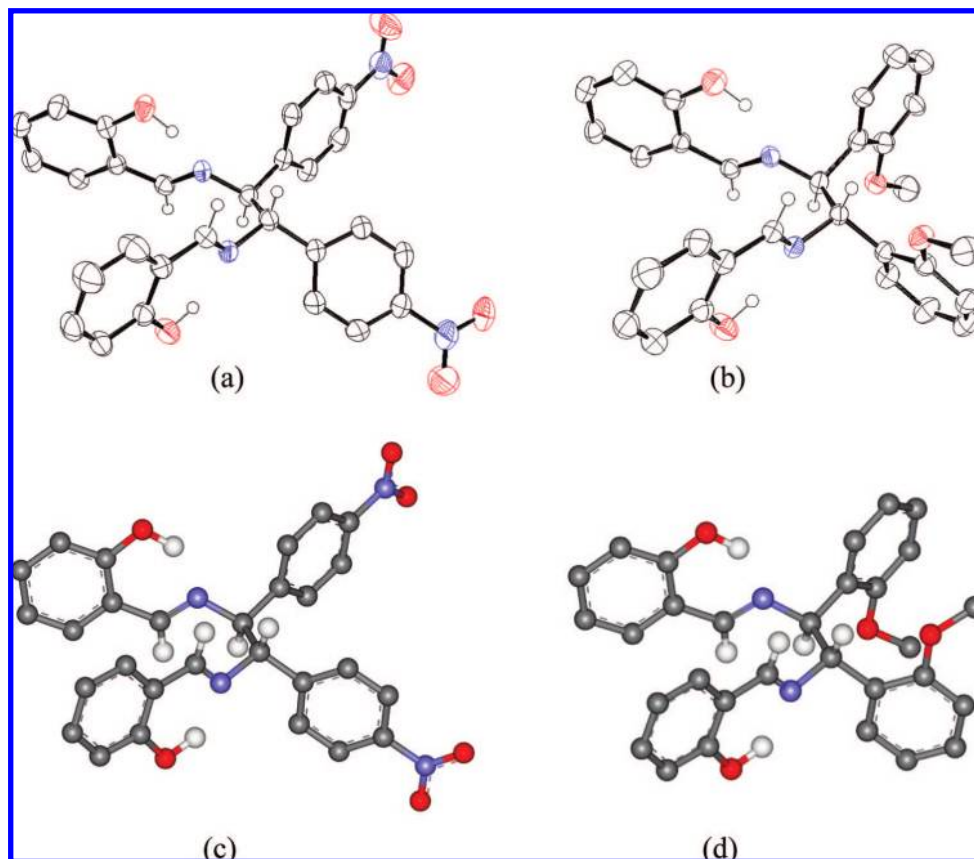
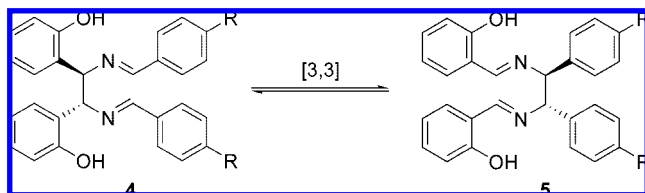


Figure 2. Solid state molecular structures of (a) (*S,S*)-**5b** and (b) (*S,S*)-**5i** with 50% probability thermal ellipsoids and global minimum structures of (c) (*S,S*)-**5b** and (d) (*S,S*)-**5i** at the molecular mechanics level. All hydrogens except for the ones in the phenol, imine, and diamine backbone have been omitted for clarity.

Table 1. Computed Energies of Diaza-Cope Rearrangement Reactions



R	ΔE (kcal/mol) ^a	K (calcd) ^b
NO ₂	-9.9	1.7×10^7
Cl	-7.6	3.8×10^5
H	-6.8	9.3×10^4
OMe	-4.6	2.6×10^3
OH	-4.7	2.5×10^3
NMe ₂	-2.2	4.4×10^2

^a DFT at the B3LYP/6-31G(d) level. ^b Gas phase at 25 °C.

Table 2. Circular Dichroism Cotton Effects of Diimines

compound	1st Cotton effect (nm)	2nd Cotton effect (nm)	isosbetic point (nm)	λ_{\max} (nm, UV-vis)
5a	338	312	320	326
5b	341	316	334	330
5i	333	308	322	322
5p	335	313	326	317

this case, heating the reaction solution (DMSO-*d*₆) at 50 °C for 2 h provides the rearranged diimine. Thus, the rearrangement reaction takes place whether benzaldehydes with electron donating, electron withdrawing, or sterically bulky substituents

are used. The key signal for all the rearrangement reactions is the phenolic ¹H NMR peaks of the product diimines (**5**). This RAHB signal appears as a singlet far downfield (δ 12.4–13.7) of any other peaks. Figure 1 shows a typical ¹H NMR spectrum taken after the rearrangement reaction is complete.

Computation. Molecular mechanics and density functional theory (DFT) computation provide valuable insight into the

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Scheme 3. Calculated Activation Enthalpies for Possible Chairlike Transition States (ts)

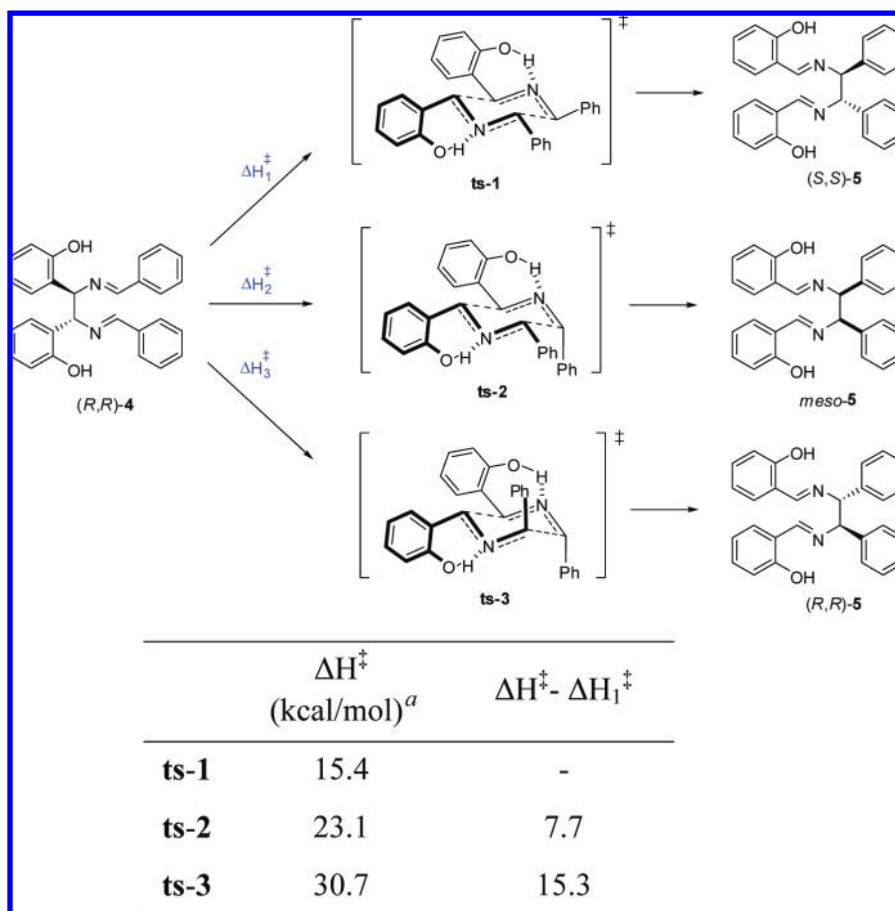
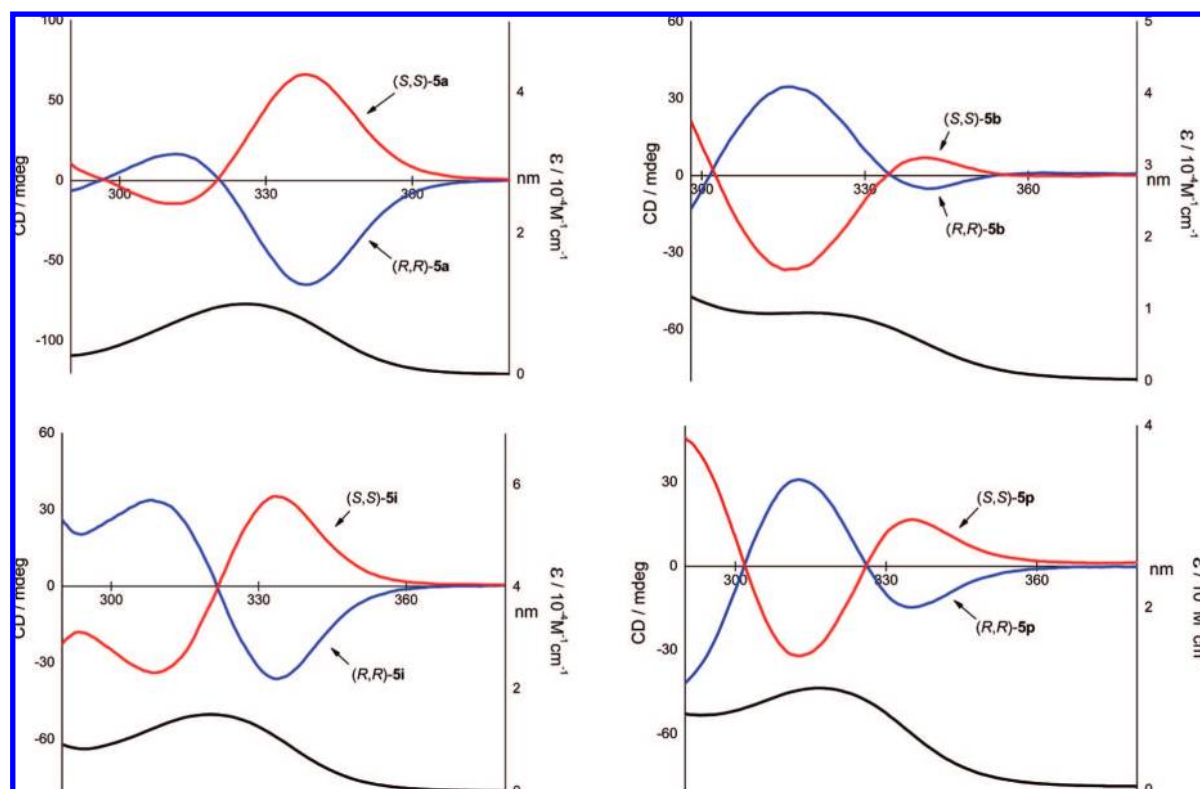
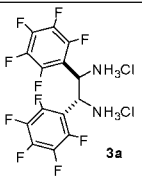
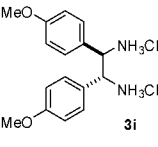
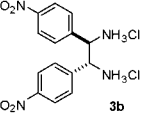
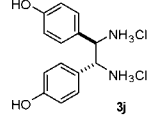
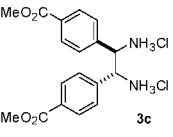
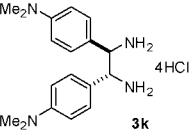
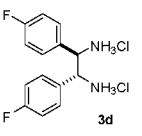
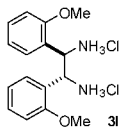
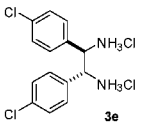
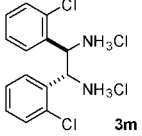
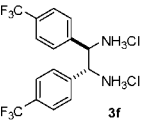
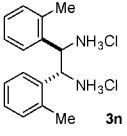
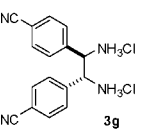
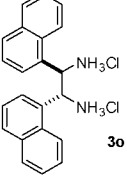
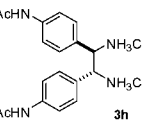
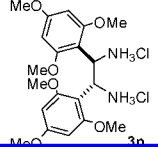
^a DFT at the B3LYP/6-31G(d) level.Figure 3. Circular dichroism spectra of **5a**, **5b**, **5i**, and **5p**, (100 μ M in THF at 25 $^\circ$ C, 1 cm cell) and their UV-vis spectra.

Table 3. Stereospecific Synthesis of Daughter Diamines

Diamine ^a	Method	Yield (%) ^b	Diamine ^a	Method	Yield (%) ^b
	A	77		A	78
	A	73		A	74
	B	87		A	69
	A	87		A	79
	A	78		A	81
	B	80		B	75
	B	85		B	78
	B	90		A	79

^a >99% ee of **5** is obtained when >99% ee of **1** is used. ^b Isolated yield.

diaza-Cope rearrangement reaction. The product diimines (**5a–p**) formed from the reaction of **1** and aryl aldehydes (**2a–p**) all have at least 11 freely rotating single bonds leading to hundreds of possible conformers. Interestingly, the global energy minimum conformers for **5b** and **5l** obtained

by molecular mechanics computation closely match the corresponding crystal structures (Figure 2). While computed structures do not always correspond to crystal structures because of solvent effects and crystal packing, molecular mechanics computation provides a fast and reliable method for finding the global energy minimum conformers in our system.

Although molecular mechanics computation is useful for obtaining the global energy minimum conformer for the product

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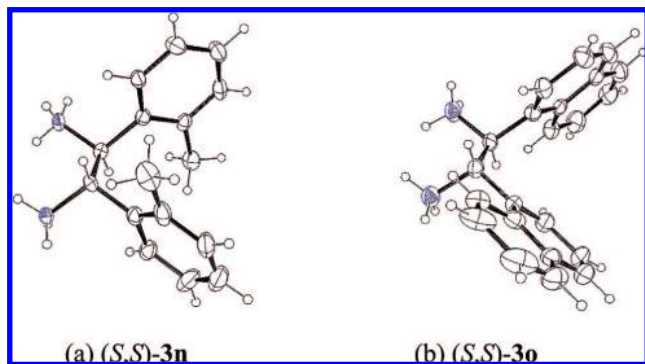


Figure 4. Crystal structures of sterically hindered diamines (**3n** and **3o**, 30% thermal ellipsoid). Chloride counteranion is not shown for clarity.

diimine (**5**), it is not so useful for predicting the values of the equilibrium constants for the rearrangement reaction (Scheme 2). In contrast to the experimental results, molecular mechanics computation shows that the initial diimines (**4**) are much more stable than the corresponding rearranged diimines (**5**). However, DFT computation shows that the rearrangement reactions with electron donating or withdrawing groups (Table 1) are all thermodynamically favorable in agreement with experimental results. DFT computation further shows that the reaction becomes increasingly less favorable with more electron donating substituents. This computational result is consistent with the observation that the rearrangement reaction takes place more slowly with electron donating substituents (e.g., **4k**). Compared to the electron withdrawing substituents, electron donating substituents are better able to stabilize the starting diimine (**4**) by conjugation. Thus the kinetics and thermodynamics of the rearrangement reaction (Scheme 2) are expected to become less favorable with electron donating substituents on the aryl ring.

DFT computation and experimental results clearly show that **5** is more stable than **4**. This is presumably due to the stronger hydrogen bonds in **5** than in **4**.^{17,18} It is interesting to consider why the RAHBs in **5** should be stronger than regular hydrogen bonds in **4**. Charged hydrogen bonds are known to be stronger than neutral hydrogen bonds.^{18b} Thus hydrogen bond between ammonium and acetate is stronger than that between ammonia and acetic acid. In charged hydrogen bonds, the hydrogen bond is reinforced by favorable electrostatic interactions. It appears that in **5**, delocalization of the lone pair electrons on the oxygen through to the nitrogen results in charge separation and strengthening of the hydrogen bond. Such delocalization is not possible in **4**. Resonance-assisted hydrogen bonds play an important role not only in chemistry but also in biology. RAHBs may be found in Watson–Crick base pairing of DNA, α -helical and β -sheet structures of protein, and pyridoxal phosphate dependent enzymatic processes.²¹

It has been shown that there is excellent agreement between the experimental and DFT computational activation enthalpies for the highly stereospecific sigmatropic rearrangement reactions.²² To understand the origin of the stereospecificity, we considered three chairlike transition states for the diaza-Cope rearrangement reaction (Scheme 3). Among these structures,

ts-1 is expected to be the most stable since all aryl substituents are in pseudoequatorial positions. DFT computation shows that **ts-1** is more stable than **ts-2** and **ts-3** by about 7.7 and 15.3 kcal/mol, respectively. Thus one phenyl group in the pseudoaxial position (**ts-2**) should result in about 4×10^5 -fold decrease in the rate of rearrangement at ambient temperature. Reaction of (*R,R*)-**4** through **ts-1** is expected to produce (*S,S*)-**5**. In contrast, reactions of (*R,R*)-**4** through **ts-2** or **ts-3** are expected to produce *meso*-**5** or (*R,R*)-**5** respectively (Scheme 3). Thus DFT computation indicates that the rearrangement should take place exclusively by **ts-1** with apparent inversion in stereochemistry. Indeed, chiral high performance liquid chromatography (HPLC) and circular dichroism (CD) spectroscopy show that there is inversion of stereochemistry with all our rearrangement reactions (see below). We do not detect any *meso*-**5** or (*R,R*)-**5** by chiral HPLC. Interestingly, there is a high degree of preorganization for the rearrangement reaction as the computed and crystal structures of **5b** and **5l** (Figure 2) all resemble the chairlike transition state (**ts**). Combination of computation, X-ray crystallography, chiral HPLC, and CD spectroscopy can be used to support our proposed mechanism for the rearrangement reaction.

Chiral HPLC. The stereospecificity of the rearrangement reaction was determined by chiral HPLC. In general, chiral diamines are derivatized before introduction into the HPLC column.²³ In our case, the product diimine can be directly injected into the column without derivatization. All of our rearrangement reactions (**4** to **5**) go to completion with excellent stereospecificity. There is no observable loss in enantiopurity on going from the initial diimines to the product diimines. This provides a convenient route to enantiopure daughter diamines (>99% ee) without the need for tedious and time-consuming optimization of resolution conditions for individual diamines. It has been shown that diamines like **3a** are difficult to purify even after many cycles of resolution.¹³ All of our rearrangement reactions take place with apparent inversion of stereochemistry as expected from the chairlike transition state with all pseudo-equatorial substituents. This has been further confirmed by CD spectroscopy.

Circular Dichroism Spectroscopy. To verify inversion of stereochemistry for the rearrangement reaction, absolute stereochemistry of the rearranged diimines (**5**) was determined by the exciton chirality method.²⁴ Space coupling of chromophores in a chiral molecule gives rise to bisignate CD curves (Cotton effect) which enables one to determine absolute configuration and conformation of small molecules. Figure 3 shows CD and UV–vis spectra of **5a**, **5b**, **5i**, and **5p**. In all cases, there are two strong Cotton effects of the same amplitude but of opposite signs in (*R,R*)-**5** and (*S,S*)-**5**. The first Cotton effect at 333–341 nm is followed by the second Cotton effect at 308–316 nm (Table 2). According to the exciton chirality analysis, (*R,R*)-**5** is expected to give a negative first Cotton effect followed by a positive second Cotton effect. Similarly (*S,S*)-**5** is expected to give a positive first Cotton effect followed by a negative second Cotton effect. Thus the CD spectra show that the diaza-Cope rearrangement reactions take place with inversion of stereochemistry.

Synthetic scale reactions. A variety of organic solvents can be used for the synthesis of the rearranged diimines (**5**). In some cases, the rearranged diimine precipitates out of ethanol as a yellow solid in 70–80% yield (method A). The rearranged

(20) The imidazolidine intermediate can also be observed by ¹H NMR. This five-membered ring intermediate is stabilized by electron withdrawing substituents.

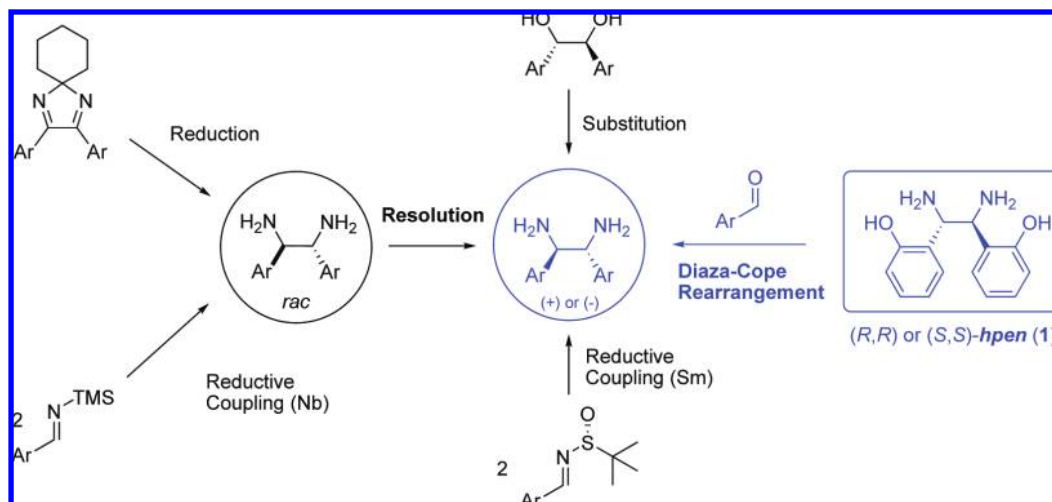
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Scheme 4. Synthesis of Chiral Vicinal Diamines



diimine can also be prepared in DMSO (method B). Once the rearrangement is complete in DMSO, extraction was used to isolate the product diimine. The extract was dried and hydrolyzed (3% concd HCl in THF) without further purification to the diamine dihydrochloride salt as a white powder in good yields (90–99%). The diamine dihydrochloride salt can be converted to the neutral form by extraction under basic conditions. Table 3 shows that a wide variety of diamines (**3**) can be prepared in high overall yields (70–90%) and excellent enantiopurity (>99% ee). Crystal structures of two of the bulky diamines are shown in Figure 4.

Comparison of the DCR Method with Other Methods. Some of the diamines in Table 3 were previously synthesized by other methods. Two of the most widely used methods for making chiral vicinal diamines are (a) Corey's²⁵ reductive amination of benzil analogues (Scheme 4) and (b) Pedersen's²⁶ reductive coupling of imines (Scheme 4). Corey et al. showed that C_2 symmetric chiral vicinal diaryl diamines can be prepared as racemic mixtures in good to excellent yields (85% to 100%) from the corresponding benzil analogues. However, the yields for resolution of the diamines with tartaric acid were generally low (36% to 64% of theoretical yield). Denmark^{10b} and Busacca's^{10c} groups used the reductive coupling method for making a variety of chiral vicinal diamines as a racemic mixture. Although the reductive coupling reaction has the advantage of being simple, the yield for the coupling step is only around 14% to 50% and the reaction requires 2 equiv of niobium.^{10b,c} Tartaric acid resolution gave acceptable separation of some diamine enantiomers,^{10,23} but it failed to give satisfactory results for separation of others like **4a**¹³ and **4k**¹⁴ even after many recrystallizations. In such cases, various chiral acids were screened for resolution¹⁴ or the diamines were derivatized with a chiral reagent and separated by column chromatography.^{10b,13} Thus the overall yields for the synthesis of enantiopure diamines are often low (10% of theoretical yield).¹⁰

One way to avoid tedious resolution of racemic diamines is to synthesize diamine enantiomers stereoselectively. Recently, samarium-mediated reductive coupling of chiral sulfinyl imines has been reported by Xu and co-workers²³ as a direct approach to synthesize enantiomerically pure diaryl vicinal diamines (Scheme 4). This method gave diamine enantiomers with variable yields (25% to 99%). Sharpless asymmetric dihydroxylation of alkenes can also lead to enantiopure diamines (Scheme

4) without the need for chiral resolution.²⁷ This method has the advantage of being catalytic although scale up may be difficult with one of the steps requiring sodium azide.

Conclusion

A wide variety of chiral vicinal diamines were prepared by diaza-Cope rearrangement (DCR) reaction. This method has now been commercialized.²⁸ DFT computational studies show that RAHB is the main driving force for all the rearrangement reactions regardless of the electron withdrawing, electron donating, or sterically bulky substituents. This method has several advantages compared to other methods for making chiral diamines. First, enantiopure mother diamine (hpen, **1**, >99% ee) provides enantiopure daughter diamines (**3**, >99% ee) in high overall yields (70–90%) without the need for individual resolution. Second, the rearrangement reaction can be easily scaled up as it takes place under mild conditions without the need for any catalysts or additives. Third, the enantiomeric excess as well as absolute configuration of the new diamines can be conveniently determined from the intermediate diimines (**5**) by using chiral HPLC and CD spectroscopy. This simple and general process may be valuable not only for steric and electronic tuning of diamine-based catalysts but also for developing novel ligands and catalysts.

Experimental Section

Procedure A. To a cloudy solution of 2.2 g (10 mmol) of 1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (**1**) in 33 mL of ethanol was added 24 mmol of aryl aldehyde. The resulting clear reaction mixture was stirred for 1 h at room temperature to give **5** as a yellow precipitate. The solid was filtered, washed with 10 mL of ethanol, and dried in vacuum.

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Procedure B. To a clear solution of 2.2 g (10 mmol) of 1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (**1**) in 50 mL of DMSO was added 24 mmol of aryl aldehyde. The resulting mixture was stirred overnight at room temperature, and then the mixture was poured into 150 mL of distilled water. The aqueous layer was extracted with diethyl ether. The combined organic layer was washed with distilled water, and dried over sodium sulfate. After evaporation of the solvent, the residue was dried in vacuum.

Hydrolysis of Diimines (5). To a clear solution of **5** (10 mmol) in 100 mL of THF was added 3.0 mL of 37% HCl solution. Stirring the reaction mixture at ambient temperature for 3 h afforded the product as a white precipitate. The solid was filtered and washed with THF to afford analytically pure **3** as the dihydrochloride salt.

Crystal Parameters. 5b: $C_{28}H_{22}N_4O_6$, $T = 150(2)$ K, monoclinic, $P21/n$, $Z = 4$, $a = 16.4941(7)$ Å, $b = 8.9269(5)$ Å, $c = 17.8748(9)$ Å, $\alpha = 90^\circ$, $\beta = 106.919(3)^\circ$, $\gamma = 90^\circ$, $V = 2518.0(2)$ Å³, $R_1 = 0.0558$, $wR_2 = 0.1390$ for $I > 2\sigma(I)$, GOF on $F^2 = 1.014$. **3n:** $C_{16}H_{24.25}Cl_2N_2O_{1.125}$, $T = 150(2)$ K, monoclinic, $C2$, $Z = 16$, $a = 30.0290(11)$ Å, $b = 15.9190(7)$ Å, $c = 19.3815(6)$ Å, $\alpha = 90^\circ$, $\beta = 127.4090(17)^\circ$, $\gamma = 90^\circ$, $V = 7359.3(5)$ Å³, $R_1 = 0.0785$, $wR_2 = 0.2020$ for $I > 2\sigma(I)$, GOF on $F^2 = 1.019$. **3o:** $C_{70}H_{82}Cl_{16}N_6O_4$, $T = 150(1)$ K, orthorhombic, $C2221$, $Z = 4$, $a = 15.6507(7)$ Å, $b = 22.6708(7)$ Å, $c = 19.8315(10)$ Å, $\alpha = 90^\circ$, β

$= 90^\circ$, $\gamma = 90^\circ$, $V = 7036.5(5)$ Å³, $R_1 = 0.0652$, $wR_2 = 0.1608$ for $I > 2\sigma(I)$, GOF on $F^2 = 0.995$.

Computational Methods. All calculations were carried out with Spartan '06 from Wavefunction Inc. DFT computation at B3LYP/6-31G(d) level was used to calculate the optimized geometry and vibrational frequencies. A vibrational analysis was performed at each stationary point to confirm its identity as an energy minimum or a transition structure. The gas-phase enthalpy was calculated as $\Delta H_{298} = \Delta ZPVE + \Delta \Delta H_{0 \rightarrow 298K} + \Delta E_0$. Zero-point vibrational energy (ZPVE) and enthalpy change ($\Delta \Delta H_{0 \rightarrow 298K}$) from 0 to 298 K at 1 atm were obtained from vibrational frequencies.

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Supporting Information Available: Characterization data, calculation results (PDF) and X-ray structural data for **3n**, **3o**, and **5b** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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