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Stereospecific Synthesis of Alkyl-Substituted Vicinal Diamines from the Mother Diamine: Overcoming the "Intrinsic Barrier" to the Diaza-Cope Rearrangement Reaction

Hyunwoo Kim, Mima Staikova, Alan J. Lough, and Jik Chin*

Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, ON, M5S 3H6 Canada

jchin@chem.utoronto.ca

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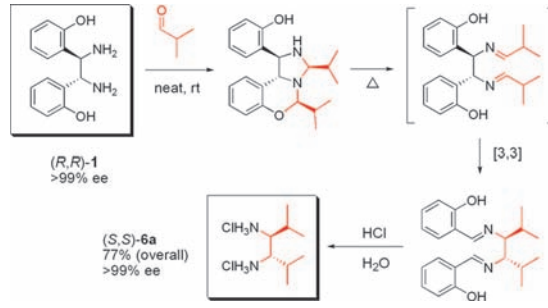
ABSTRACT



Addition of isobutyraldehyde to 1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (mother diamine) cleanly gives a stable, fused imidazolidine-dihydro-1,3-oxazine ring complex. However, vigorous heating of the fused ring complex gives the diaza-Cope rearrangement product with excellent yield and stereoselectivity. A variety of alkyl aldehydes have been used to make corresponding alkyl diamines with excellent yield and stereospecificity. DFT computation shows that the intrinsic barrier for the rearrangement involving alkyl imines is about 7.9 kcal/mol greater than that involving aryl imines.

The elegant synthesis of aryl-substituted *meso* vicinal diamines using the diaza-Cope rearrangement reaction was first reported over 30 years ago by Vögtle and Goldschmitt.[1] More recently, we synthesized a wide variety of aryl-substituted chiral vicinal diamines by the rearrangement reaction (Scheme 1) from the readily available 1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (mother diamine, **1**).[2] However it has been a challenge to synthesize alkyl-substituted vicinal diamines by the rearrangement reaction.[3] While aryl-substituted chiral vicinal diamines[4] are important as ligands for a wide variety of stereoselective catalysts,[5] alkyl-substituted chiral vicinal diamines are found in many bioactive compounds[4,6] including tamiflu,[7] lorabid,[8] and eloxatin.[9] Here we investigate why

(1) (a) Vögtle, F.; Goldschmitt, E. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 767. (b) Chin, J.; Mancin, F.; Thavarajah, N.; Lee, D.; Lough, A.; Chung, D. S. *J. Am. Chem. Soc.* **2003**, *125*, 15276.

(2) (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) Kim, H.; Nguyen, Y.; Lough, A. J.; Chin, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 8678. (c) Kim, H.; Choi, D. S.; Yen, C. P.-H.; Lough, A. J.; Song, C. E.; Chin, J. *Chem. Commun.* **2008**, 1335. (d) Kim, H.-J.; Kim, H.; Alhakimi, G.; Jeong, E. J.; Thavarajah, N.; Studnicki, L.; Koprianiuk, A.; Lough, A. J.; Suh, J.; Chin, J. *J. Am. Chem. Soc.* **2005**, *127*, 16370. (e) Kim, H.-J.; Kim, W.; Lough, A. J.; Kim, B. M.; Chin, J. *J. Am. Chem. Soc.* **2005**, *127*, 16776.

(3) (a) Previous attempts in our laboratory failed with alkyl aldehydes (unpublished). (b) Attempts with alkyl ketones also failed: Vögtle, F.; Goldschmitt, E. *Chem. Ber.* **1976**, *109*, 1.

(4) (a) Kim, H.; So, S. M.; Kim, B. M.; Chin, J. *Aldrichimica Acta* **2008**, *41*, 77. (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.

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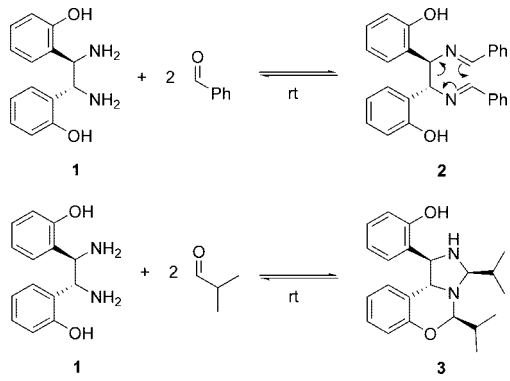
the alkyl-substituted vicinal diamines are difficult to synthesize by the rearrangement reaction[10] and how these difficulties may be overcome.

Scheme 1



When benzaldehyde is added to **1**, the corresponding diimine (**2**) is formed readily followed by the rearrangement reaction at ambient temperature.[2] In sharp contrast, when isobutyraldehyde is added to **1**, a fused imidazolidine-dihydro-1,3-oxazine ring compound (**3**) is formed. In principle, 1, 2, or 3 equiv of isobutyraldehyde could add to **1** to form one, two or three new rings, respectively. Fourteen different products could result from the cyclization reactions including all possible stereoisomers.[11] Surprisingly, only one major product (**3**) is formed stereospecifically and regioselectively in excellent yield (>99%) when the diamine is added to 2 or more equiv of the aldehyde.[11]

Figure 1a shows the crystal structure of the fused imidazolidine-dihydro-1,3-oxazine ring (**3**).[12] There are two new stereogenic centers in the product (both *R* configuration (Scheme 1)). One internal hydrogen bond can be seen between the phenolic group and the secondary amine group (O···N, 2.73 Å; H···N, 1.99 Å; O−H, 0.84 Å). The global energy minimum structure of **3**[13] (Figure 1b) is in excellent agreement with the crystal structure and the solution structure as determined by 2D ^{1}H NMR (Figure S1, Supporting Information). Thus the most stable of the many possible configurational and conformational isomers of **3** is the one that is formed.

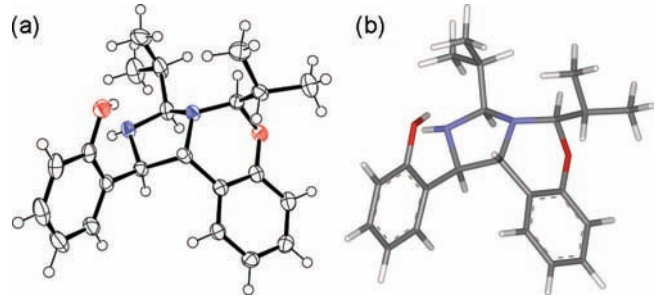


Figure 1. (a) Crystal structure of **3** (50% thermal ellipsoid). (b) Global energy minimum structure of **3**.

Although **3** is stable at room temperature, it cleanly gives the rearranged diimine (**5a**) when heated at 150 °C for 3 h (Scheme 2). We propose that **3** is in equilibrium with the diimine (**4a**), which rearranges to give the product (**5a**).

Hydrolysis of **5a** gave (*S*,*S*)-1,2-diamino-1,2-diisopropylethane dihydrochloride (**6a**), which has been previously synthesized by a different route for the purpose of making NHE3 inhibitors.[14] ^{1}H NMR shows that the concentration of the diimine intermediate (**4a**) does not accumulate to any observable extent during the conversion of **3** to **5a**. Thus the equilibrium appears to greatly favor **3** over **4a**.

A variety of alkyl aldehydes may be used to make alkyl diamines by our method (Table 1). The enantioselectivity of the rearrangement reaction was determined by HPLC.[11] (*R*,*R*)-**3** gave (*S*,*S*)-**5a** in 93% yield with no observable loss

(5) (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691. (c) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40. (d) Yamakawa, M.; Yamada, I.; Noyori, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2818. (e) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840. (f) Kim, H.; Yen, C.; Preston, P.; Chin, J. *Org. Lett.* **2006**, *8*, 5239.

(6) Kotti, S. R. S. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101.

(7) (a) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681. (b) Albrecht, S.; Harrington, P.; Iding, H.; Karpf, M.; Trussardi, R.; Wirz, B.; Zutter, U. *Chimia* **2004**, *58*, 621. (c) Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310. (d) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312. (e) Cong, X.; Yao, Z.-J. *J. Org. Chem.* **2006**, *71*, 5365. (f) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5734. (g) Bromfield, K. M.; Gradén, H.; Hagberg, D. P.; Olsson, T.; Kann, N. *Chem. Commun.* **2007**, 3183. (h) Shie, J.-J.; Fang, J.-M.; Wang, S.-Y.; Tsai, K.-C.; Cheng, Y.-S. E.; Yang, A.-S.; Hsiao, S.-C.; Su, C.-Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 11892. For recent reviews, see: (i) Farina, V.; Brown, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7330. (j) Shibasaki, M.; Kanai, M. *Eur. J. Org. Chem.* **2008**, 1839.

(8) (a) Palomo, C.; Aizpurua, J. M.; Legido, M.; Galarza, R.; Deya, P. M.; Dunoguès, J.; Picard, J. P.; Ricci, A.; Seconi, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1239. (b) Misner, J. W.; Fisher, J. W.; Gardner, J. P.; Pedersen, S. W.; Trinkle, K. L.; Jackson, B. G.; Zhang, T. Y. *Tetrahedron Lett.* **2003**, *44*, 5991. (c) Ciufolini, M. A.; Dong, Q. *Chem. Commun.* **1996**, 881.

(9) (a) Kidani, Y.; Inagaki, K.; Iigo, M.; Hoshi, A.; Kuretani, K. *J. Med. Chem.* **1978**, *21*, 1315. (b) Dullin, A.; Dufrasne, F.; Gelbcke, M.; Gust, R. *Arch. Pharm., Pharm. Med. Chem.* **2004**, *337*, 654. (c) Boga, C.; Fiorelli, C.; Savoia, D. *Synthesis* **2006**, 285.

(10) (a) Roth, W. R.; Lennartz, H.-W.; Doering, W. von E.; Birladeanu, L.; Guyton, C. A.; Kitagawa, T. *J. Am. Chem. Soc.* **1990**, *112*, 1722. (b) Gajewski, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 4393.

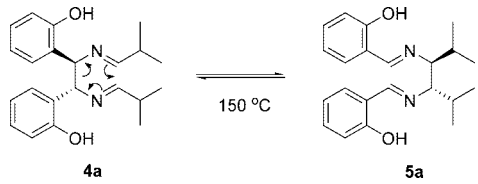
(11) See Supporting Information.

(12) Crystal structure of **3**: $C_{22}H_{28}N_2O_2$, T = 100(2) K, orthorhombic, $P2(1)2(1)2(1)$, Z = 8, a = 9.79070(10) Å, b = 18.3356(2) Å, c = 22.0661(2) Å, a = 90°, b = 90°, g = 90°, V = 3961.27(7) Å^3, R_1 = 0.0246, wR_2 = 0.0648 for $I > 2\sigma(I)$, GOF on $F2$ = 1.013. Crystal structure of **5b**: $C_{28}H_{36}N_2O_2$, T = 150(2) K, orthorhombic, $P2(1)2(1)2(1)$, Z = 4, a = 5.9303(3) Å, b = 10.3195(7) Å, c = 39.850(3) Å, a = 90°, b = 90°, g = 90°, V = 2438.7(3) Å^3, R_1 = 0.0514, wR_2 = 0.1223 for $I > 2\sigma(I)$, GOF on $F2$ = 1.043. Crystal structure of **6b**: $C_{14}H_{32}Cl_{2.67}N_2O_{0.67}$, T = 150(1) K, cubic, $I(2)1(3)$, Z = 12, a = 17.9117(6) Å, b = 17.9117(6) Å, c = 17.9117(6) Å, a = 90°, b = 90°, g = 90°, V = 5746.6(3) Å^3, R_1 = 0.0468, wR_2 = 0.1041 for $I > 2\sigma(I)$, GOF on $F2$ = 1.022.

(13) Geometry optimization was performed at the B3LYP/6-31G(d) level using Spartan 06 Windows from Wavefunction, Inc.

(14) (a) Heinelt, U.; Lang, H.-J.; Hofmeister, A.; Wirth, K. *PCT Int. Appl. WO2003053434*, 2003. (b) Roland, S.; Mangeney, P.; Alexakis, A. *Synthesis* **1999**, 228.

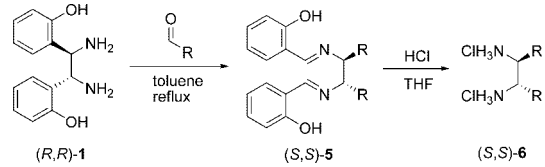
Scheme 2. Diaza-Cope Rearrangement of Alkyl Diimine (**4a**)



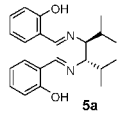
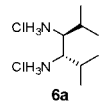
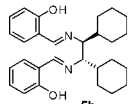
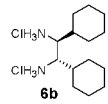
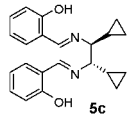
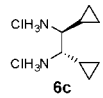
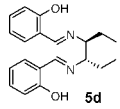
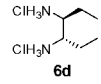
4a **5a**

in enantiopurity (>99%). The inversion of stereochemistry, confirmed by CD spectroscopy,[11] is expected from the chairlike transition state with all equatorial substituents.[2] Although the rearrangement reaction for making alkyl diamines requires considerably harsher conditions than for making aryl diamines, the yield and stereoselectivity remains exceptionally high.

Table 1. Synthesis of Alkyl Vicinal Diamines



(*R*,*R*)-**1** (*S*,*S*)-**5** (*S*,*S*)-**6**

rearranged diimine (**5**)	yield[a] (%)	ee[b] (%)	diamine dihydrochloride (**6**)	yield[a] (%)
 **5a**	85(93)[c]	>99	 **6a**	91
 **5b**	80	>99	 **6b**	95
 **5c**	73	>99	 **6c**	90
 **5d**	71	>99	 **6d**	94

[a] Isolated yield. [b] Determined by HPLC using a Chiralpak AD-H column.[9] [c] Isolated yield starting from **3**.

Figure 2a shows the crystal structure of the rearranged diimine (**5b**)[12] formed from the reaction of **1** and cyclohexane carboxaldehyde. Acid hydrolysis of the diimine (**5b**) cleanly gives the corresponding diamine dihydrochloride (**6b**, Figure 2b).[12]

One reason why a much harsher condition is required to make alkyl diamines than to make aryl diamines may be the unfavorable equilibrium to form the diimine (**4a**) from the

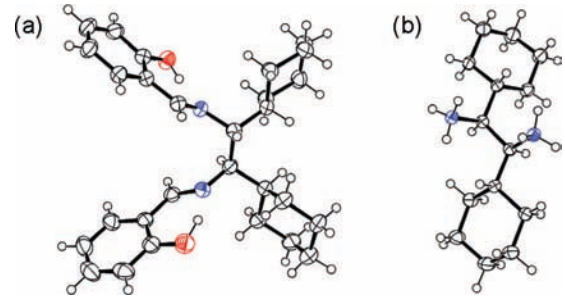


Figure 2. (a) Crystal structure of (*R*,*R*)-**5b** (50% thermal ellipsoid). (b) Crystal structure of (*S*,*S*)-**6b** (50% thermal ellipsoid). Chloride conteranion not shown.

fused ring (**3**) in the alkyl diamine synthesis. Another reason may be the alkyl/aryl substituent effect in the diaza-Cope rearrangement reaction. Detailed kinetic, stereochemical, and computational studies support a concerted mechanism with a chairlike transition state for the rearrangement of unsubstituted 1,5-hexadiene.[15] Aromatic substituents have been shown to stabilize the transition state of the [3,3]-sigmatropic rearrangement reaction.[10]

To gain some insight into the substituent effect of the diaza-Cope rearrangement reaction, we computed the energy values (DFT at the B3LYP/6-31G(d) level)[16] for **2**, **7**, **4a**, and **5a** (Figure 3) along with those for the two corresponding transition states (**2**‡ and **4a**‡). A chairlike transition state with all equatorial substitutions was used in the computation of **2**‡ and **4a**‡.[2] Preorganized, transition-state-like structures were used for the computation of the other four structures (**2**, **7**, **4a**, and **5a**) as in our previous study.[2]

The two imine bonds in **4a** are isolated, whereas in **5a**, **2** and **7** they are conjugated with the aromatic rings. Thus the rearrangement of **4a** to **5a** is expected to be thermodynamically more favorable than the rearrangement of **2** to **7**. Computation shows that the rearrangement of **4a** is thermodynamically more favorable than for the rearrangement of **2** by about 5.5 kcal/mol. Despite the thermodynamic driving force, the energy barrier for the rearrangement of **4a** is about 5.5 kcal/mol higher than that for the rearrangement of **2**. On the basis of these calculations, the equilibrium constant for conversion of **4a** to **5a** is expected to be about 10^4 times greater than that for conversion of **2** to **7**, but the rate of the latter reaction is expected to be about a 10^4 times greater.

(15) (a) Cope, A. C.; Hardy, E. M. *J. Am. Chem. Soc.* **1940**, *62*, 441. (b) Woodward, R. B.; Hoffmann, R. *The Conservation of Obital Symmetry*; Verlag Chemie: Weinheim/Bergstr. Germany and Academic Press: New York, 1970. (c) Dewar, M. J. S. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 761. (d) Wiest, O.; Black, K. A.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 10336. (e) Borden, W. T.; Davidson, E. R. *Acc. Chem. Res.* **1996**, *29*, 67.

(16) 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.

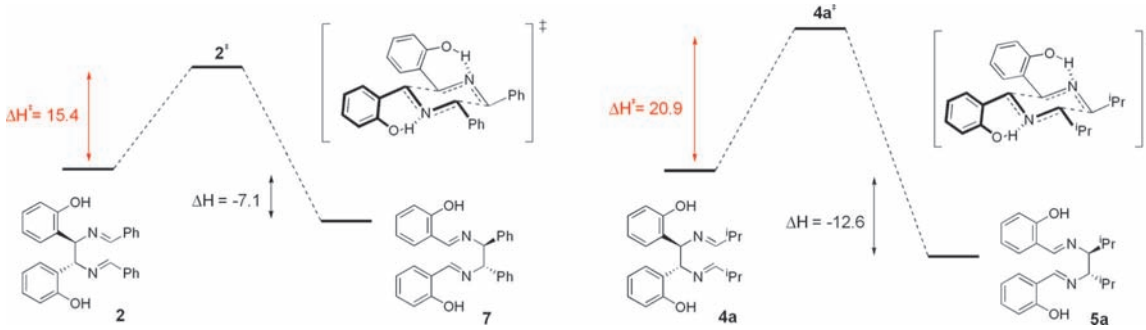


Figure 3. Energy profile for the diaza-Cope rearrangement of aryl and alkyl diimines (ΔH and $\Delta H^{\ddagger}$ values in kcal/mol).

It is interesting to compare the two rearrangement reactions (Figure 3) in terms of the Marcus equation.[17] Although the Marcus equation was initially derived for electron transfer reactions, it has since been used to analyze proton transfer reactions and other organic reactions.[18] According to the Marcus equation ($\Delta G^{\ddagger} = \Delta G_0{}^{\ddagger}(1 + \Delta G/4\Delta G_0{}^{\ddagger})^2$), the kinetic barrier of a reaction ($\Delta G^{\ddagger}$) is separated into the thermodynamic barrier (ΔG) and the so-called intrinsic barrier of the reaction ($\Delta G_0{}^{\ddagger}$; defined as the kinetic barrier in the absence of thermodynamic influence ($\Delta G = 0$)). By solving the Marcus equation, the intrinsic barrier can be expressed in terms of the kinetic barrier and the thermodynamic barrier ($\Delta G_0{}^{\ddagger} = [-(\Delta G/2 - \Delta G^{\ddagger}) + (\Delta G^{\ddagger}(\Delta G^{\ddagger} - \Delta G))^{0.5}]/2$). The value of the intrinsic barrier for conversion of **4a** to **5a** based on the computed values of $\Delta G^{\ddagger}$ and ΔG is 26.8 kcal/mol.[19] Similarly the value of the intrinsic barrier for the conversion of **2** to **7** is 18.9 kcal/mol. Thus the alkyl/aryl substituent effect on the kinetics of the diaza-Cope rearrangement reaction appears to be significant (7.9 kcal/mol).

It has been shown that the diimine formed between benzaldehyde and chiral *dpen* (1,2-diphenyl-1,2-diaminoethane) racemizes by diaza-Cope rearrangement reaction.[20] In principle, it should be possible to make alkyl vicinal diamines from the reaction of chiral *dpen* and alkyl aldehydes, since the diaza-Cope rearrangement reaction is expected to be thermodynamically favorable. However, ^{1}H NMR indicates that addition of 2 equiv of isobutyraldehyde to *dpen* results in production of a mixture of compounds (including the diimine, the imidazolidine, and an enamine formed between the imidazolidine and the aldehyde).[11] This mixture gives many products upon heating. Thus the hydroxyl groups in **1** are crucial for preventing side reactions and also directing the rearrangement reaction cleanly to completion by resonance-assisted hydrogen bonds.[2,21]

Understanding the diaza-Cope rearrangement reaction for making alkyl vicinal diamines is of considerable mechanistic and synthetic interest. Harsher conditions are required for making the alkyl diamines than for making the aryl diamines for two main reasons. First, alkyl aldehydes form fused ring compounds (**3**) with **1**, whereas aryl aldehydes form diimines (**2**) with **1**. Second, the intrinsic barrier for the diaza-Cope rearrangement reaction is much higher with alkyl substituents than with aryl substituents. Remarkably, the hydroxyl groups, in **1** not only facilitate the diaza-Cope rearrangement reaction but also suppress side reactions in the synthesis of alkyl vicinal diamines. Although more work is needed to show the usefulness of the diaza-Cope rearrangement reaction in the synthesis of complex bioactive compounds like tamiflu and lorabid, a detailed understanding of the mechanism has allowed the first stereospecific synthesis of alkyl-substituted vicinal diamines by the rearrangement reaction.

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Supporting Information Available: Experimental data including crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Marcus, R. A. *J. Chem. Phys.* **1956**, *24*, 966.

(18) (a) Guthrie, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 5529. (b) Guthrie, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 5520. (c) Guthrie, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 12878. (d) Murdoch, J. R. *J. Am. Chem. Soc.* **1972**, *94*, 4410. (e) Murdoch, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 2159. (f) Murdoch, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 2660.

(19) $\Delta H^{\ddagger}$ and ΔH were used instead of $\Delta G^{\ddagger}$ and ΔG.

(20) Vögtle, F.; Goldschmitt, E. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 480.

(21) Gilli, P.; Bertolasi, V.; Ferretti, V.; Gilli, G. *J. Am. Chem. Soc.* **2000**, *122*, 10405.