Diastereoselective diaza-Cope rearrangement reaction†

Hyunwoo Kim,[a] Doo Seoung Choi,[b] Cindy Pai-Hui Yen,[a] Alan J. Lough,[a] Choong Eui Song*[b] and Jik Chin*[a]

Received (in Cambridge, UK) 1st November 2007, Accepted 20th December 2007
First published as an Advance Article on the web 23rd January 2008
DOI: 10.1039/b716253g

Steric effect is used to obtain a highly diastereoselective rearrangement reaction.

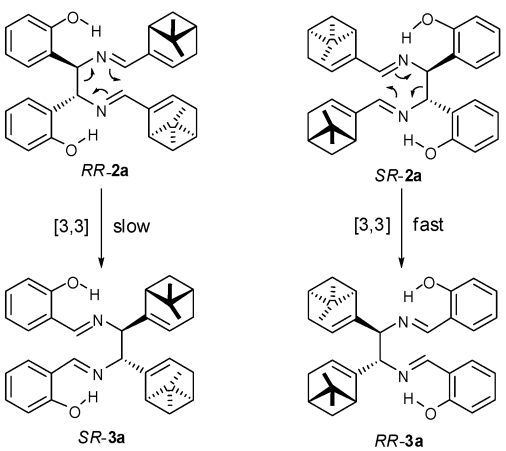
The Cope rearrangement is an extensively studied organic reaction with considerable synthetic and mechanistic interest.[1] Important variations of the reaction including the oxy-Cope,[2] Claisen,[3] and aza-Cope[4] rearrangement reactions have also attracted much attention. Many of these reactions have been found to be particularly useful for making chiral molecules through stereospecific transfer of chirality. We recently reported syntheses of chiral diamines through stereospecific transfer of chirality using diaza-Cope rearrangement reactions.[5] Here we report the reaction of *R*-myrtenal (*R*-**1**) with a racemic mixture of 1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (*rac*-**2**) to give a 1 : 1 mixture of *RR*-**2a** and *RR*-**3a** (Scheme 1).[6] This represents the first highly diastereoselective diaza-Cope rearrangement reaction producing one of the most bulky chiral diamines.[7]

Reaction of 2 equiv. of *R*-**1** (0.2 M) with *rac*-**2** (0.1 M) in ethanol cleanly gave *RR*-**3a** and *RR*-**2a** as a 1 : 1 mixture in excellent yield (Scheme 1). Fig. 1 shows the crystal structures of *RR*-**3a** and *RR*-**2a**.[8] Interestingly, the diimine (*SR*-**2a**) formed between *S*-**2** and *R*-**1** undergoes resonance-assisted H-bond (RAHB)[9] directed diaza-Cope rearrangement reaction[5,10] to give *RR*-**3a** within minutes in ethanol at ambient temperature while the diimine (*RR*-**2a**) formed between *R*-**2** and *R*-**1** does not rearrange to *SR*-**3a** to any appreciable extent under the same condition (Scheme 1).

Fig. 2(a) shows the partial ^{1}H NMR spectrum of the mixture of the diimines (*RR*-**3a** and *RR*-**2a**) formed from the reaction of *R*-**1** with *rac*-**2**. The C–H signals for the diamine backbone of *RR*-**3a** and *RR*-**2a** appear at δ 4.27 ppm and δ 4.81 ppm, respectively. In addition, the alkene C–H signal for *RR*-**3a** (δ 5.48 ppm) is clearly distinct from that of *RR*-**2a** (δ 6.04 ppm).[11] The NMR spectra for diimines *RR*-**3a** (Fig. 2(b)) and *RR*-**2a** (Fig. 2(c)) were also obtained separately from the reactions of *R*-**1** with *S*-**2** and *R*-**2**, respectively.

It is surprising that *SR*-**2a** rearranges to *RR*-**3a** so much more readily than *RR*-**2a** rearranges to *SR*-**3a**. The crystal structures of *RR*-**2a** and *RR*-**3a** (Fig. 1) together with computation (see below) provide valuable insights into the diastereoselectivity of the diaza-Cope rearrangement reaction. The crystal structure of *RR*-**2a** represents the first of its kind. While crystal structures of 'rearranged' diimines have been previously reported,[5,12] it is generally difficult to get crystals of 'initial' diimines formed with **2** as they normally undergo rapid diaza-Cope rearrangement reactions. Although we did not obtain crystal structures of *SR*-**3a** and *SR*-**2a**, computation shows that their structures are analogous to those of *RR*-**2a** and *RR*-**3a**, respectively. Thus there is minimal structural change on going from *RR*-**2a** to *SR*-**3a** and from *SR*-**2a** to *RR*-**3a**.

The rearrangements of *RR*-**2a** and *SR*-**2a** are expected to take place by chair-like six-membered ring transition states with all substituents in the equatorial positions ($\mathbf{TS_1}$ and $\mathbf{TS_2}$). Consistent with this proposed mechanism, the crystal structure of the product (*RR*-**3a**) obtained from the rearrangement of *SR*-**2a** shows that inversion of stereochemistry about the diamine backbone has taken place with the rearrangement reaction. There is remarkable resemblance between the crystal structure of *RR*-**2a** (Fig. 1) and the proposed structure of $\mathbf{TS_1}$. Similarly the crystal structure of *RR*-**3a** (Fig. 1) closely resembles the structure of $\mathbf{TS_2}$. In this respect, the two crystal structures may be regarded as rare transition state analogs that provide valuable insights into the origin of the diastereoselectivity.



Scheme 1

[a] *Department of Chemistry, University of Toronto, 80 St. George street, Toronto, M5S 3H6, Canada. E-mail: jchin@chem.utoronto.ca; Fax: (+1)-416-978-7113*
[b] *Institute of Basic Science, Department of Chemistry, Sungkyunkwan University, Suwon, 440-746, Korea. E-mail: s1673@skku.edu; Fax: (+82)-31-290-7075*

† Electronic supplementary information (ESI) available: Experimental procedures, compound characterization data, and calculation results. See DOI: 10.1039/b716253g

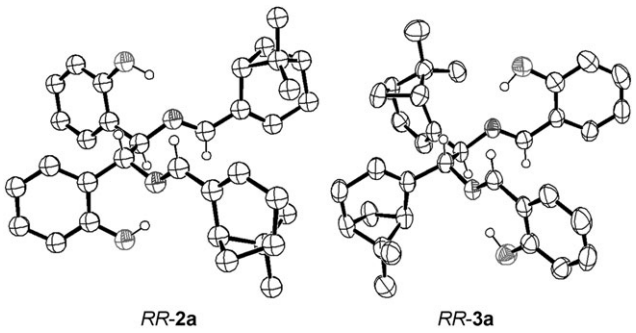


Fig. 1 ORTEP diagrams of *RR*-**2a** and *RR*-**3a** with 50% thermal ellipsoids. All hydrogens except for those in the phenol, imine and diamine backbone have been omitted for clarity.

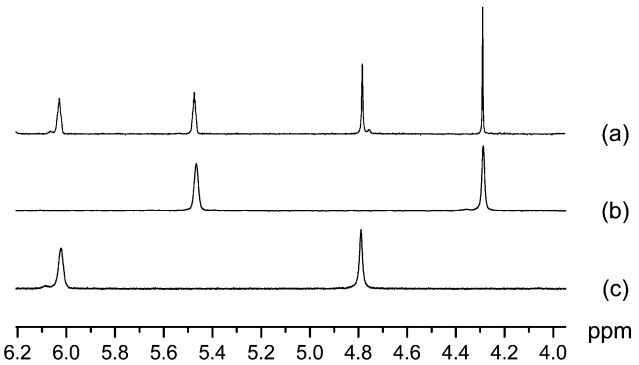
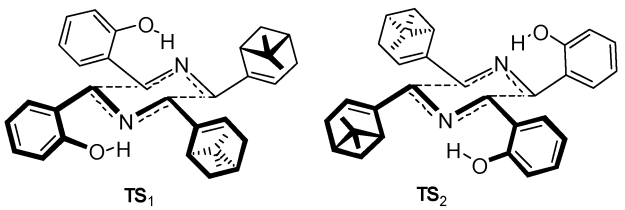


Fig. 2 Partial ^{1}H NMR spectra (DMSO-d_6) from the reactions of *R*-**1** with (a) *rac*-**2** to give a 1 : 1 mixture of *RR*-**3a** and *RR*-**2a**, (b) *S*-**2** to give *RR*-**3a**, and (c) *R*-**2** to give *RR*-**2a**.



If *RR*-**2a** resembles $\mathbf{TS_1}$, why does it not rearrange to *SR*-**3a** as rapidly as *SR*-**2a** rearranges to *RR*-**3a** through $\mathbf{TS_2}$? In order to understand the origin of the diastereoselectivity of the rearrangement reaction, we calculated the structures and energies of *RR*-**2a**, *SR*-**2a**, *SR*-**3a**, *RR*-**3a**, $\mathbf{TS_1}$ and $\mathbf{TS_2}$. There is excellent agreement between the crystal structures of *RR*-**2a** and *RR*-**3a** with their computed global energy minimum structures.[13] Computation further shows that the global energy minimum structures *SR*-**2a** and *RR*-**3a** resemble that of $\mathbf{TS_1}$ and global energy minimum structures of *RR*-**2a** and *SR*-**3a** resemble that of $\mathbf{TS_2}$. In addition, there is structural resemblance between *RR*-**2a** and *SR*-**2a** (also between $\mathbf{TS_1}$ and $\mathbf{TS_2}$ and between *SR*-**3a** and *RR*-**3a**). The only major structural difference between *RR*-**2a** and *SR*-**2a** (and the other two pairs) is that the four myrtenal methyl groups in the former are pointed inwards whereas those in the latter are pointed outwards.

The computed distance between the imine carbons in *RR*-**2a** (3.84 Å) is greater than those in *SR*-**2a** (3.64 Å). Thus, the steric congestion between the four myrtenal methyl groups in *RR*-**2a** that are pointed inwards (Scheme 1 and Fig. 1) appear to decrease the rate of C–C bond formation (to give *SR*-**3a**). In *SR*-**2a**, *RR*-**3a** and $\mathbf{TS_2}$, the four myrtenal methyl groups are pointing away from each other allowing rapid rearrangement. The steric congestion between the methyl groups in *SR*-**3a** is expected to be even greater than that in *RR*-**2a** since the two myrtenal groups in *SR*-**3a** are directly bonded to each other. The difference in computed energies of *SR*-**3a** and *RR*-**3a** (4.09 kcal mol^{-1}) is greater than that of *RR*-**2a** and *SR*-**2a** (0.53 kcal mol^{-1}). The computed transition state energy for $\mathbf{TS_1}$ is about 3.74 kcal mol^{-1} higher than that for $\mathbf{TS_2}$. Thus the computed energy barrier for the conversion of *RR*-**2a** to *SR*-**3a** is higher than that for the conversion of *SR*-**2a** to *RR*-**3a** by about 3.21 kcal mol^{-1}. This translates to a rate ratio of about 230 : 1 for the rearrangement reaction in the gas phase at 25 °C. Steric effect appears to play an important role in the diastereoselectivity of the rearrangement reaction. We recently showed that in chiral diamine catalyzed synthesis of warfarin, steric effect also plays an important role in the stereoselectivity.[12]

The value of the rate constant for the rearrangement of *SR*-**2a** to *RR*-**3a** ($k = 9.6 \times 10^{-5}$ s^{-1} at 25 °C, in DMSO-d_6) is about 400 times greater than that for the rearrangement of *RR*-**2a** to *SR*-**3a** ($k = 2.4 \times 10^{-7}$ s^{-1}) in qualitative agreement with the above computation that excludes any solvent effects. The rearrangement of *SR*-**2a** to *RR*-**3a** in ethanol is too fast for accurate measurement of the rate constant by ^{1}H NMR methods. Hydrolysis of *RR*-**3a** gave the sterically bulky diamine *RR*-**3** in excellent yield. Chiral diamines including bulky ones such as 1,2-bis(2,4,6-trimethylphenyl)-1,2-diaminoethane has been shown to be useful as ligands for a variety of catalysts.[7,14]

Chiral resolution by diastereomeric salt formation is one of the most common and useful ways of separating racemic mixtures of amines (or acids). In this process, the solubility difference of the diastereomeric salts produced from the racemic mixture of an amine and an enantiopure acid is used to separate the amines. We have shown that *R*-myrtenal (*R*-**1**) reacts with racemic 1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (*rac*-**2**) to give diamines *R*-**2** and *RR*-**3** after hydrolysis of the diimines (Scheme 1). While resolution by chemical rearrangement may not become the next general technique for separating racemic mixtures of amines or aldehydes, this represents the first highly diastereoselective diaza-Cope re arrangement reaction. In addition, we can pinpoint the origin of the diastereoselectivity by a combination of computational and crystallographical studies. The origin of the selectivity stems from the steric effect of the myrtenal methyl groups. There is excellent agreement between the transition state analog crystal structures (*RR*-**3a** and *RR*-**2a**) and their global energy minimum structures. Computation further shows that the energy barrier for the rearrangement of *SR*-**2a** to *RR*-**3a** is significantly lower than that for the rearrangement of *RR*-**2a** to *SR*-**3a** (Scheme 1) in agreement with the kinetic data.

Financial supports by the National Sciences and Engineering Research Council of Canada (to J. C.), by Korea Research Foundation (KRF-2005-005-J11901 to C. E. S.) and Korea Science and Engineering Foundation (R01-2006-000-10426-0

and R11-2005-008-00000-0 to C. E. S.) are gratefully acknowledged.

Notes and references

1 (*a*) A. C. Cope and E. M. Hardy, *J. Am. Chem. Soc*., 1940, **62**, 441; (*b*) S. R. Wilson, *Org. React*., 1993, **43**, 93; (*c*) D. A. Hrovat, B. R. Beno, H. Lange, H.-Y. Yoo, K. N. Houk and W. T. Borden, *J. Am. Chem. Soc*., 1999, **121**, 10529.

2 (*a*) D. A. Evans and A. M. Golob, *J. Am. Chem. Soc*., 1975, **97**, 4765; (*b*) E. Lee, I. J. Shin and T. S. Kim, *J. Am. Chem. Soc*., 1990, **112**, 260; (*c*) E. L. O. Sauer and L. Barriault, *J. Am. Chem. Soc*., 2004, **126**, 8569; (*d*) F. Haeffner, K. N. Houk, Y. R. Reddy and L. A. Paquette, *J. Am. Chem. Soc*., 1999, **121**, 11880.

3 (*a*) L. Claisen, *Ber. Dtsch. Chem. Ges*., 1912, **45**, 3157; (*b*) F. E. Ziegler, *Chem. Rev*., 1988, **88**, 1423.

4 (*a*) M. H. Weston, K. Nakajima, M. Pavez and T. G. Back, *Chem. Commun*., 2006, 3903; (*b*) D. Enders, M. Knopp and R. Schiffers, *Tetrahedron: Asymmetry*, 1996, **7**, 1847; (*c*) M. Sugiura, C. Mori and S. Kobayashi, *J. Am. Chem. Soc*., 2006, **128**, 11038; (*d*) D. Fiedler, R. G. Bergman and K. N. Raymond, *Angew. Chem., Int. Ed*., 2004, **43**, 6748.

5 H.-J. Kim, H. Kim, G. Alhakimi, E. J. Jeong, N. Thavarajah, L. Studnicki, A. Koprianiuk, A. J. Lough, J. Suh and J. Chin, *J. Am. Chem. Soc*., 2005, **127**, 16370.

6 The first *R* in *RR*-**3** refers to the configuration of the diamine backbone (at both chirality centers) and the second *R* refers to the myrtenal configuration.

7 (*a*) D. A. Watson, M. Chiu and R. G. Bergman, *Organometallics*, 2006, **25**, 4731; (*b*) A. Kokura, S. Tanaka, T. Ikeno and T. Yamada, *Org. Lett*., 2006, **8**, 3025; (*c*) H. Fujii and Y. Funahashi, *Angew. Chem., Int. Ed*., 2001, **40**, 40; (*d*) M. Yamakawa, I. Yamada and R. Noyori, *Angew. Chem., Int. Ed*., 2002, **41** 3638.

8 *Crystal structure* of *RR*-**2a**, T = 150(2) K, trigonal, $P31$, Z = 9, a = 24.194(3), b = 24.194(3), c = 13.040(3) Å, α = 90, β = 90, γ = 120°, V = 6610.2(19) Å^3, $R1$ = 0.0595, $wR2$ = 0.1017 for $I > 2\sigma(I)$, GOF on F^2 = 0.977. *Crystal structure* of *RR*-**3a**, T = 150(1) K, hexagonal, $P6522$, Z = 6, a = 14.1593(4), b = 14.1593(4) Å, c = 25.3297(10) Å, α = 90, β = 90, γ = 120°, V = 4397.9(2) Å^3, $R1$ = 0.0464, $wR2$ = 0.1194 for $I > 2\sigma(I)$, GOF on F^2 = 1.030. CCDC 665963 and 665964. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b716253g.

9 P. Gilli, V. Bertolasi, V. Ferretti and G. Gilli, *J. Am. Chem. Soc*., 2000, **122**, 10405.

10 (*a*) F. Vögtle and E. Goldschmitt, *Chem. Ber*., 1976, **109**, 1; (*b*) F. Vögtle and E. Goldschmitt, *Angew. Chem., Int. Ed. Engl*., 1974, **13**, 480; (*c*) F. Vögtle and E. Goldschmitt, *Angew. Chem., Int. Ed. Engl*., 1973, **12**, 767; (*d*) R. Gust and H. Schönenberger, *Eur. J. Med. Chem*., 1993, **28**, 103.

11 The ^{1}H NMR signal for the alkene C–H is a broad singlet in DMSO-d_6 and a multiplet in $CDCl_3$ (ESI†).

12 H. Kim, C. Yen, P. Preston and J. Chin, *Org. Lett*., 2006, **8**5239.

13 All calculations were performed using Spartan '06 Windows from Wavefunction Inc. Preliminary global minimum energy structures were obtained by molecular mechanics computation and further minimized by DFT computation (B3LYP at the 6-31G* level).

14 (*a*) C. E. Song, *Chem. Commun*., 2004, 1033; (*b*) D. Savoia, *Top. Organomet. Chem*., 2005, **15**, 1; (*c*) D. Lucet, T. Le Gall and C. Mioskowski, *Angew. Chem., Int. Ed*., 1998, **37**, 2581; (*d*) S. Roland and P. Mangeney, *Top. Organomet. Chem*., 2005, **15**, 191; (*e*) J. A. J. Breuzard, M. L. Christ-Tommasino and M. Lemaire, *Top. Organomet. Chem*., 2005, **15**, 231; (*f*) X. Li, L. B. Schenkel and M. Kozlowski, *Org. Lett*., 2000, **2**, 875; (*g*) O. Chuzel and O. Riant, *Top. Organomet. Chem*., 2005, **15**, 59.