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Stereospecific Synthesis of α-Substituted *syn*-α,β-Diamino Acids by the Diaza-Cope Rearrangement

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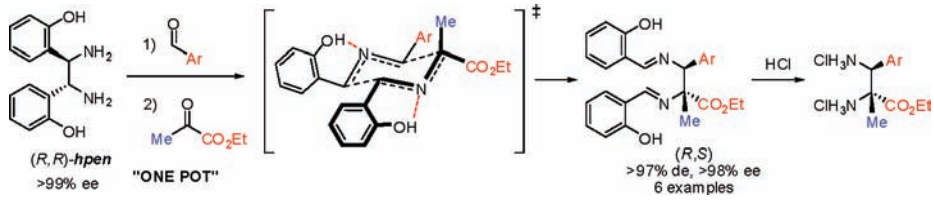
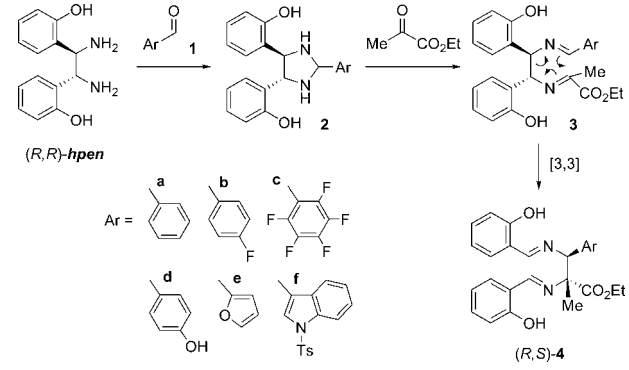
ABSTRACT



Diaza-Cope rearrangement is used to make a variety of α-substituted *syn*-α,β-diamino acids. The rearrangement takes place with complete transfer of stereochemical integrity (>97% de and >98% ee) giving only one of four possible stereoisomers as determined by X-ray crystallography, ^{1}H NMR, and chiral HPLC. The observed stereospecificity can be explained in terms of DFT computation. This represents the first 1,4-diaza-Cope rearrangement with a ketone.

It has been known for over 30 years that diimines derived from *meso*-1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (hpen) and a wide variety of aryl aldehydes undergo diaza-Cope rearrangement (DCR) to give interesting *meso* vicinal diamines.[1] More recently, we developed a stereospecific synthesis of chiral vicinal diamines by the rearrangement of diimines prepared from (*R*,*R*)/(*S*,*S*) hpen and aryl or alkyl aldehydes.[2] However, it has been a challenge to use ketones for the rearrangement. The reaction did not work when the aldehydes were replaced with acetone.[3] Despite inherent difficulties with ketones, DFT computation indicated to us that electron-deficient ketones may work by lowering the kinetic and thermodynamic barriers to the rearrangement reaction. We examined the reactivity of α-ketoesters in the rearrangement reaction (Scheme 1). There has been much interest in developing synthetic methods for making unnatural amino acids[4] including diamino acids.[5] The diaza-Cope rearrangement provides a highly stereospecific "one pot" route to α-substituted *syn*-α,β-diamino ester diimines (**4a** to **4f**).

Scheme 1. Stereospecific Diaza-Cope Rearrangement



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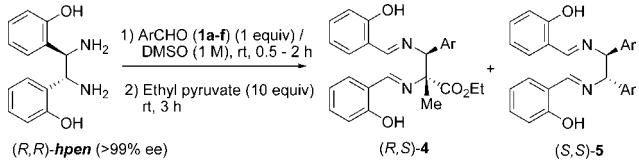
In a typical reaction, aryl aldehyde (2.0 mmol) is reacted with hpen (1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane) (2.0 mmol) in DMSO (2.0 mL) to form an imidazolidine intermediate. In solution, the five-membered ring intermediates (**2a** to **2f**) are in equilibrium with the corresponding ring-opened monoimines. Although ring-opened monoimines become more significant (~10%) with electron-rich aldehydes, the equilibrium favors the five-membered rings in DMSO solution. The imidazolidine ring formation is sluggish for indole-3-carboxaldehyde due to its electron-rich character. However, tosylation of the aldehyde (**1f**) results in facile formation of the imidazolidine (**2f**). A large excess (20 mmol) of ethyl pyruvate is added to the intermediate mixture and stirred for 3 h at ambient temperature to give the rearranged diimines (**4a** to **4f**). Remarkably, only a single diastereomer of the mixed diimine was detected by ^{1}H NMR spectra for all cases. Although some degree of disproportionation leading to symmetric diaryl diimines (**5**) is unavoidable, the desirable diimines (**4a** to **4f**) can be readily separated by column chromatography in isolated yields of 52−67% (Table 1). It

Table 1. Stereospecific Synthesis of α-Substituted *syn*-α,*β*-Diamino Ester Diimines



			(*R*,*S*)-**4**		
entry	Ar	(*R*,*S*)-**4**/(*S*,*S*)-**5**[a]	yield (%)[b]	de (%)[a]	ee (%)[c]
1	Ph (**a**)	12/1	60	>97	>98
2	4-FC_6H_4 (**b**)	15/1	65	>97	>98
3	C_6F_5 (**c**)	8/1	65	>97	>98
4	4-HOC_6H_4 (**d**)	5/1	58	>97	>98
5	2-furanyl (**e**)	10/1	67	>97	>98
6	*N*-tosyl-3-indolyl (**f**)	10/1	52	>97	>97

[a] Determined by ^{1}H NMR analysis of the crude mixture. [b] Isolated yield after column chromatography. [c] Determined by chiral-phase HPLC.

can be seen from Table 1 that the diaza-Cope rearrangement is highly stereospecific even with pyruvate as with aldehydes (within the detection limits of NMR for de and HPLC for ee). Thus, this one-pot reaction allows us to prepare interesting analogues of natural amino acids such as phenylalanine (**4a**), tyrosine (**4d**), and tryptophan (**4f**) as well as a variety of unnatural amino acids in enantiomerically pure form.

The absolute configuration of one of the product diimines **4b** was determined by X-ray crystallographic analysis. Figure 1 shows the crystal structure of a square-planar Ni(II)

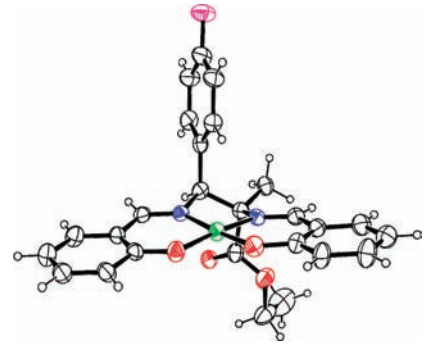


Figure 1. Crystal structure of the nickel(II) complex of **4b** (ORTEP diagram with thermal ellipsoids at 30% probability).

complex formed from **4b**.[6] The crystal structure shows that the configuration at the quaternary center is *R*, while that at the other stereocenter is *S* when the *R*,*R* form of hpen is used for the synthesis. In the crystal structure, the aryl and ester groups occupy the axial positions.

Hydrolysis of the diimine (**4a**) gave the corresponding α-substituted *syn*-α,*β*-diamino ester in 81% yield (Supporting Information). α,*β*-Diamino acids are a special class of vicinal diamines present in many natural products and biologically active compounds.[5] α-Substituted amino acids are attractive building blocks for their use as robust analogues of natural amino acids and as powerful enzyme inhibitors.[7] Although a variety of synthetic methods for making α,*β*-diamino acids or α-substituted amino acids have been reported, it has been a challenge to synthesize α-substituted α,*β*-diamino acids. Only recently their efficient stereoselective synthesis was reported through the aza-Henry (nitro-Mannich) reaction.[8] Interestingly, the *syn*/*anti* selectivity for the aza-Henry reaction can be controlled by complementary catalysts: a Ni_2−Schiff base catalyst[9] provides the *anti* products, while a bifunctional organocatalyst[10] provides the *syn* products. In addition to catalytic C−C bond forming reactions, we propose that the sigmatropic rearrangements can provide a highly stereospecific and convergent route to α-substituted

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(6) Crystal data: $C_{27}H_{24.26}Cl_{2.74}FN_2NiO_4$, T = 150(2) K, orthorhombic, 0.26 × 0.06 × 0.05 mm^3, *P*212121, Z = 4, $\tilde{n}_{calcd}$ = 1.496 Mg/m^3, a = 10.9019(9) Å, b = 13.4448(11) Å, c = 18.6462(16) Å, a = 90°, b = 90°, g = 90°, V = 2733.0(4) Å^3, R_1 = 0.0718, wR_2 = 0.1655 ($I > 2s(I)$); R_1 = 0.1221, wR_2 = 0. 1961 (all data), GOF on F^2 = 1.047.

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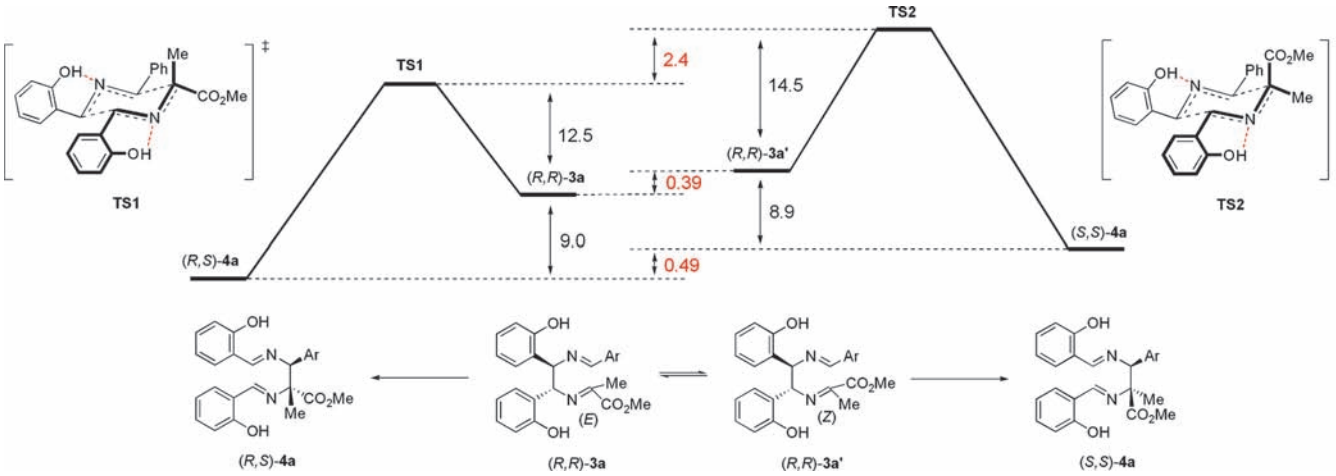

Figure 2. Energy profile for the diaza-Cope rearrangement of (*R*,*R*)-**3a** (enthalpy values in kcal/mol).

syn-α,*β*-diamino acids. The Claisen rearrangement has been used for the diastereoselective synthesis of α-substituted amino acids.[7]

We anticipated the stereospecific rearrangement based on DFT computation (B3LYP at the 6-31G(d) level). Figure 2 shows the energy profile for diaza-Cope rearrangement of the starting diimine (*R*,*R*)-**3a**[11] to give the diaminoester diimine (*R*,*S*)-**4a**. The starting ketoimine can exist in the *E* ((*R*,*R*)-**3a**) or *Z* ((*R*,*R*)-**3a′**) forms. Computation shows that the *E* isomer is slightly more stable than the *Z* isomer (0.39 kcal/mol). The rearrangement of the *E* isomer through the most stable, chairlike, six-membered ring transition state (**TS1** with four equatorial and one axial substituents) leads to diaminoester diimine (*R*,*S*)-**4a**. The rearrangement of the *Z* isomer through the most stable, chairlike, six-membered ring transistion state (**TS2** with four equatorial and one axial substituents) leads to diaminoester diimine (*S*,*S*)-**4a**. Computation shows that the enthalpy change for rearrangement of (*R*,*R*)-**3a** to (*R*,*S*)-**4a** (−9.0 kcal/mol) is comparable to the enthalpy change for rearrangement of (*R*,*R*)-**3a′** to (*S*,*S*)-**4a** (−8.9 kcal/mol). However, the kinetic barrier for conversion of (*R*,*R*)-**3a** to (*R*,*S*)-**4a** (12.5 kcal/mol) is about 2.0 kcal/mol lower than the kinetic barrier for conversion of (*R*,*R*)-**3a′** and (*S*,*S*)-**4a** (14.5 kcal/mol). We suggest that the reaction is under kinetic control as the selectivity is expected to be low under thermodynamic control. Assuming that the starting diimines (*E* and *Z* isomers) are in rapid equilibrium prior to the rearrangement, the difference in the transition state energies (2.4 kcal/mol) translates to a product ratio ((*R*,*S*)-**4a**/(*S*,*S*)-**4a**) of about 57 at 25 °C. On the basis of the *A* values[12] of the methyl and ester groups (1.8 and 1.1 kcal/mol, respectively), the methyl group would be expected to be on the equatorial position and the ester on the axial position of cyclohexane. Interestingly, computation shows that the transition state with the ester in the equatorial position (**TS1**) is more stable than the transition state with the methyl group in the equatorial position (**TS2**) consistent with the observed product stereochemistry ((*R*,*S*)-**4b**, Figure 1).

In conclusion, a ketone has been used for the first time in 1,4-diaza-Cope rearrangements to give diamino acids with quaternary chiral centers. The excellent stereospecificity of the reaction can be rationalized by DFT computation and confirmed by HPLC, ^{1}H NMR, and X-ray crystallography.

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Supporting Information Available: Experimental, spectroscopic, computational, and crystallographic details. This material is available free of charge via the Internet at http://pubs.acs.org.

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