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## The Origins of Stereoselectivity in the $\alpha$ -Alkylation of Chiral Hydrazones

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### Abstract

Density functional theory calculations and experiment reveal the origin of stereoselectivity in the deprotonation–alkylation of chiral *N*-amino cyclic carbamate (ACC) hydrazones. When the ACC is a rigid, camphor-derived carbamate, the two conformations of the azaenolate intermediate differ in energy due to conformational effects within the oxazolidinone ring and steric interactions between the ACC and the azaenolate. An electrophile adds selectively to the less-hindered  $\pi$ -face of the azaenolate. Although it was earlier reported that use of ACC auxiliaries led to  $\alpha$ -alkylated ketones with *ers* of 82:18 to 98:2, B3LYP calculations predict higher stereoselectivity. Direct measurement of the *dr* of an alkylated hydrazone prior to removal of the auxiliary confirms this prediction; the removal of the auxiliary can compromise the overall stereoselectivity of the process.

### Introduction

The  $\alpha$ -alkylation of ketones is a useful synthetic operation, most often achieved via electrophilic addition to a derived azaenolate. Compared with enolates, azaenolates provide improved reactivities, yields, and regioselectivities, and can incorporate nitrogen-based chiral auxiliaries.<sup>i</sup> Enders' SAMP/RAMP auxiliaries—the proline-based (*S*)- and (*R*)-1-amino-2-methoxymethylpyrrolidines (Scheme 1) are widely used.<sup>if,g</sup> An attractive feature of the SAMP/RAMP methodology is the well-defined stereochemical predictability; the appropriate enantiomer of the auxiliary can be chosen in advance. There have been many studies, both experimental and theoretical, of the mechanisms and stereoselectivities of alkylations of azaenolates derived from dialkylhydrazones, imines, and oximes.<sup>ii</sup>

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Supporting Information Available. B3LYP geometries and energies, complete citations for Refs. xvii and xviii, experimental procedures, and analytical data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

We recently discovered that chiral *N*-amino cyclic carbamate (ACC) auxiliaries are convenient alternatives for ketone  $\alpha$ -alkylations (Scheme 2).<sup>iii</sup> ACCs react easily with ketones to afford hydrazones, and can be recovered quantitatively from the products after alkylation. Deprotonation of an ACC hydrazone is rapid; the stereoselectivity of alkylation is high even without the use of extreme low temperature; and yields are excellent. Among the ACCs that we have investigated to date, camphor-based auxiliary **4** (Scheme 2) has proven to give the best yields and enantioselectivities.

A mechanism for the stereoselective alkylation of a SAMP/RAMP hydrazone was proposed by Enders on the basis of crystallographic, spectroscopic, and computational evidence.<sup>ig,iv,v</sup> and is depicted in Scheme 1. Deprotonation of the hydrazone (**1**) under equilibrating conditions gives rise to the lithium azaenolate (**2**), which has an *E* configuration at the CC bond and a *Z* configuration at the CN bond.<sup>vi</sup> The bottom face of **2** is blocked by the pyrrolidine ring, and reaction with an electrophile takes place selectively at the top ( $\beta$ ) face.<sup>vii</sup>

We proposed<sup>iii</sup> that a similar mechanism is followed in the alkylation of an ACC azaenolate, but that the formation of the azaenolate from the hydrazone is controlled by the orientation of the carbonyl group. As shown in Scheme 3, the generalized ACC hydrazone **9** would prefer to exist in the conformation depicted as **9a**, where steric interactions between  $R^2$  and the larger substituent (L) on the auxiliary are minimized. Coordination of LDA to the carbonyl group would then lead to a “*syn*-directed” deprotonation,<sup>viii</sup> giving the *E*<sub>CC</sub>/*Z*<sub>CN</sub>-azaenolate **10a** as a 5-membered chelate. The bottom face of **10a** is sterically blocked, and alkylation should take place selectively at the top ( $\beta$ ) face.

We present here a computational study of the deprotonation of ACC hydrazones and the alkylation of the lithium azaenolates. Density functional theory calculations provide information about the transition states that lead to the selectivities shown in Scheme 2. However, computations predict even higher stereoselectivities than were originally reported.<sup>iii</sup> This discovery prompted us to measure directly the *dr* of an alkylated hydrazone, prior to its conversion to the ketone. Consistent with theoretical predictions, the *dr* of the hydrazone was higher than the *er* of the final ketone, revealing that the removal of the auxiliary indeed compromised the overall stereoselectivity of the process.

## Results and Discussion

To explore the structural properties of ACC hydrazones, we first examined the parent ACC hydrazone **11** (Figure 1). At the B3LYP/6-31G(d) level, two isomers of **11** were located, which differ in the conformation about the N–N bond. The more stable isomer, **11-syn**, has a synclinal arrangement of the N–C<sub>C=O</sub> bond and the N=C bond (CNNC<sub>C=O</sub> dihedral angle 71°). The other isomer (**11-anti**) has an *anti* arrangement of these bonds (dihedral angle 150°), and is 4.7 kcal mol<sup>-1</sup> less stable ( $\Delta H_{0K}$ ). Its lower stability is due to repulsive interactions between the C=N and C=O lone pairs. In both isomers of the hydrazone, the ring nitrogen is pyramidal with an average bond angle of 114°. In this respect, the ACC hydrazone differs from simple carbamates (cf. the species **12** and **13**, Scheme 4), and instead

resembles an *N,N*-dialkylhydrazone (**14**). The NR<sub>2</sub> lone pair in **11** and **14** lies roughly in the same plane as the C=N bond, due to steric effects.<sup>ix</sup>

To study the directed deprotonation of **11**, Li(NMe<sub>2</sub>)(THF) was used as a model for LDA in THF solution. Both **11-syn** and **11-anti** can undergo an intramolecular deprotonation reaction, following coordination of Li(NMe<sub>2</sub>)(THF) to the carbonyl oxygen. The transition states, **TS-11-syn** and **TS-11-anti**, are shown in Figure 2. The reaction involving **11-syn** represents the “*syn*-directed” deprotonation described above (Scheme 3), whereas the reaction of **11-anti** leads to the opposite result, formation of a carbanion *trans* to the ACC group. The “*syn*-directed” deprotonation pathway is favored: **TS-11-syn** lies 1.4 kcal mol<sup>-1</sup> lower than **TS-11-anti**. The absolute barriers, relative to the reactant complexes, are very low or negative in the gas phase ( $\Delta H^\ddagger = 0.3$  and  $-0.6$  kcal mol<sup>-1</sup>, respectively). Because the lowest-energy TS (**TS-11-syn**) appears to have a vacant coordination site on the lithium, we reoptimized its geometry with a second THF coordinated. The second THF was found to bind in a slightly endergonic fashion ( $\Delta G +2.4$  kcal mol<sup>-1</sup> relative to **TS-11-syn** + THF). For the *anti* geometry, the lithium is already 4-coordinate in **TS-11-anti** and a stable structure containing a second THF could not be located.

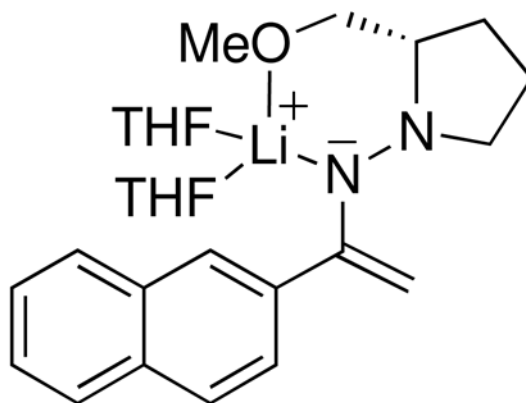
For the chiral hydrazone **15**, derived from the ACC **4**, there are four possible stereoisomers. These are shown in Figure 3(a). Unlike the achiral hydrazone **11**, **15** can only adopt a *syn* conformation. Steric crowding between the rigid bicycloalkane unit and the hydrazone  $\alpha$ -methyl group is too severe for *anti* conformers to be energy minima. The two *syn* conformers, **15-syn-front** and **15-syn-back**, correspond to the proposed structures **9a** and **9b** of Scheme 3, respectively (the terms “front” and “back” refer to the orientation of the carbonyl group). Consistent with the earlier model,<sup>iii</sup> **15-syn-front** is 3.5 kcal mol<sup>-1</sup> more stable than **15-syn-back**. The destabilization of **15-syn-back** can be traced to the conformation about the N–C<sub>4</sub> bond in the oxazolidinone ring. Although the two conformers of **15-syn** are formally related by rotation about the N–N bond, their interconversion also induces a change in configuration at the ring nitrogen. This is depicted in Figure 3(b), which shows Newman projections along the N–C<sub>4</sub> bond after the N=CMe<sub>2</sub> group has been replaced by a hydrogen atom (green). The N–C<sub>4</sub> bond in **15-syn-back** shows substantial eclipsing, with CNCC and NNCC dihedral angles of 12° and 22°, respectively. By contrast, the smallest dihedral angles about N–C<sub>4</sub> in **15-syn-front** are 29° and 56°. The energy difference between the two structures in Figure 3(b) is 2.2 kcal mol<sup>-1</sup> ( $\Delta E$ ).

Transition states for the deprotonation of **15** by coordinated Li(NMe<sub>2</sub>)(THF) are shown in Figure 4. The relative energies of the transition states are the same as those of the hydrazones themselves; **TS-15-syn-front** is 3.5 kcal mol<sup>-1</sup> lower in energy than **TS-15-syn-back**. The barriers relative to reactants (0.5 and 1.1 kcal mol<sup>-1</sup>, respectively) are similar to those for the achiral **TS-11-syn** and **TS-11-anti**. The eclipsing interactions about N–C<sub>4</sub> that were present in **15-syn-back** are also present in **TS-15-syn-back**. There is also a destabilizing steric interaction (shown by the red line) between the hydrazone  $\alpha$ -methyl group and the nearby methyl group on the auxiliary. The chiral ACC effectively blocks *anti* deprotonation and makes the front ( $\beta$ ) deprotonation considerably easier than the back ( $\alpha$ ). The front/back selectivity is calculated to be only marginally affected by solvation. When the transition

structures were optimized in THF using the Conductorlike Polarizable Continuum Model (CPCM),<sup>x,xi</sup> the preference for **TS-15-syn-front** was  $\Delta\Delta H^\ddagger = 3.3$  kcal mol<sup>-1</sup> ( $\Delta\Delta G^\ddagger = 4.2$  kcal mol<sup>-1</sup> at 298.15 K). A transition state related to **TS-15-syn-front**, but containing a second THF in the coordination sphere of Li<sup>+</sup>, was found to be 1.9 kcal mol<sup>-1</sup> less stable ( $\Delta G$ ) in the gas phase.

The overall stereoselectivity of the deprotonation–alkylation sequence is determined by the addition of the azaenolate to the electrophile. The geometry of lithium azaenolate **16**, and transition states for its reaction with MeCl, are shown in Figure 5. Two THF ligands were included in the coordination sphere of Li<sup>+</sup>. During the alkylation, the ACC can be oriented with its carbonyl group lying in front of or behind the plane of the azaenolate. MeCl can add to either conformer, and can approach from either the front or back. Figure 5 shows four transition states, which correspond to these four possible arrangements of the ACC and MeCl with respect to the plane of the azaenolate. The relative enthalpies and free energies are given below each transition state, both for the gas phase and with a THF solvent model in addition to the two explicit THFs.

The lithium azaenolate **16** is subject to the same conformational effects described above for the corresponding hydrazone **15**. The ring nitrogen is less pyramidal than in the corresponding hydrazone, with an average bond angle of 117° in **16-front** and 118° in **16-back**. Pyramidalization (109°) at the ring nitrogen has previously been observed in the crystal structure of the SAMP hydrazone **17**.<sup>vii</sup> The lithium azaenolate **16-back**, like its hydrazone precursor, is destabilized by eclipsing interactions about the N–C<sub>4</sub> bond. **16-back** is also destabilized by steric interactions between the azaenolate and one of the methyl groups on the auxiliary [red line in Figure 5(a)], similar to those present in the TS for its formation (**TS-15-syn-back**, Figure 4). These two effects destabilize **16-back** by 5 kcal mol<sup>-1</sup> relative to **16-front**. The front-back difference increases to 7 kcal mol<sup>-1</sup> in their TSs for reaction with MeCl. Additionally, regardless of the conformation of **16**, there is also a 7 kcal mol<sup>-1</sup> preference for MeCl to add to the  $\pi$ -face where the carbonyl group (coordinated to Li<sup>+</sup>) is located (**TS-16-A**, **TS-16-D**). Addition to the opposite face (**TS-16-B**, **TS-16-C**) is disfavored due to steric repulsion between MeCl and the bicycloalkane group, as indicated by the red lines in Figure 5(b). Thus, the alkylation of **16** takes place exclusively through the lower-energy conformer **16-front**, and MeCl adds selectively to the front side (**TS-16-A**). The large stereochemical preference is the result of both steric effects and Li<sup>+</sup>---Cl<sup>-</sup> attraction in **TS-16-A**.



**17**

Having established the facial selectivity of alkylation at an unsubstituted azaenolate terminus, we then investigated the alkylation of a substituted azaenolate. Deprotonation at a secondary carbon introduces the additional consideration of  $E_{CC}/Z_{CC}$  selectivity. We suggested earlier<sup>iii</sup> that  $E_{CC}$  azaenolates are formed preferentially, on the basis that the allylation of a 3-pentanone-derived hydrazone and a cyclohexanone-derived hydrazone both led to ketones that had the same configuration at the newly-formed stereocenter. Transition states for the deprotonation of an unsymmetrical hydrazone (**18**) by  $\text{Li}(\text{NMe}_2)(\text{THF})$  are shown in Figure 6. The calculated barriers confirm the  $E_{CC}$  selectivity. The TS leading to azaenolate **19- $E_{CC}$**  is favored by  $2.9 \text{ kcal mol}^{-1}$  over the TS leading to **19- $Z_{CC}$** . Similar selectivity for formation of  $E_{CC}$  azaenolates has previously been established for SAMP/RAMP-hydrazones.<sup>vi</sup>

Once formed, the azaenolate **19- $E_{CC}$**  is unlikely to undergo conversion to the  $Z_{CC}$  isomer. We calculate a C=C rotational barrier of  $43 \text{ kcal mol}^{-1}$  for the azaenolate derived from **11**, and the barrier for the more-hindered azaenolate **19- $E_{CC}$**  is likely quite higher. The reaction of **19- $E_{CC}$**  with MeCl is calculated to have a similar stereoselectivity to that of **16**; front-side addition of MeCl to **19- $E_{CC}$**  is favored by  $6.9 \text{ kcal mol}^{-1}$  ( $\Delta\Delta H_{0\text{K}}^\ddagger$ ) over back-side addition (Supporting Information).

Although the B3LYP gas-phase calculations for alkylations of **16** and **19- $E_{CC}$**  predict the correct major products,<sup>iii</sup> they also predict higher stereoselectivity than that reported previously. For example, the allylation of hydrazone **20** with allyl bromide (Scheme 5) was reported to give ketone **22** with an *er* of 96:4, but the gas-phase activation energies for the reactions of the azaenolates **16** or **19- $E_{CC}$**  with MeCl predict the product **22- $\beta$**  would be formed exclusively. This high selectivity decreases only slightly with a bulkier electrophile; for example, the alkylation of **16** by EtCl is calculated to have a stereoselectivity of  $5.7 \text{ kcal mol}^{-1}$  (c.f.  $6.5 \text{ kcal mol}^{-1}$  for MeCl).

The very high predicted gas-phase selectivities prompted us to reappraise the experimental selectivities. In our initial study,<sup>iii</sup> *ers* were determined for the ketone products, following

hydrolytic cleavage of the auxiliary. We repeated the allylation of **20** (Scheme 5), and this time measured the *diastereomer ratio* of **21-β** to **21-α**. HPLC analysis revealed that **21-β** and **21-α** were formed in a ratio of >99:1.<sup>xii</sup> Subsequent hydrolysis of the auxiliary led to **22-β** and **22-α** in a ratio of 96:4. Thus, despite the reasonably mild conditions and short reaction time, erosion of stereochemical integrity occurs during the hydrolysis. We are now seeking improved conditions for auxiliary cleavage.

The predicted stereoselectivity in solution, however, is nevertheless not as high as in the gas phase. For example, in the reaction of the azaenolate **16** with MeCl, the TS leading to the minor product (**TS-16-C**) has a larger degree of charge transfer to MeCl (0.35e) than the lowest-energy TS (**TS-16-A**, 0.29e).<sup>xiii</sup> This would be expected to lead to enhanced stabilization of the minor TS in solution. We calculated CPCM free energies of solvation for the gas-phase structures in THF. The calculated value of  $\Delta\Delta G^\ddagger$  in THF at  $-78^\circ\text{C}$  is only 1.1 kcal mol<sup>-1</sup>, corresponding to a *dr* of 95:5. The same value of  $\Delta\Delta G^\ddagger$  is obtained if the transition structures are fully optimized in the solvent model. Although this value is not expected to be quantitatively accurate (an accurate treatment of solvent effects would require more sophisticated modeling, including treatment of different coordination states for Li<sup>+</sup>), and indeed underestimates the experimental *dr*, it does indicate that the predicted stereoselectivity is sensitive to solvation.

## Conclusion

B3LYP calculations support the model for the stereoselectivity of ketone  $\alpha$ -alkylation shown in Scheme 3. The crucial features are that: (i) the conformation of the intermediate azaenolate is controlled by conformational effects in the oxazolidinone ring and by steric repulsion between the chiral auxiliary and the deprotonated group, and (ii) an electrophile reacts preferentially with the lower-energy azaenolate, from the side opposite the bulky bicycloalkane group. These features resemble the mechanism of stereoiduction in the alkylation of SAMP/RAMP hydrazones.<sup>iv,v</sup>

## Theoretical Calculations

B3LYP calculations<sup>xiv–xvi</sup> were performed with Gaussian 03<sup>xvii</sup> and Gaussian 09.<sup>xviii</sup> The nature of each optimized point was checked by calculation of the vibrational frequencies, and transition states were further verified by IRC calculations.<sup>xix,xx</sup> Zero-point energy and thermal corrections were derived from the B3LYP/6-31G(d) frequencies, scaled by Radom's factors.<sup>xxi</sup> The effects of basis set size were investigated through calculations of the transition states **TS-11-syn** and **TS-11-anti** with the 6-311+G(2d,p) basis (leaving frequencies unscaled); this raised the selectivity in favor of **TS-11-syn** from 1.4 to 2.9 kcal mol<sup>-1</sup>, while the bond lengths involving the transferring proton changed by only 0.01–0.02 Å. The effects of solvation were simulated by means of CPCM calculations<sup>x,xii</sup> using UAKS radii. Free energies of solvation were calculated for the gas-phase-optimized geometries, and were added to the gas-phase free energies to obtain the solution-phase free energies. We also performed geometry optimizations for selected species in THF (Gaussian 09). Solution-phase free energies are quoted at 1 mol L<sup>-1</sup>. Molecular graphics were produced with the CYLview program.<sup>xxii</sup> For simplicity, we have only considered monomeric species where

the Li<sup>+</sup> is coordinated by one NMe<sub>2</sub><sup>-</sup> and one or two THF ligands (for the deprotonation step), or by two THF ligands (for the alkylation step). A fuller treatment would involve adducts having alternative coordination numbers and aggregation states, as well as multiple conformational isomers. Collum<sup>xxiii</sup> has shown, for example, that at high THF concentrations, the lithium azaenolate derived from cyclohexanone phenylimine exists predominantly as a monomeric species with three THF ligands coordinated to Li<sup>+</sup>. The structures, aggregation states, and reactivities of lithium enolates and related species have been studied computationally by Pratt.<sup>xxiv</sup> In our simple model complexes, sampling of different THF conformations showed energetic variations amounting to a few tenths of a kcal mol<sup>-1</sup>.

## Experimental Methods

### Allylation of **20**

*n*-BuLi (2.5 M in hexanes, 100  $\mu$ L, 0.250 mmol) was added dropwise over ca. 2 min to a stirred and cooled (-78 °C) solution of diisopropylamine (38.2  $\mu$ L, 0.272 mmol) in THF (1.0 mL) (Ar atmosphere). The mixture was cooled for 30 min with an ice-H<sub>2</sub>O bath, and then cooled to -40 °C. A solution of **20** (60.0 mg, 0.227 mmol) in THF (1.0 mL) was added by cannula, with additional THF (2  $\times$  0.3 mL) as a rinse, and the mixture was stirred for 45 min. Allyl bromide (23.7  $\mu$ L, 0.272 mmol) was then added and stirring was continued for 5 min. The cold bath was removed and the mixture was stirred for an additional 40 min and then partitioned between Et<sub>2</sub>O and H<sub>2</sub>O. The aqueous phase was extracted with Et<sub>2</sub>O (twice) and the combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>), filtered, and evaporated under reduced pressure to give crude **21**. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  5.90–5.70 (m, 1H), 5.18–4.94 (m, 2H), 4.25 (dd, *J* = 8.1, 4.1 Hz, 1H), 3.18–3.04 (m, 1H), 2.50–2.24 (m, 4H), 2.14–1.80 (m, 4H), 1.76 (t, *J* = 4.4 Hz, 1H), 1.26–1.32 (m, 2H), 1.23 (s, 3H), 1.16 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H). HPLC analysis of this material showed a 99.3:0.7 mixture of **21**- $\beta$ -**21**- $\alpha$ .<sup>xxv</sup>

The crude material was purified via flash chromatography over silica gel using 10:90 EtOAc-hexanes to give **21** as a pure, light-yellow oil (66 mg, 96%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  5.90–5.70 (m, 1H), 5.18–4.94 (m, 2H), 4.25 (dd, *J* = 8.1, 4.1 Hz, 1H), 3.18–3.04 (m, 1H), 2.50–2.24 (m, 4H), 2.14–1.80 (m, 4H), 1.76 (t, *J* = 4.4 Hz, 1H), 1.26–1.32 (m, 2H), 1.23 (s, 3H), 1.16 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  184.4, 155.5, 136.6, 116.7, 82.9, 73.4, 47.9, 43.1, 37.6, 35.6, 35.1, 26.7, 25.8, 24.8, 21.5, 19.3, 17.3, 10.4; ESI-MS *m/z* [M + H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub>: 305.44, found 305.1. HPLC analysis of this material showed exclusively **21**- $\beta$ .<sup>xxv</sup>

### Hydrolysis of **21**- $\beta$

*p*-TsOH·H<sub>2</sub>O (83 mg; 0.436 mmol) was added to a stirred solution of **21**- $\beta$  (66 mg, 0.218 mmol) in acetone (2 mL). The mixture was stirred for 15 min and then partitioned between Et<sub>2</sub>O and saturated aqueous NaHCO<sub>3</sub>. The aqueous phase was extracted with Et<sub>2</sub>O (twice) and the combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>), filtered, and evaporated under reduced pressure to give a colorless oil. GC analysis of this material showed a 96:4 mixture of **22**- $\beta$ -**22**- $\alpha$ .<sup>xxv</sup> Flash chromatography of the remaining crude

material over silica gel using 5:95 Et<sub>2</sub>O-pentane gave **22** (25.8 mg, 94%) as a pure, colorless oil. Spectroscopic data was identical to that reported previously.xxvi

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

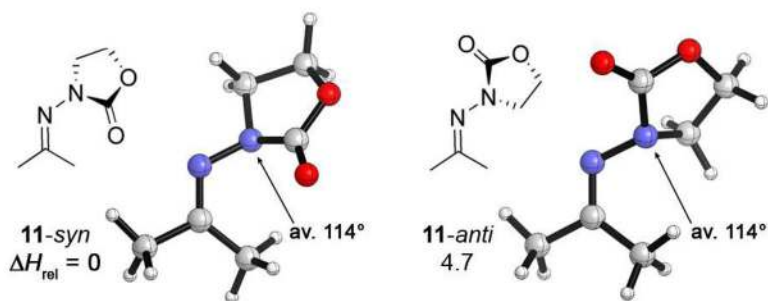
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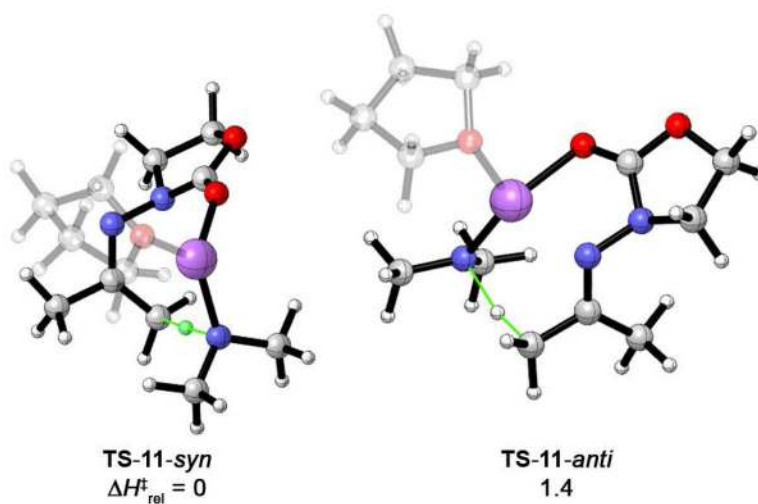
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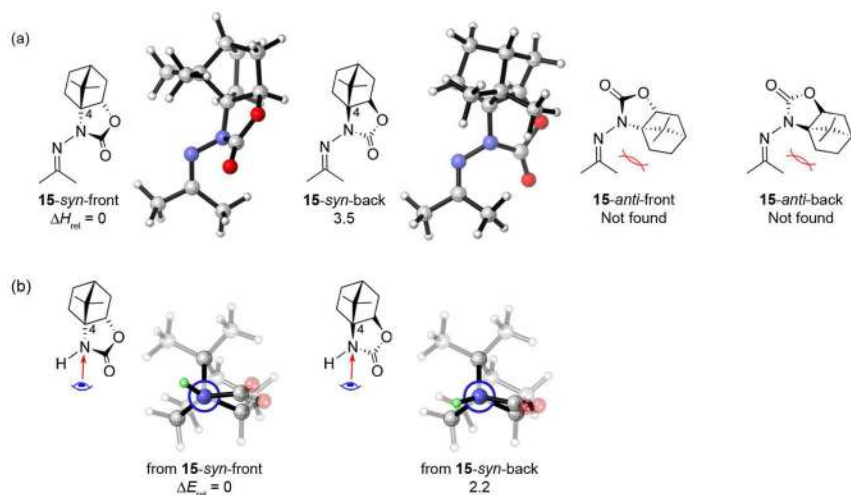
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**Figure 1.** Conformers of the ACC hydrazone **11** ( $\Delta H$  in kcal mol<sup>-1</sup> at 0 K).

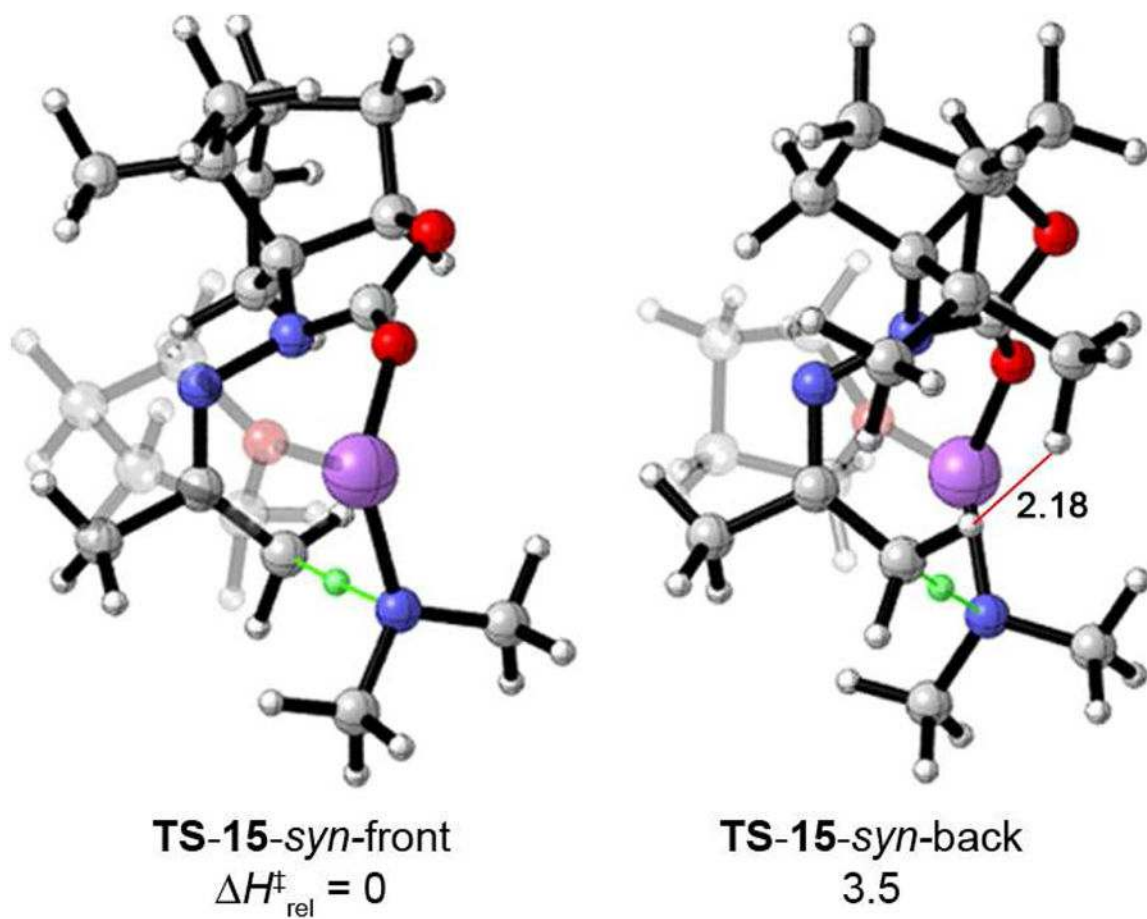


**Figure 2.** Transition states for deprotonation of **11** by Li(NMe<sub>2</sub>)(THF). THF ligands are fogged out for clarity. The “*syn*-directed” deprotonation, leading to the Z<sub>CN</sub> azaenolate, is favored. ( $\Delta H_{\text{rel}}^{\ddagger}$  in kcal mol<sup>-1</sup> at 0 K.)



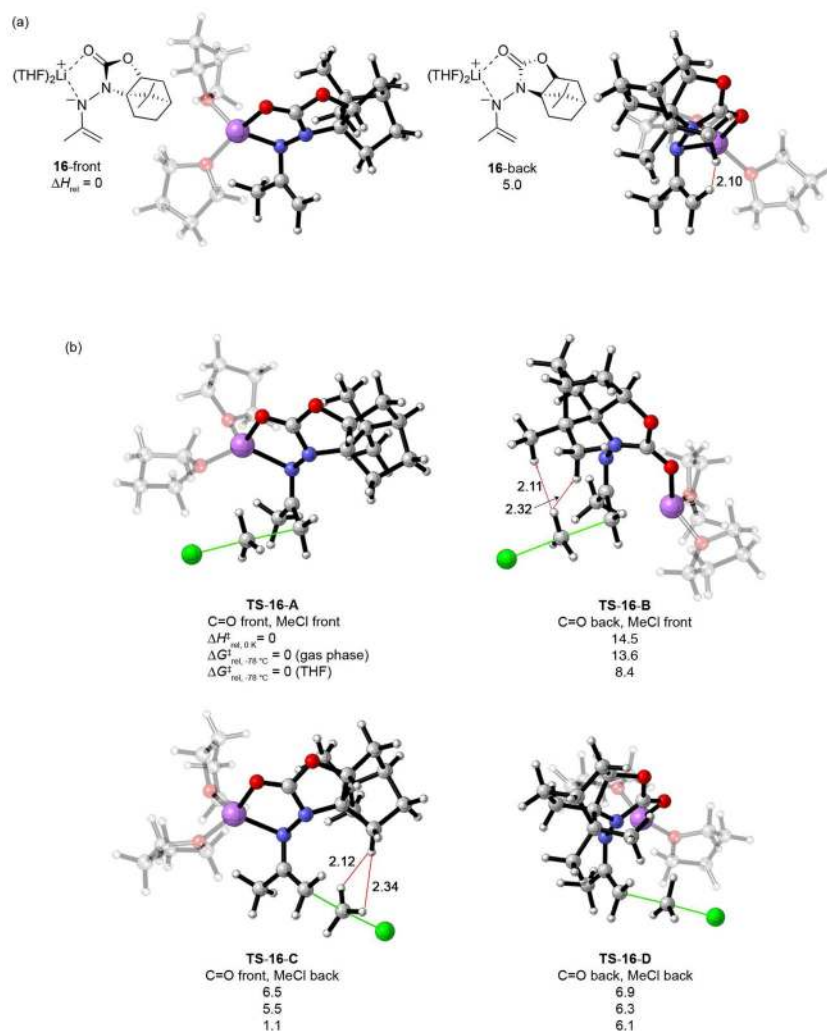
**Figure 3.**

(a) Conformers of the hydrazone **15** and (b) Newman projections showing the conformation about the N–C<sub>4</sub> bond in the oxazolidinone ring [N=CMe<sub>2</sub> unit has been removed and replaced by H (green) at a distance of 1 Å, while the remaining atoms were held fixed]. Only the *syn* conformation is available to **15**, because the *anti* conformers would be subject to severe steric interactions between the auxiliary and the nearby alkyl group on the hydrazone. The rigid bicycloalkane moiety enforces destabilizing eclipsing interactions about the N–C<sub>4</sub> bond in **15-syn-back**.

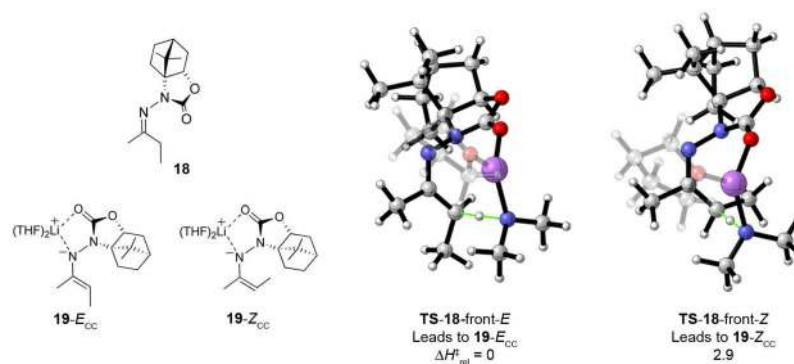


**Figure 4.**

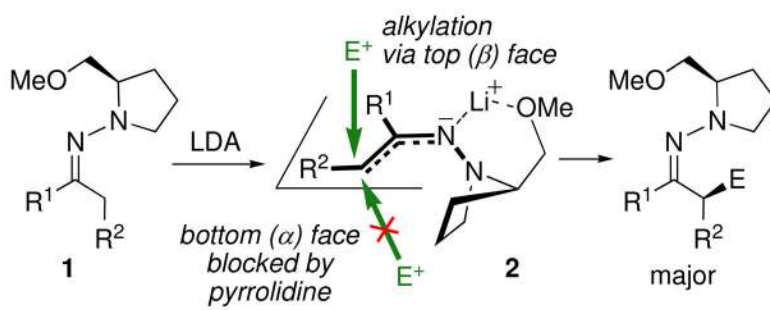
Transition states for deprotonation of **15** by Li(NMe<sub>2</sub>)(THF). Deprotonation from the front (β) face is favored. The transition state for deprotonation from the back is destabilized both by eclipsing interactions about N–C<sub>4</sub> and by steric interactions between the hydrazone and the auxiliary (red line). (Interatomic distances in Å.)

**Figure 5.**

(a) Conformers of the lithium azaenolate **16** and (b) transition states for alkylation of **16** by MeCl. Both the azaenolate and the TSs for alkylation prefer the carbonyl-front conformation. Addition of MeCl to the  $\beta$  face of the azaenolate (**TS-16-A**) is preferred by  $6.5 \text{ kcal mol}^{-1}$  over addition to the  $\alpha$  face (**TS-16-C**) in the gas phase. A similar but smaller preference is retained in solution.

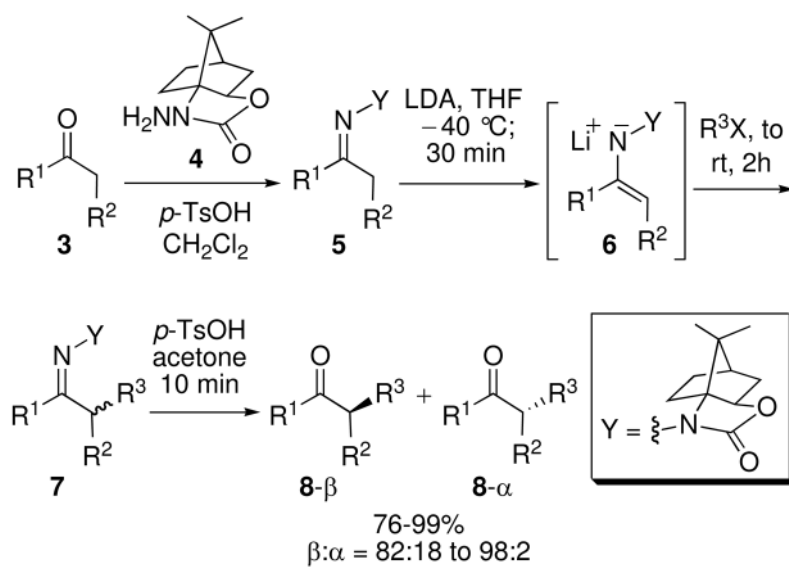


**Figure 6.** Transition states for deprotonation of the substituted hydrazone **18** by Li(NMe<sub>2</sub>)(THF). The TS leading to the *E*<sub>CC</sub> isomer of the azaenolate is 2.9 kcal mol<sup>-1</sup> lower in energy than the TS leading to the *Z*<sub>CC</sub> azaenolate.

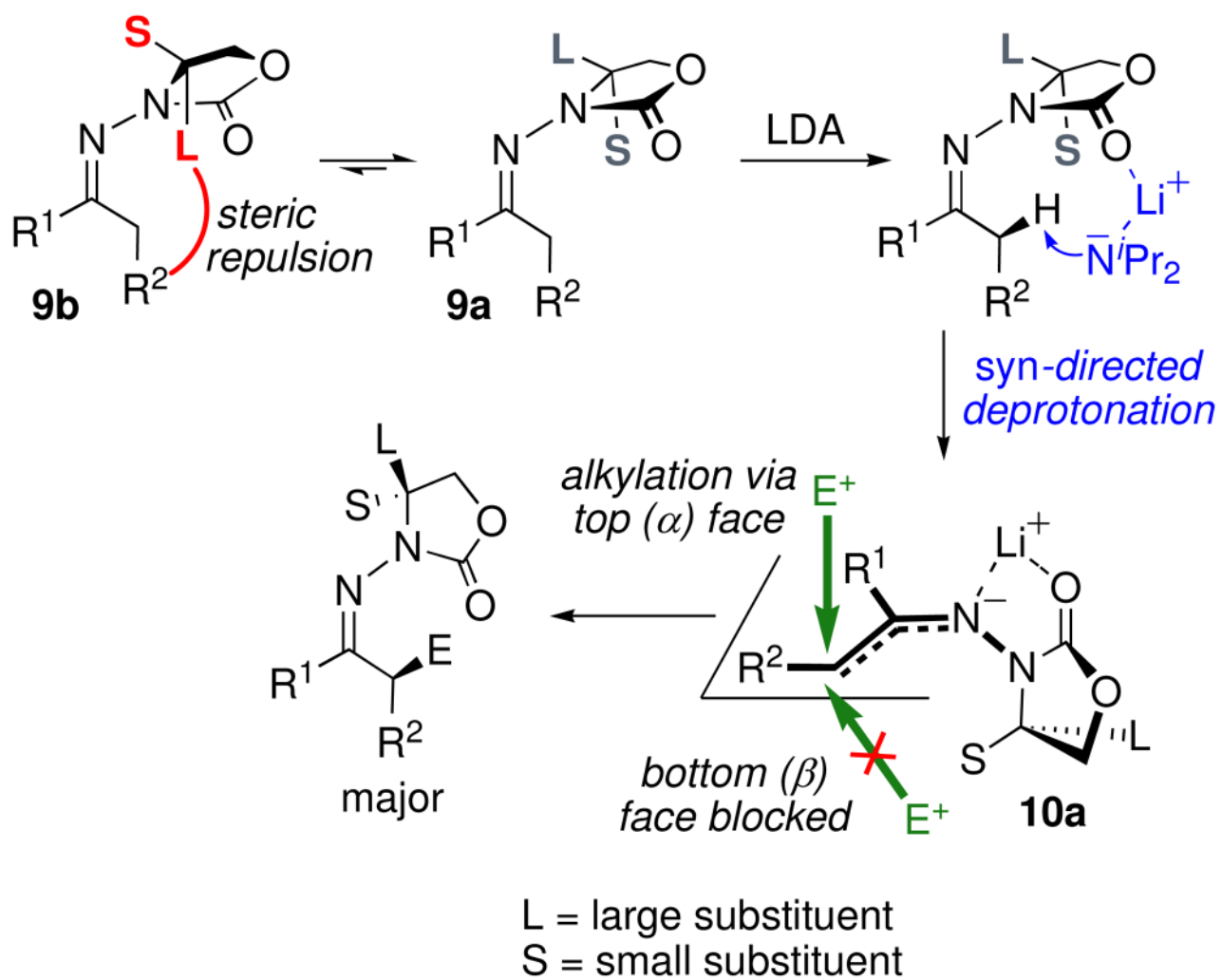


**Scheme 1.**  
Stereoselective  $\alpha$ -alkylation of a RAMP hydrazone



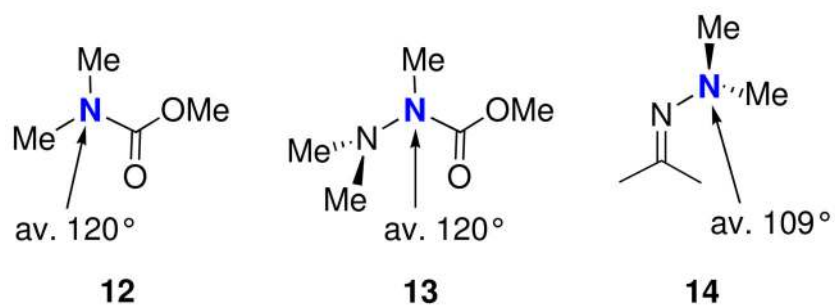


**Scheme 2.**  
Asymmetric  $\alpha$ -alkylation of ketones, mediated by ACC 4

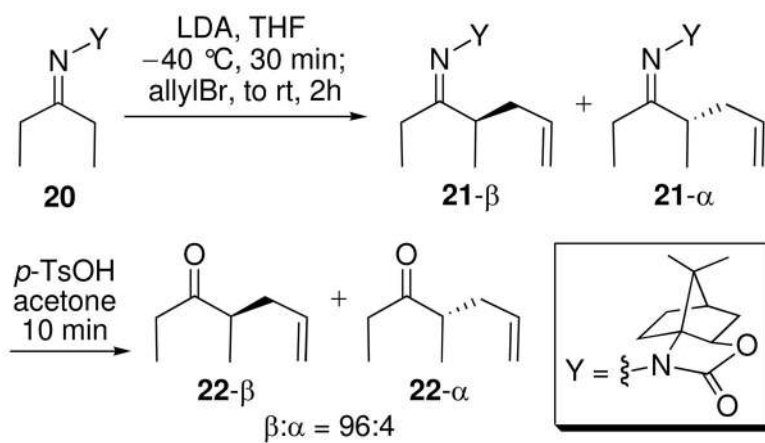


Scheme 3.

Model proposed to explain stereoselectivity in the alkylation of ACC hydrazones<sup>iii</sup>



**Scheme 4.**  
Average bond angles at nitrogen in model species



**Scheme 5.**  
Asymmetric  $\alpha$ -allylation of **20**