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Dual mechanisms of an organocatalytic homodimerization reaction

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ABSTRACT

The L-proline organocatalytic homodimerization of 2-cyclohexenone has been studied and it is concluded that the mechanism of the reaction follows competing pathways involving either a two-step imine/enamine addition or a concerted Diels–Alder cycloaddition where the ultimate product distribution is dependent upon the ratio of the organocatalyst to 2-cyclohexenone and a base present.

The self-condensation reaction of α,β-unsaturated enals[1] and the homodimerization reaction of α,β-unsaturated enones[2] have been known for many years. Usually these reaction processes use strong bases as catalysts but recently it has been shown that organocatalysts, such as L-proline, can be usefully employed to yield the dimeric products. While the mechanism of the L-proline organocatalytic self-condensation reaction of the α,β-unsaturated enals[3] appears to proceed via an imine/enamine addition mechanism the analogous reaction pathway for homodimerization of α,β-unsaturated enones has been postulated to proceed through a concerted Diels–Alder reaction.[4]

Homodimerization of 2-cyclohexenone (**I**) with pyrrolidinium perchlorate in the presence of a catalytic amount of pyrrolidine followed by aqueous hydrolysis of the initial dicationic dipyrrolidinium product yielded a tricyclo[6.2.2.0^{2,7}]dodeca-3,9-dione, **1**, as the major product.[5] The major homodimer having structure **1** was later shown by others to have the configuration of the *endo*-isomer as derived from the dimerization of the ethylene ketal of **I** by a proposed acid catalyzed Diels–Alder route.[6] We were interested to determine whether a L-proline organocatalytic homodimerization of **I** with either pyrrolidine or L-methyl-prolinate as the base would proceed by a stepwise enamine/iminium ionaddition mechanism or a concerted Diels–Alder pathway. While we now show that the *endo*-homodimer is the major product of this organocatalytic reaction we have also isolated interesting side products that implicate a dominant reaction mechanism that involves a stepwise enamine/iminium ion addition process when an amine is present along with the organocatalyst L-proline. Consequently this report details our research using neat conditions to explore this interesting homodimerization reaction.

The reaction of a 1:1 mixture of pyrrolidine with **I** (3 mmol) was conducted under neat conditions at room temperature (rt). Upon stirring a fast reaction was initiated producing the expected conjugate addition process leading to an equilibrium mixture that was well to the side of the adduct (99:1 by NMR). When L-proline was added to this resultant equilibrium mixture, and stirring was continued for 24 h, the homodimer was found to be the major product in ~40% yield, based upon **I**, after aqueous work-up and column chromatography.[7] This result implied that an organocatalyst like L-proline could catalyze the conversion of the conjugate addition adduct to the homodimer **1**. The question that thus needed to be answered was how? Consequently we explored the mechanism of how an organocatalyst like L-proline could promote the homodimerization of **I** in the presence of either pyrrolidine or L-methyl prolinate as the Bronsted base.

A model reaction [1–5 mmol scale] of L-methyl-prolinate and **I** neat was studied to evaluate the feasibility and the applicable conditions. Initially we utilized a 1:1 equiv mmol ratio of the reactants (rt) and found that the conjugate or 1,4-addition process was nearly complete after stirring for 5 h to yield an equilibrium mixture that was well to the side of the adduct (95:5 by NMR). If the formed adduct was allowed to stir for an additional 10 h it was found that there was no apparent continuation beyond this equilibrium process. However after this 10 h induction period/lag time the major homodimerization reaction was initiated and completed within a 3 h period along with a minor intramolecular cyclization process derived from the conjugate addition adduct. Aqueous acid work-up and subsequent chromatographic separation of the reaction mixture produced the major *endo*-homodimer product **1** in reasonable isolated yield (~30%). Minor amounts[8] of four other products could also be isolated: One being **2**, two others being L-proline and its dimer and the fourth being the *exo*-homodimer of **1**.

When the mmol ratio of the same two reactants as above was set at 1.15:1 a similar sequence was found. The conjugate addition reaction required 4 h to complete and then the homodimerization process was initiated, after another 8 h induction period/lag time, with overall completion taking 15 h. If this reaction mixture was allowed to sit for an additional 24 h, without aqueous work-up, a precipitate was noted within the resultant thick liquid. Removal by filtration of the precipitate led to its identification as L-proline. After removal of the L-proline the thick liquid was subjected to an

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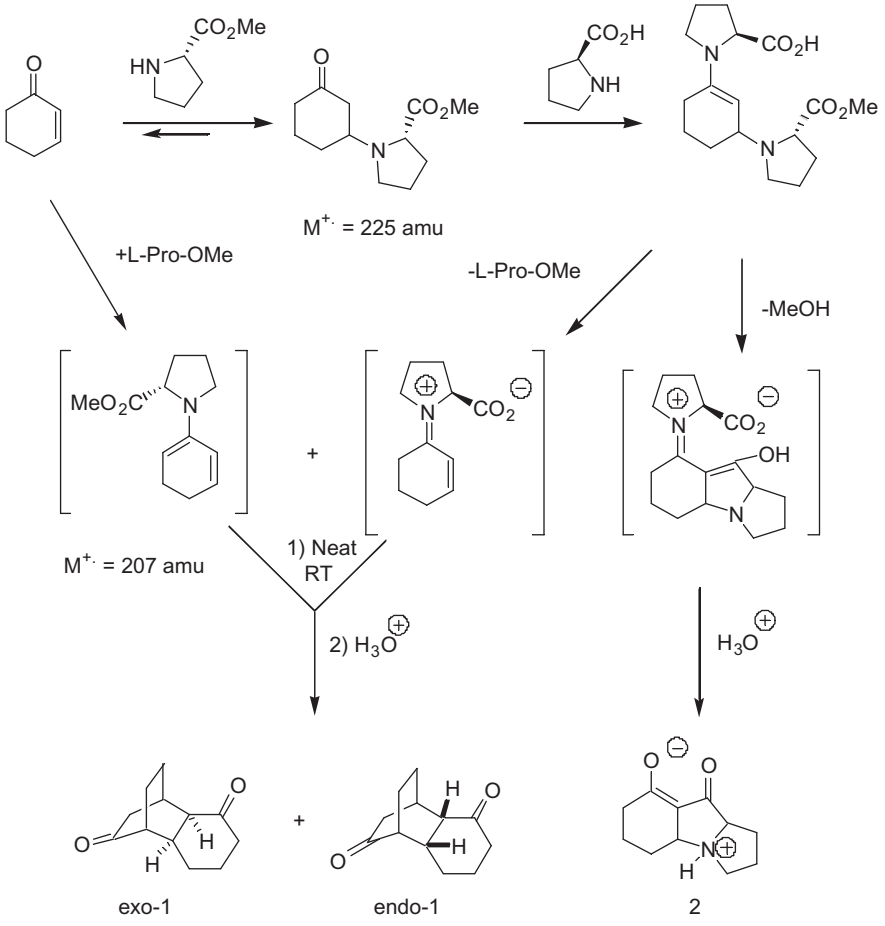
aqueous acid work-up and chromatographic separation resulted in the same major (*endo*-**1**) and minor products consisting of the *exo*-isomer of **1**, the intramolecular cyclization product **2** along with the dimer of L-proline presumably derived from L-methyl prolinate.[8] Interestingly the amount of L-proline precipitate was shown to be ~0.12 equiv mmol or essentially equal to the mmol excess of L-methyl-prolinate that was initially utilized. We surmised that L-proline was produced during the induction period/lag time by hydrolysis and was an autocatalyst for the homodimerization leading to **1.** Consequently when this same reaction was initiated using an equiv mmol ratio (1:1) of reactants, to which was added 10 mol % of L-proline, dissolved in a minimal amount (<30 μl) of methanol for homogeneity, the conjugate addition/homodimerization process was shown to go to completion without an induction period/lag time in <6 h. The above results implied that the conjugate addition adduct is the initial intermediate in this organocatalytic reaction sequence leading to homodimerization (see Scheme 1[9]). However the mechanism of production of **1**, either the *endo*-homodimer or even its *exo*-homodimer isomer, was not apparent. Thus we decided to examine the L-proline organocatalytic homodimerization of **I** in the presence of the Bronsted base pyrrolidine in detail in an attempt to determine whether the intermediates could be observed without interference from side-reactions involving L-methyl prolinate which had produced the L-proline dimer and the intramolecular cyclization product **2**.

The rt neat reaction of **I** and pyrrolidine (1:1 equiv mmol), with L-proline as the organocatalyst dissolved in a minimal amount of methanol for homogeneity, was followed over a 24 h period or more utilizing GC/ESI-MS as the primary method of analysis.[7] Increasing the L-proline catalyst load from 10 to 50 mol % indeed showed that the rate of gain of the homodimerization products increased at the expense of the conjugate addition adduct. The analysis of the derived GC/MS data, with respect to homodimer formation, can be summarized as follows: (1) an intermediate having a molecular ion with $M^{+\cdot}$ = 149 amu was observable in early GC traces and corresponded to the diene amine **3**; (2) the initial rate of formation of *exo*-**1** was always greater than that of its *endo*-isomer regardless of catalyst load; (3) the final (24 h) *endo*-**1** to *exo*-**1** ratio changed from 9:1 to 1:1 as the load of the organocatalyst, L-proline, increased from 10 to 50 mol %; (4) in late GC traces the major products, prior to aqueous acid work-up, proved to have MS molecular ions of $M^{+\cdot}$ = 245 amu; (5) GC bands exhibiting $M^{+\cdot}$ = 245 amu were only noted when L-proline was present as the organocatalyst; (6) partial conversion of GC fractions having a 245 amu $M^{+\cdot}$ could be induced to provide an increased amount of homodimer, with *endo*-**1** being the major isomer, by treating the crude reaction mixture with acetic acid; (7) isolation of a small amount of the side product having $M^{+\cdot}$ = 246·1852 amu (high resolution) could be achieved by dissolution of the crude reaction mixture in CH_2Cl_2, followed by a HCl wash, and subsequent isolation from the organic layer of compound **4**·HCl; (8) prolonged stirring (rt) of any of these crude reaction mixtures for more than 24 h eventually lead to ~1:1 *endo*/*exo*-**1** ratio regardless of the starting conditions; (9) reaction of **I** and L-proline (1:0.15 mmol) without any pyrrolidine gave no **1** but when the ratio of **I** to L-proline was increased (1:1.15 mmol) a small homodimer fraction having an *exo*/*endo*-**1** ratio of 3:1 was produced initially (5 h) which eventually converted to a ratio of 1:2.5 (3 days) *albeit* in low yield and with several other higher

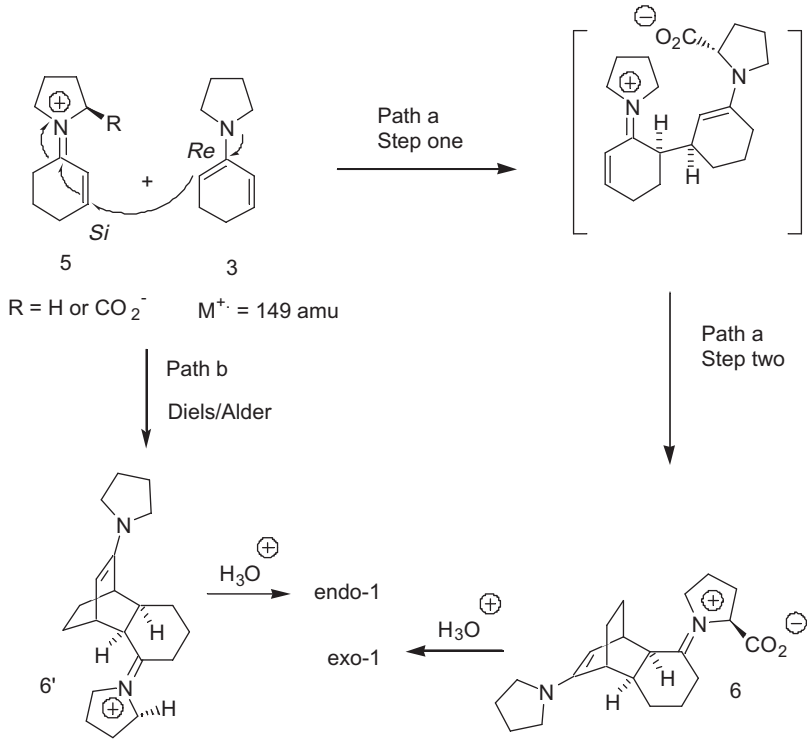


Scheme 1.

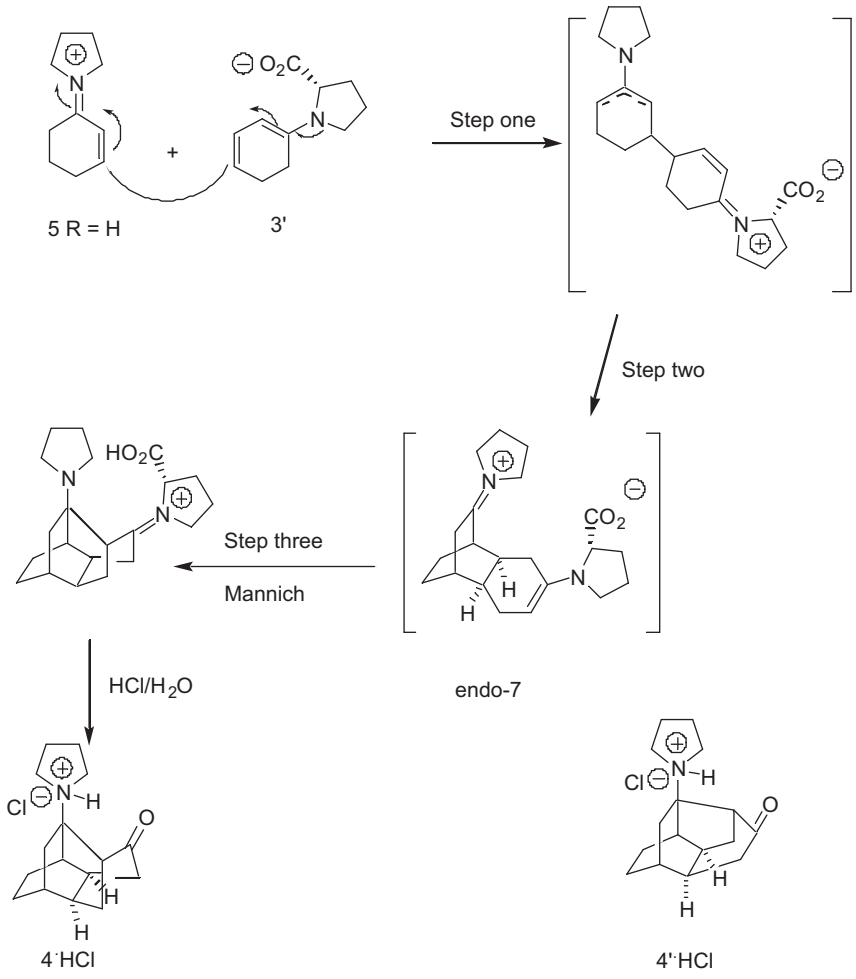
molecular mass materials in the crude mixture; and (10) the reaction of **I** and L-proline (1:1) with triethylamine (15 mol %) replacing pyrrolidine initially (5 h) lead to a mixture of homodimers (*exo*/*endo* = 2.4:1) which upon prolonged stirring (1 week) resulted in isomerization (*exo*/*endo* = 1:1) in very low yield. The interpretation of all these data is displayed in Schemes 2 and 3[9] and summarized below with respect to the two mechanisms being proposed.

Our overall conclusion from the above evidence is that this homodimerization reaction (see Scheme 2) can follow both the proposed mechanistic pathways but the actual outcome of the reaction is dependent upon the ratio of L-proline to **I** that is used to initiate the process and whether an amine base is present or not. The mechanistic pathways leading to the homodimerization of **I** appear to be initiated by the rapid establishment of a conjugate addition equilibrium whereby a 3-*N*-pyrrolidino-cyclohexanone adduct is formed initially. This intermediate adduct can then undergo 1,2-addition with either pyrrolidine to form the diene amine **3** (R = H) and the iminium cation **5** (R = H) or with L-proline to form the comparable **3′** (R = CO_2^-) and **5** (R = CO_2^-). The intermediates **3** (R = H) + **5** (R = CO_2^-) can undergo a stepwise imine/enamine addition process (Scheme 2, path a) leading to *exo*-**1** initially. Subsequently **3** + **5** (R = H) can undergo the concerted Diels–Alder reaction process (Scheme 2, path b) leading to *endo*-**1** once L-proline has been sequestered as the *exo*-**1** hydrolysis precursor **6** prior to hydrolysis. A stepwise mechanism where a prochiral enamine nucleophilic face, as in **3**, attacks a prochiral electrophilic face, as in **5** (R = CO_2^-) leads to a first intermediate. Consequently the first step in path a of Scheme 2 proceeds via a Re to Si nucleophilic face to an electrophilic face bond formation.[10a] The second step bond formation then rapidly results in the production of the *exo*-configuration by rotation of the covalently bonded rings of the first intermediate with respect to one another. This lowest energy route via path a is controlled by the transient formation of a salt bridge dimer between the carboxylate of the L-prolino-enamine of **I** {**5** (R = CO_2^-)}and the pyrrolidinium cation of **I** {**3** (R = H)}. Once the L-proline catalyst has been sequestered as the *exo*-**1** hydrolysis precursor **6** then the higher energy Diels–Alder pathway can lead to the *endo*-**1** hydrolysis precursor **6′** via a slower concerted reaction of **3** + **5** (R = H) via path b.[10b] As the load of L-proline is increased the *exo*/*endo* ratio decreases in accord with these mechanisms presumably because of the introduction of the increased H-bond capabilities.[11] Amines play an important role here as is evidenced by the inability of L-proline to produce significant **1** in their absence. The crucial role played by pyrrolidine, besides for enamine/iminium cation formation from the conjugate addition product, is as a Bronsted base for salt bridge formation between **3** (R = H) and **5** (R = CO_2^-) but it can also act as a catalyst for the isomerization of *endo*-**1** to *exo*-**1** which was always observed with the prolongation of the process. As the load of L-proline increases the role of pyrrolidine changes from being a Bronsted base to a Bronsted acid thus coaxing the homodimerization mechanism to convert from the salt bridge-assisted pathway to a H-bond-assisted one.[11]

The most revealing result, however, was the observation of the minor product **4**·HCl. The isolation of the **4**·HCl salt can only result from a three-step mechanism[12] where the tandem two-step enamine/imine addition of **3′** + **5** (R = H) cascades into a Mannich reaction, step three, (see Scheme 3) yielding after acid hydrolysis the salt of the β-pyrrolidino-carbonyl-adduct **4**·HCl. This racemic[13] HCl salt was isolable (mp = 187–190 °C) in ~5% yield and its structure was proven using HRMS in conjunction with 1D and 2D PMR and CMR analyses as well as the observation that an AgCl precipitate formed when ethanolic solutions of $AgNO_3$ and **4**·HCl were mixed. Particularly noteworthy is an intramolecular hydrogen bond (D_2O exchangeable) in the PMR spectrum at 12.6 ppm which presents COSY cross peaks with methylene protons from a pyrrolidinium ion. The COSY also indicates that **4**·HCl adopts a *cis*-configuration for the bridgehead protons. The 1D-CMR exhibits 16 carbon resonances in which DEPT spectra account for five CH's, nine CH_2's as well as one C=O and one quaternary C–N^+. The 2D HETCOR spectrum allows for the completion of the assignment of the structure by displaying a correlation between the C=O and 1-*CH* and 1-CH_2 while the quaternary C–N^+ correlates with the same *CH*, a different CH, and a different CH_2. Modeling predicts two possible structures that are very similar but differ in the rela-



Scheme 2.



Scheme 3.

tive positioning of the C=O (see Scheme 3 comparing structure **4**·HCl to **4′**·HCl). The structure represented by **4**·HCl has a similar strength intramolecular hydrogen bond (C–N^+–H···O=C) to that of **4′**·HCl but the most compelling reason to favor the structure **4**·HCl as the minor product over that of **4′**·HCl is a mechanistic one. A Mannich reaction in the third and last step of this cascade can only occur if the two-step enamine/imine process leads to the salt bridge-stabilized intermediate endo-**7** which can exclusively collapse via a Mannich process to produce **4**·HCl after hydrolysis. A comparable *exo*-intermediate to *endo*-**7** cannot lead to a Mannich process following either a two-step addition mechanism or a concerted Diels–Alder pathway and thus the hydrolysis product **4′**·HCl can be eliminated from consideration.

In conclusion we have shown that the homodimerization of 2-cyclohexenone(**I**) in the presence of the Bronsted base pyrrolidine and the organocatalyst L-proline proceeds predominantly through a two-step mechanism[12] after an initial conjugate adduct is formed. We have characterized several reaction intermediates and isolated an interesting side-product that supports the two-step enamine/imine process as the preferred organocatalytic mechanism over a concerted Diels–Alder reaction pathway.

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7. *General procedure for preparation of* ***1***: Freshly distilled amine (1–10 mmol) and L-proline (0.1–0.5 equiv mmol) were stirred while 2-cyclohexenone (1–10 mmol) was added. This mixture was stirred for the designated period of time and then an aliquot was withdraw, dissolved in diethyl-ether and analyzed by GC/ESI-MS to determine the intermediates. For the analysis of the ratio of homodimer isomers aq acid was added to the ether solution followed by the same analysis after drying the ether layer.
8. *Preparation and isolation of* ***2***: The reaction was run as described[7] except L-methyl-prolinate (3.0 mmol) was the freshly prepared amine. After 6 h the thick red liquid was diluted with 30 ml of CH_2Cl_2 and washed with 15 ml of 10% aq citric acid soln, followed by 15 ml of satd $NaHCO_3$ soln. The organic layer was dried over anhyd $MgSO_4$, filtered and concentrated to deliver a red oil in 85% yield. Column chromatography over silica gel eluted the homodimers (hexane/$CHCl_3$), followed by the L-proline dimer ($CHCl_3$) and then a fraction containing **2** (EtOAc/CH_3OH). Preparative RPLC of this mixture containing **2**, using a CH_3CN/H_2O gradient, produced two fractions with the early fraction delivering a yellow solid (**2**) mp = 159–163 °C; $C_{11}H_{15}NO_2$; MS/ESI:

M+H$^+$ = 194 amu; FT-IR (KBr): ν = 3179 (w), 2953 (m), 2876 (w), 1642 (s) cm^{-1}; PMR ($CDCl_3$): 1.7–2.2 (m, 7H), 3.2 (td, 1H), 3.3 (td, 1H), 3.5 (dt, 2H), 3.7 (exch., 1H), 4.0 (dt, 2H), 4.2 (t, 1H) ppm; CMR ($CDCl_3$): δ = 22, 23, 28, 30, 44, 45, 60, 61, 110, 164, 166 ppm.

9. At the suggestion of a referee we have included the mass of intermediate molecular ions determined by GC/ESI-MS. These M$^{+\cdot}$ mass values (amu) were characterized by their associated cracking patterns. [Note for example: Schmid, M.B.; Zeitler, K.; Gschwind, R.M. *Angew. Chem., Int. Ed,* **2010** *49*, 4997.]
10. (a) There are two possible structures for intermediate **5** (CO_2^-). In theory these two structures are interconvertible diastereomeric zwitterions with either a *Z* or *E* iminium cation bonded to the *S*-prolinate anion. The nucleophilic face of **3** that attacks the electrophilic face of *Z*,*S*-**5** (R = CO_2^-) in the first step thus determines the ultimate stereochemical result of homodimerization. (b) Homodimers produced by hydrolysis of **6** and **6′** may be one of several rate-limiting steps in the crude reaction mixture where the concentration of H_2O is very low. [For example: Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. *J. Am. Chem. Soc.* **2010**, *132*, 6.]
11. The L-proline organocatalyst must be present to derive either of the homodimeric isomers and thus it dictates the two-step mechanistic pathway that produces *exo*-**1** initially in preference to *endo*-**1**. This two-step mechanism can in theory also deliver the *endo*-**1** isomer [**3** (Re) + *E*,*S*-**5** (Re) first step[9a]] but this latter two-step pathway must surmount a higher barrier than the former mechanism. The one-step and energetically similar H-bond assisted Diels–Alder reaction to this latter pathway can derive *endo*-**1** with pyrrolidine but an acid catalyst[5,6a] is required.
12. (a) Westermann, B.; Ayaz, M.; van Berkel, S. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 846; (b) Grondel, C.; Jeanty, M.; Enders, E. *Nat. Chem.* **2010**, *2*, 167.
13. The racemic nature of isolated **4**·HCl is due to the excess base that was utilized in the organocatalytic reaction. Pyrrolidine, a fairly strong base ($pK_a \sim 11.3$), is able to initiate either an isomerization or racemization process during the course of the reaction. [For example: Blackmond, D.G.; Moran, A.; Hughes, M.; Armstrong, A. *J. Am. Chem. Soc.* **2010**, *132*, 7598.]