Supporting Information

Kinetic Correlation Between Aldehyde/Enamine Stereoisomers in Reactions between Aldehydes with a-Stereocenters and Chiral Pyrrolidine-Based Catalysts

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Table of Contents:

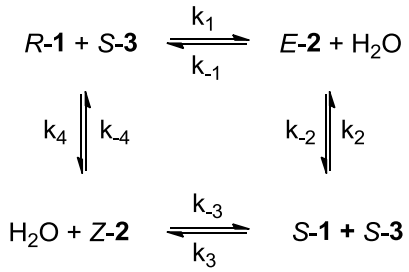
1. Materials and General Procedures

Dry toluene and $CHCl_3$ were obtained by passing the previously degassed solvent through activated alumina column. Toluene-d8 was purchased from Cambridge Isotope Laboratories, Inc. (D, 99.5%) in ampoules of 1 mL. $CDCl_3$ was purchased from Cambridge Isotope Laboratories, Inc. (D, 99.5%) in bottles of 100 g. Propanal (97%) and 2-phenylpropanal (95%) were purchased from Alfa Aesar and both were always carefully distilled prior to use. The (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether, (*R*)-2-phenyl-1-propanol and (*S*)-2-phenyl-1-propanol were purchased from Sigma-Aldrich.

NMR spectra were recorded on Bruker DRX-600 equipped with a 5 mm DCH cryoprobe, DRX-500, and AMX-400 instruments and calibrated using residual undeuterated solvent as an internal reference. Ultra high performance liquid chromatography (UHPLC) was performed on Eksigent ExpressLC-Ultra.

2. Mathematical model for the enamine formation of an aldehyde with α-stereocenters

Thermodynamic and Kinetic Relationships



By definition:

$$K_{1,eq} = \frac{k_1}{k_{-1}};\ K_{2,eq} = \frac{k_2}{k_{-2}};\ K_{3,eq} = \frac{k_3}{k_{-3}};\ K_{4,eq} = \frac{k_4}{k_{-4}}$$

General relationships:

$$K_{1,eq} \cdot K_{3,eq} = K_{2,eq} \cdot K_{4,eq} \quad \text{microscopic reversibility} \quad (1)$$

$$\frac{K_{1,eq}}{K_{2,eq}} = 1 \quad \frac{K_{3,eq}}{K_{4,eq}} = 1 \quad \text{enantiomer equivalence} \quad (2)$$

$$\frac{[E\text{-}\mathbf{2}]_{eq}}{[Z\text{-}\mathbf{2}]_{eq}} = \frac{k_1}{k_{-1}} \cdot \frac{k_{-4}}{k_4} = \frac{k_2}{k_{-2}} \cdot \frac{k_{-3}}{k_3} \quad \text{equilibirum } E/Z \quad (3)$$

Measured quantities:

$$\frac{k_1}{k_4} = a\ (4) \qquad \frac{k_3}{k_2} = b\ (5) \qquad \frac{k_3}{k_1} = c\ (6) \qquad \frac{k_1}{k_{-1}} \cdot \frac{k_{-4}}{k_4} = \frac{k_2}{k_{-2}} \cdot \frac{k_{-3}}{k_3} = d\ (7)$$

Therefore:

$$k_1 = a \cdot k_4 \qquad k_3 = b \cdot k_2$$

$$\frac{k_3}{k_4} = a \cdot c\ (8)\ \text{from (4) and (6)} \qquad \frac{k_2}{k_1} = \frac{c}{b}\ (9)\ \text{from (5) and (6)}$$

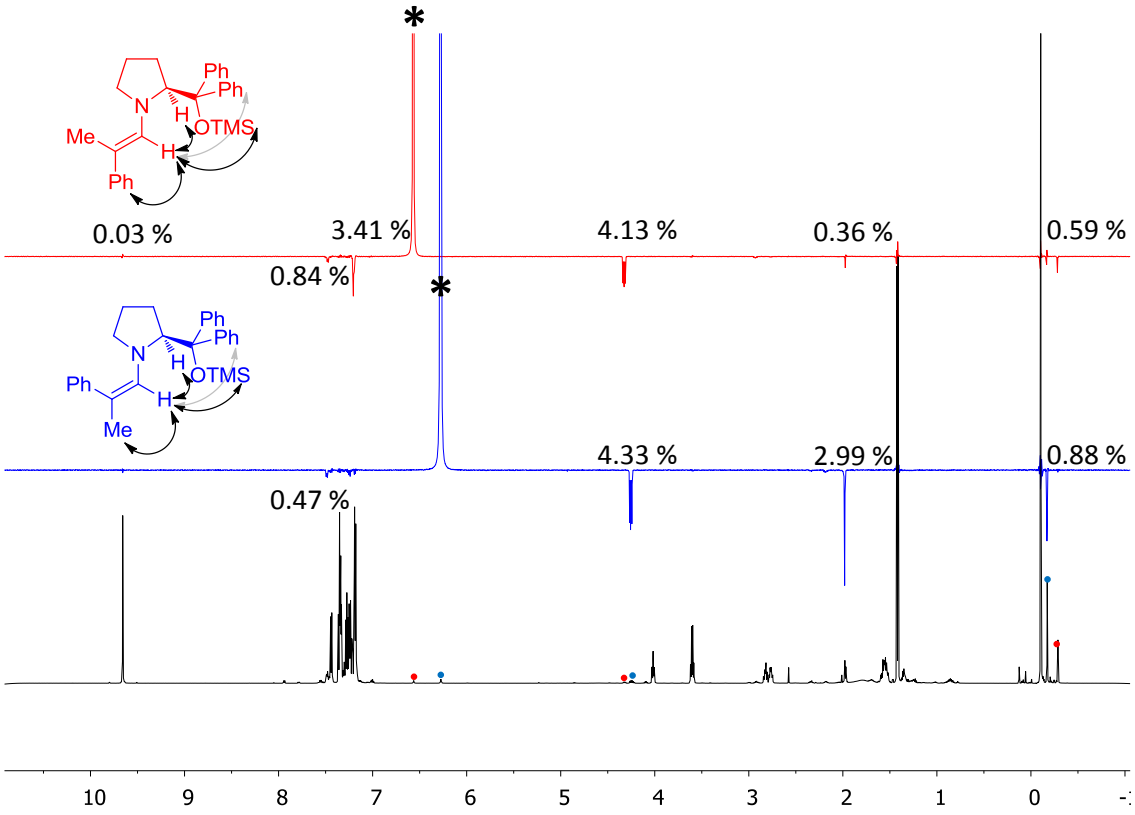
From enantiomer equivalence:

$$\frac{k_{-3}}{k_{-4}} = \frac{k_3}{k_4} = a \cdot c\ (10)\ \text{from (2) and (8)} \qquad \frac{k_{-1}}{k_{-2}} = \frac{k_1}{k_2} = \frac{b}{c}\ (11)\ \text{from (2) and (9)}$$

3. NMR identification of enamines

3.1. (*S*)-α,α-Diphenyl-2-pyrrolidinemethanol trimethylsilyl with 2-phenylpropanal

The NMR spectra were recorded on Bruker DRX-600 equipped with a 5 mm DCH cryoprobe. The nOe experiments were registered using a mixing time of 400 ms.

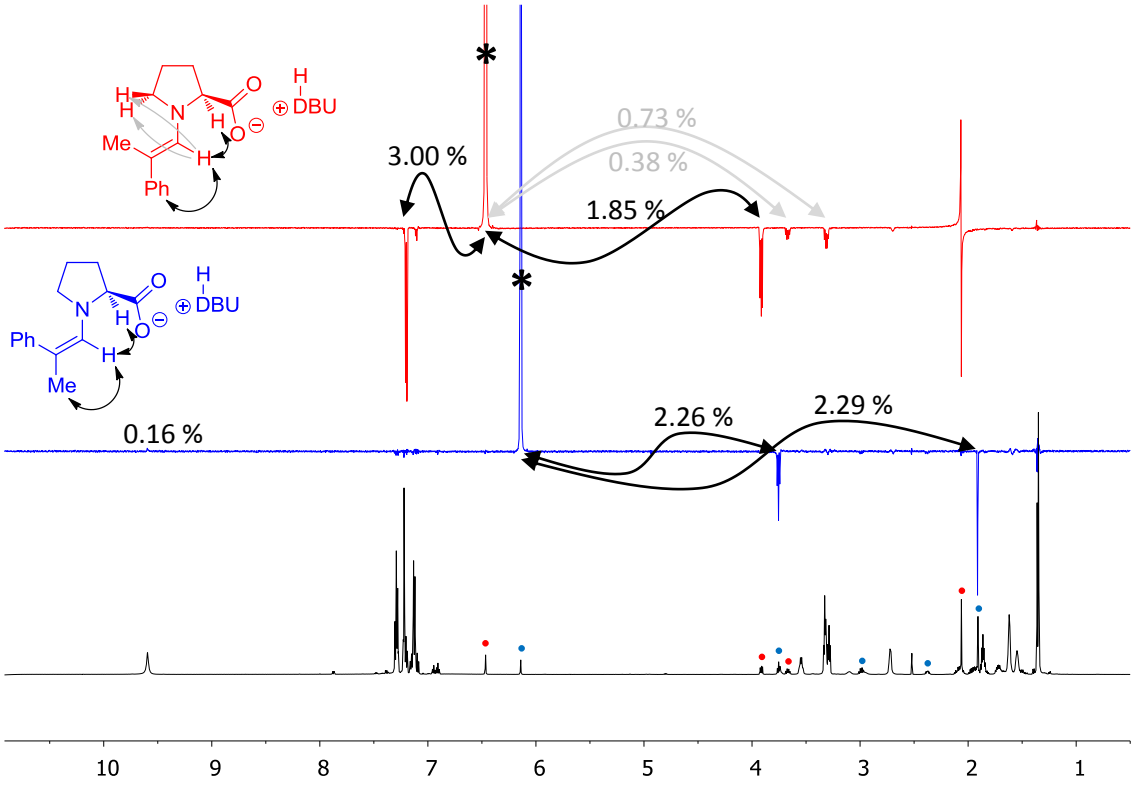


The nOe contacts of the olefinic proton with the methyl group (for the *Z* isomer) or the olefinic phenyl group (for the *E* isomer) were used to assign the *E* and *Z* isomers.

The nOe signals between the olefinic proton and the proton of the stereogenic carbon and the absence of nOe contacts between the olefinic proton and the two protons of the methylene group attached to the nitrogen atom confirm that the s-*trans* conformation is predominant.[1]

3.2. 1,8-Diazobicycloundec-7-ene (L)-prolinate with 2-phenylpropanal

The NMR spectra were recorded on Bruker DRX-600 equipped with a 5 mm DCH cryoprobe. The nOe experiments were registered using a mixing time of 400 ms.



The nOe contacts of the olefinic proton with the methyl group (for the *Z* isomer) or the olefinic phenyl group (for the *E* isomer) were used to assign the *E* and *Z* isomers.

In the *Z* enamine, the nOe signals between the olefinic proton and the proton of the stereogenic carbon and the absence of nOe contacts between the olefinic proton and the two protons of the methylene group attached to the nitrogen atom confirm that the s-*trans* conformation is predominant.[1]

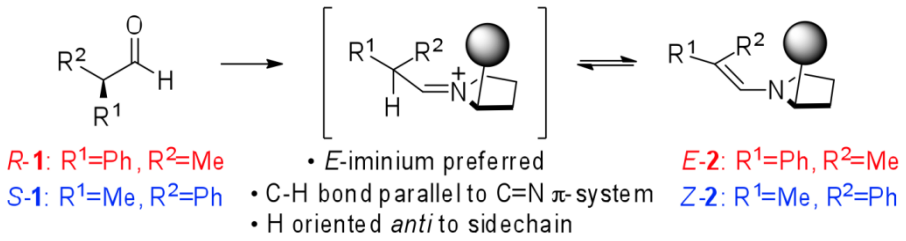
In the *E* enamine, the nOe signals between the olefinic proton and the proton of the stereogenic carbon and the weak nOe contact between the olefinic proton and the two protons of the methylene attached to the nitrogen atom suggests that there is a minor contribution from the s-*cis* for the *E*-enamine.[1]

4. Kinetic measurements of *E* and *Z* enamines formation

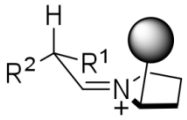
The (*R*)-2-phenylpropanal and (*S*)-2-phenylpropanal were prepared following the method described in the literature.[2]

The traces from the enantiopure aldehydes will yield the four forward rate constants k_1, k_2, k_3, and k_4. However, small differences in the concentrations of substrate, catalyst, and ubiquitous water can affect these absolute numbers from run to run. Therefore we prefer to use ratios of rate constants derived in a single experiment since any anomalies will be factored out using this procedure.

The observed stereochemical relationship can be rationalized by invoking selective formation of the *E*-iminium intermediate and removal of the proton from the alpha-carbon in a stereoelectronically controlled orientation parallel to the iminium pi-system, with the proton placed on the sterically more accessible face opposite to the catalyst sidechain. The stereochemical relationship is maintained in the reverse reaction by protonation on the less hindered face of the *s-trans*-enamine conformer.



Eventual equilibration of the *E*- and *Z*-enamines is possible because of the accessibility of alternative (but less favored) TSs for the deprotonation of the intermediate iminium, *i.e.* reaction *via* the Z-iminium, or in a conformation of the *E*-iminium where the C-H bond is oriented *syn*-to the sidechain.



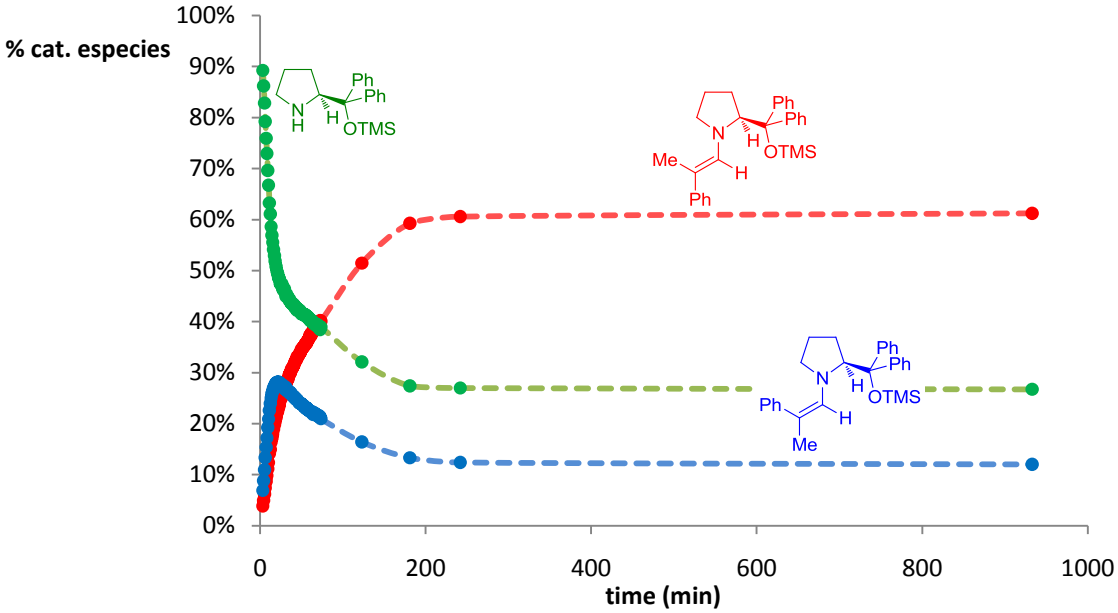
4.1. (*S*)-α,α-Diphenyl-2-pyrrolidinemethanol trimethylsilyl with 2-phenylpropanal

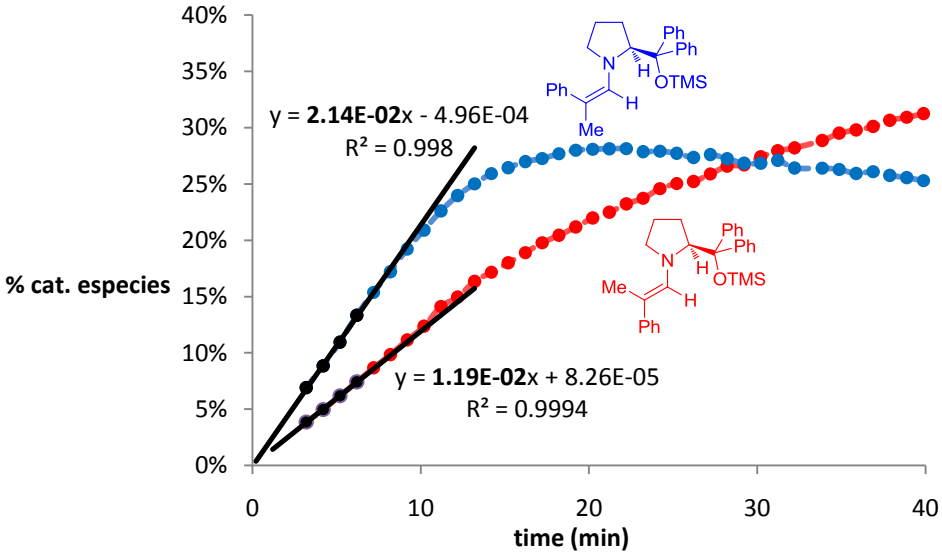
0.6 mL of a 0.17 M stock solution of (*S*)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl in $CDCl_3$ were added to 42.4 mg (0.316 mmol) of 2-phenylpropanal diluted in 0.1 mL of $CDCl_3$ in a NMR tube at room temperature and NMR spectra were registered immediately.

Enamine formation from racemic 2-phenylpropanal:

At initial times:

$$\frac{\frac{d[E]}{dt}}{\frac{d[Z]}{dt}} \approx \frac{k_1}{k_3}$$



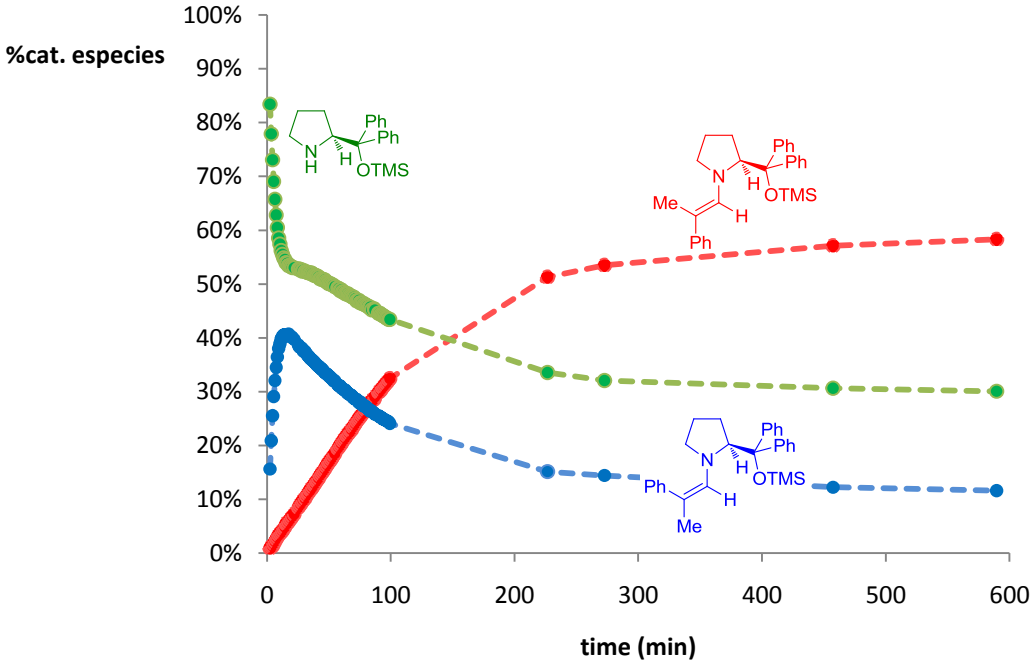


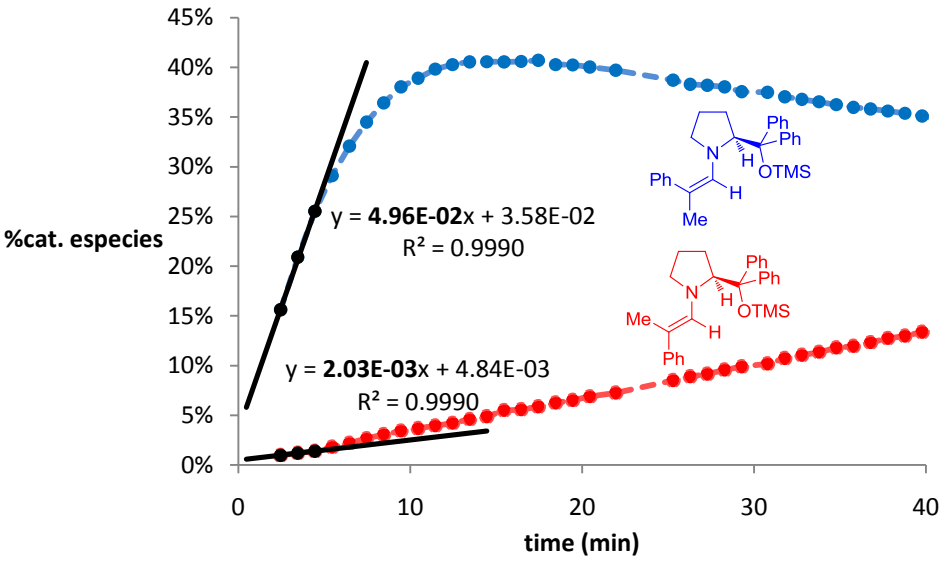
$$\frac{\frac{d[Z]}{dt}}{\frac{d[E]}{dt}} \approx \frac{0.0214}{0.0119} = \boxed{1.80 \approx \frac{k_3}{k_1}}$$

Enamine formation from (*S*)-phenylpropanal:

At initial times:

$$\frac{\frac{d[E]}{dt}}{\frac{d[Z]}{dt}} \approx \frac{k_3}{k_2}$$



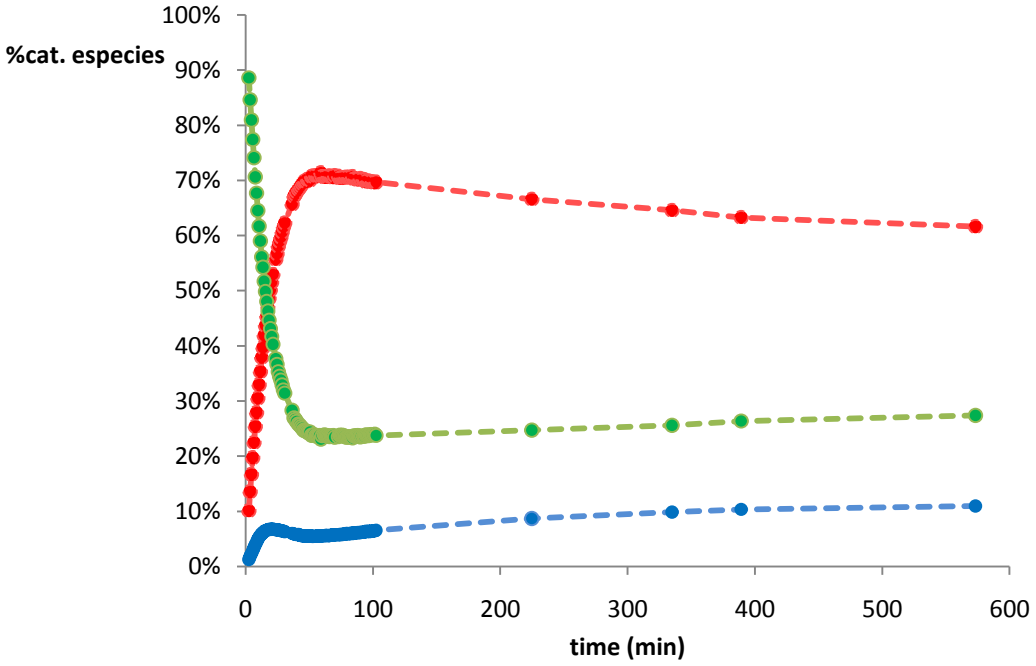


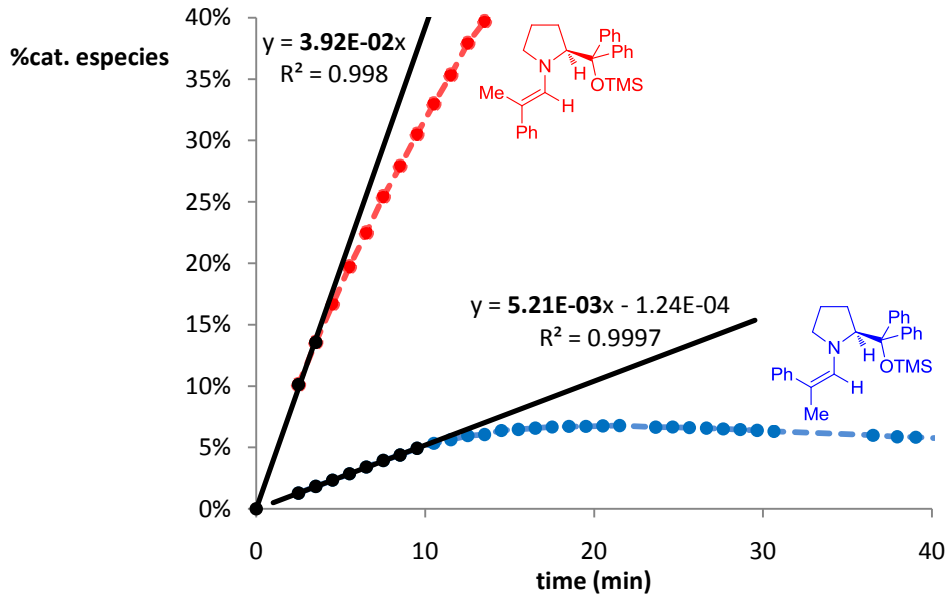
$$\frac{\frac{d[Z]}{dt}}{\frac{d[E]}{dt}} \geq \frac{49.6}{2.03} = \boxed{24.43 \leq \frac{k_3}{k_2}}$$

Enamine formation from (*R*)-phenylpropanal:

At initial times:

$$\frac{\frac{d[E]}{dt}}{\frac{d[Z]}{dt}} \approx \frac{k_1}{k_4}$$



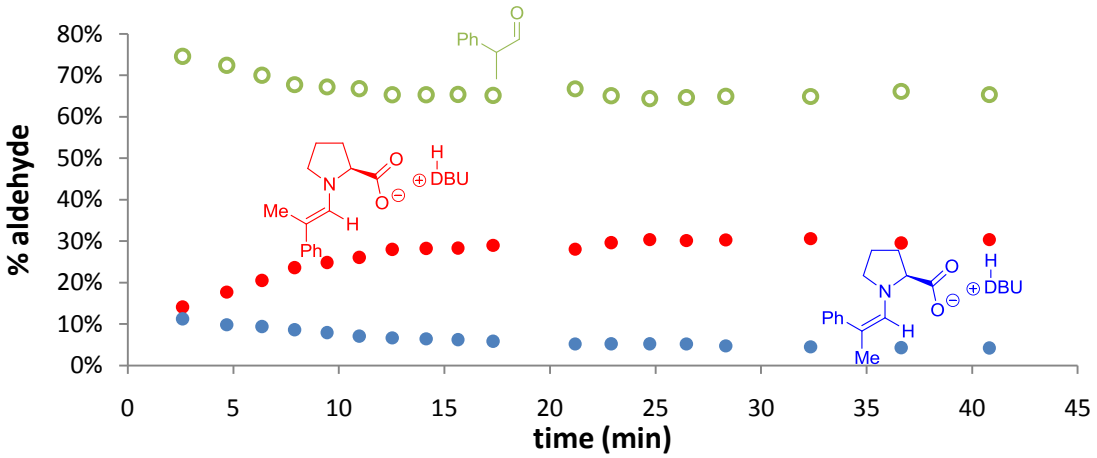


$$\frac{\frac{d[E]}{dt}}{\frac{d[Z]}{dt}} \geq \frac{39.2}{5.21} = \boxed{7.52 \leq \frac{k_1}{k_4}}$$

4.2. 1,8-Diazobicycloundec-7-ene (L)-prolinate with 2-phenylpropanal

0.6 mL of a 0.17 M stock solution of DBUprolinate in $CDCl_3$ were added to 42.4 mg (0.316 mmol) of 2-phenylpropanal diluted in 0.1 mL of $CDCl_3$ in a NMR tube at room temperature and NMR spectra were registered immediately.

Enamine formation from racemic 2-phenylpropanal.



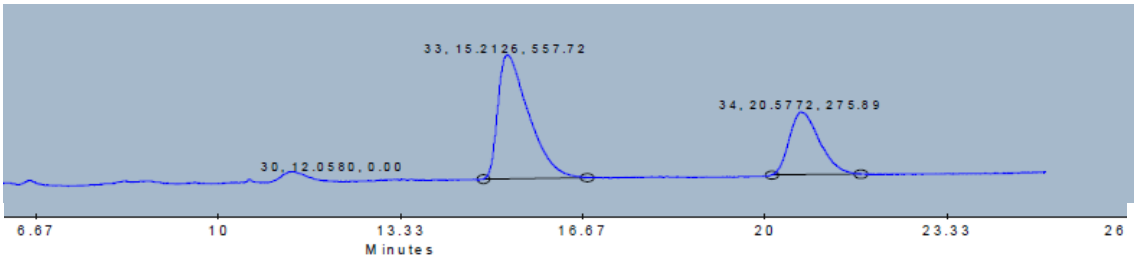
The reaction with this catalyst is too fast to obtain quantitative initial rates for the racemic and both enantiomers of 2-phenylpropanal.

5. General protocol for α-amination reaction

0.3 mL (0.32 mmol) of a 1.05 M stock solution of DEAD in $CHCl_3$ and 0.1 mL (0.32 mmol) of a stock solution (3.16 M) of aldehyde in $CHCl_3$ were successively added to a mixture of 0.1 mL (0.095 mmol) of a stock solution of acetic acid in $CHCl_3$ and 0.5 mL (0.106 mmol) of a stock solution of catalyst in $CHCl_3$. When the reaction was finished it was quenched with $NaBH_4$ in methanol. After 5 minutes an aqueous solution of KOH was added at 0 °C and the resulting mixture was stirred for 1 h at rt.[3]

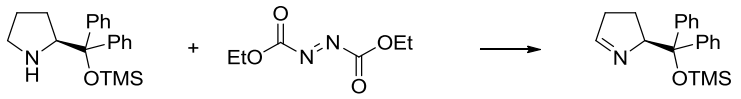
The mixture was extracted with CH_2Cl_2, the solvent was evaporated and the crude product was purified by flash column chromatography (3:1 Et_2O/cyclohexane) to yield the oxazolidinone derivative .[3]

UHPLC Eksigent of the product **4a** (entry 6 Table 1): Chiralcel OD-H 0.50 ID x 150 mm, 5 µ, hexane:^{i}PrOH 95:5 (time 0) to 85:15 (time 25 min), 10 µL/min.



The analysis of product **4b** was described previously.[4]

Unfortunately, it was not possible to obtain any results for the α-amination in absence of acetic acid because the catalyst was totally and irreversibly reduced by DEAD.[5]



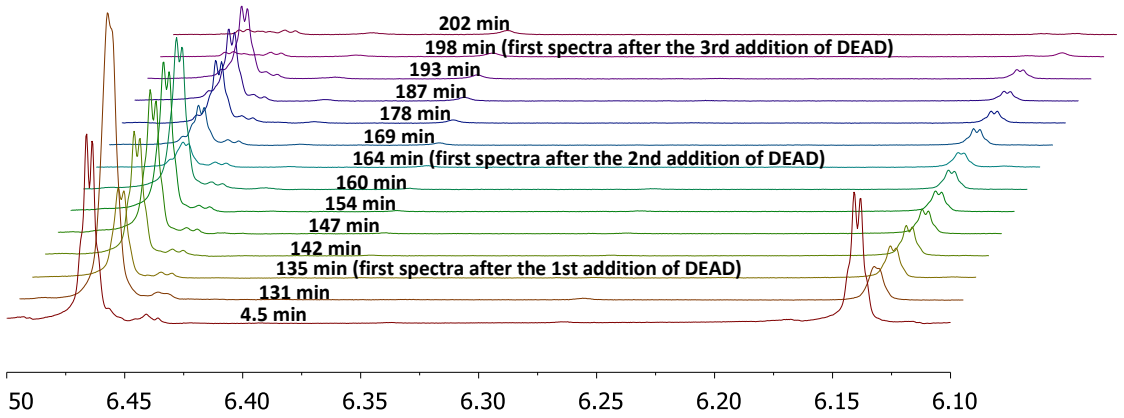
6. Experiments of α-amination in different conditions

In the case of DBUprolinate, the enamine formation equilibrium is much faster than the equilibrium with diphenylprolinolTMS, and it arrives to the thermodynamic ratio in aprox. 20 min (30 fold faster than DPPTMS).

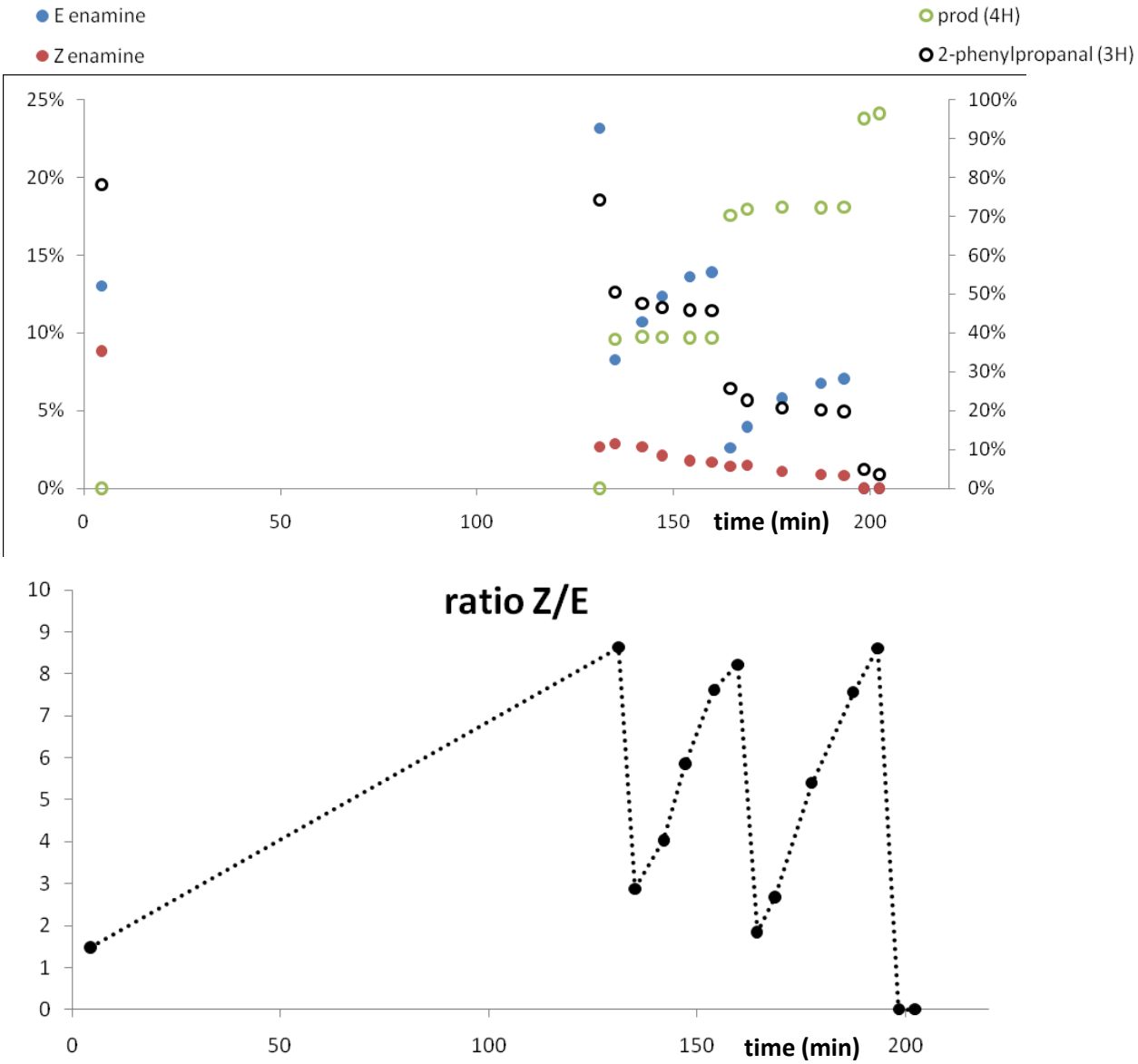
If we assume that in the conditions of the reaction the equilibration is not possible, that *E* and *Z* enamines are generated in equimolar quantities, and also that both *E* and *Z* enamines have similar facial selectivities, the result of a racemic product makes sense.

To check if that hypothesis is correct, we carried out the reaction with a 33 mol% of catalyst and premixing the aldehyde with the catalyst for 30 min before DEAD (1.0 equiv) was added. In these conditions the product was formed with –12% ee.* In addition, this result proves that the inversion in the selectivity is also possible for aldehydes with α-sterocenters. The fact that *E* enamine gives the *S* enantiomer of the product is in agreement with the model proposed by Blackmond *et al.* previously.[6]

We repeated the reaction with 33 mol% of catalyst and preequilibrating the aldehyde, but adding only 33 mol% of DEAD in three different injections after the enamines reached thermodynamic equilibrium. In this case, the final product was yielded with –21% ee.



* The negative value is used to indicate the reversal selectivity compared with Proline. So positive values mean *R* is the major enantiomer and negative values are used when *S* enantiomer is the major one.



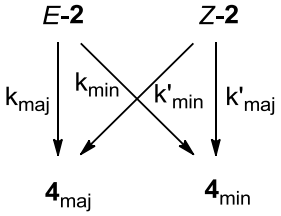
As we show in point 8 of this supporting information, acids catalyze enamine formation. In the presence of one equivalent of acetic acid (with respect to catalyst), the total amount of enamine decreased but the thermodynamic *E*/*Z* ratio was achieved in the first NMR spectra that was registered (<2.5 min). When the reaction was carried out in the presence of one equivalent of acetic acid, without any equilibration time and DEAD added in only one portion, the product was yielded with –34% ee.

7. Mathematical model for the product *ee* estimation of a reaction from a mixture of *E* and *Z* enamines in equilibrium

In a reaction where *E* and *Z* enamines are in equilibrium and the selectivity of the reaction is determined in the enamine addition step where both enamines have the same reactivity, the ee of the product and the selectivity can be calculated.

Assumptions:

- $[E]_{eq} > [Z]_{eq}$
- $k_{maj} = k_{maj'}$ and $k_{min} = k_{min'}$.
- selectivity factor: $s = k_{maj}/k_{min}$ and is ≥ 1.



$$ee(\%) = \frac{4_{maj} - 4_{min}}{4_{maj} + 4_{min}} \cdot 100 =$$

$$= \frac{k_{maj} \cdot [E\text{-}\mathbf{2}] + k_{min} \cdot [Z\text{-}\mathbf{2}] - \left(k_{min} \cdot [E\text{-}\mathbf{2}] + k_{maj} \cdot [Z\text{-}\mathbf{2}]\right)}{k_{maj} \cdot [E\text{-}\mathbf{2}] + k_{min} \cdot [Z\text{-}\mathbf{2}] + k_{min} \cdot [E\text{-}\mathbf{2}] + k_{maj} \cdot [Z\text{-}\mathbf{2}]} \cdot 100 =$$

$$= \frac{k_{maj} \cdot ([E\text{-}\mathbf{2}] - [Z\text{-}\mathbf{2}]) - k_{min} \cdot ([E\text{-}\mathbf{2}] - [Z\text{-}\mathbf{2}])}{k_{maj} \cdot ([E\text{-}\mathbf{2}] + [Z\text{-}\mathbf{2}]) + k_{min} \cdot ([E\text{-}\mathbf{2}] + [Z\text{-}\mathbf{2}])} \cdot 100 =$$

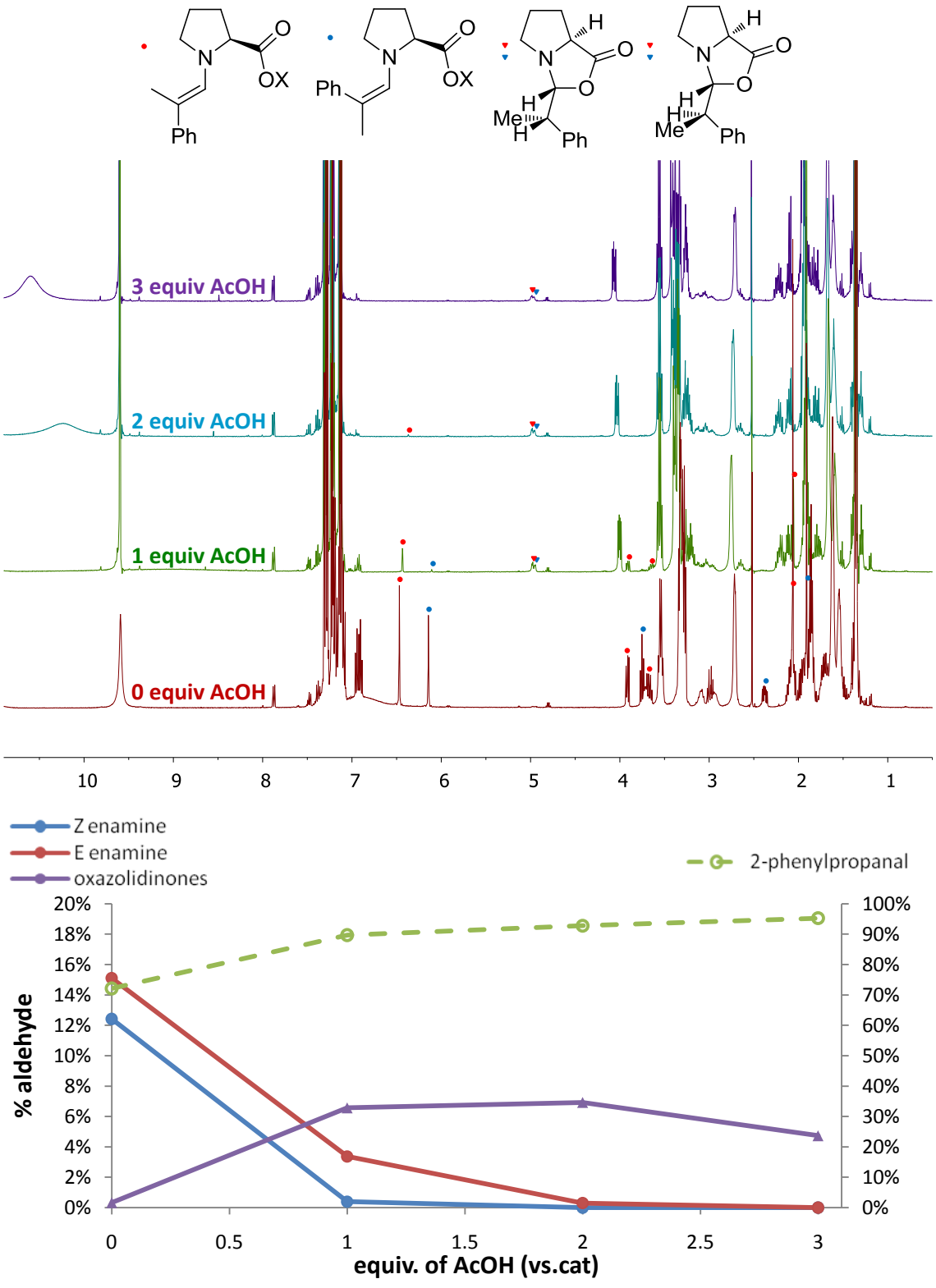
$$= \frac{(k_{maj} - k_{min}) \cdot ([E\text{-}\mathbf{2}] - [Z\text{-}\mathbf{2}])}{(k_{maj} + k_{min}) \cdot ([E\text{-}\mathbf{2}] + [Z\text{-}\mathbf{2}])} \cdot 100 = ee(\%) \quad (12)$$

$$ee(\%) = \frac{\frac{(k_{maj} - k_{min})}{k_{min}} \cdot \frac{([E\text{-}\mathbf{2}] - [Z\text{-}\mathbf{2}])}{[E\text{-}\mathbf{2}]}}{\frac{(k_{maj} + k_{min})}{k_{min}} \cdot \frac{([E\text{-}\mathbf{2}] + [Z\text{-}\mathbf{2}])}{[E\text{-}\mathbf{2}]}} \cdot 100 =$$

$$= \frac{(s-1) \cdot \left(1 - \frac{[Z\text{-}\mathbf{2}]}{[E\text{-}\mathbf{2}]}\right)}{(s+1) \cdot \left(1 + \frac{[Z\text{-}\mathbf{2}]}{[E\text{-}\mathbf{2}]}\right)} \cdot 100 = ee(\%) \quad (13)$$

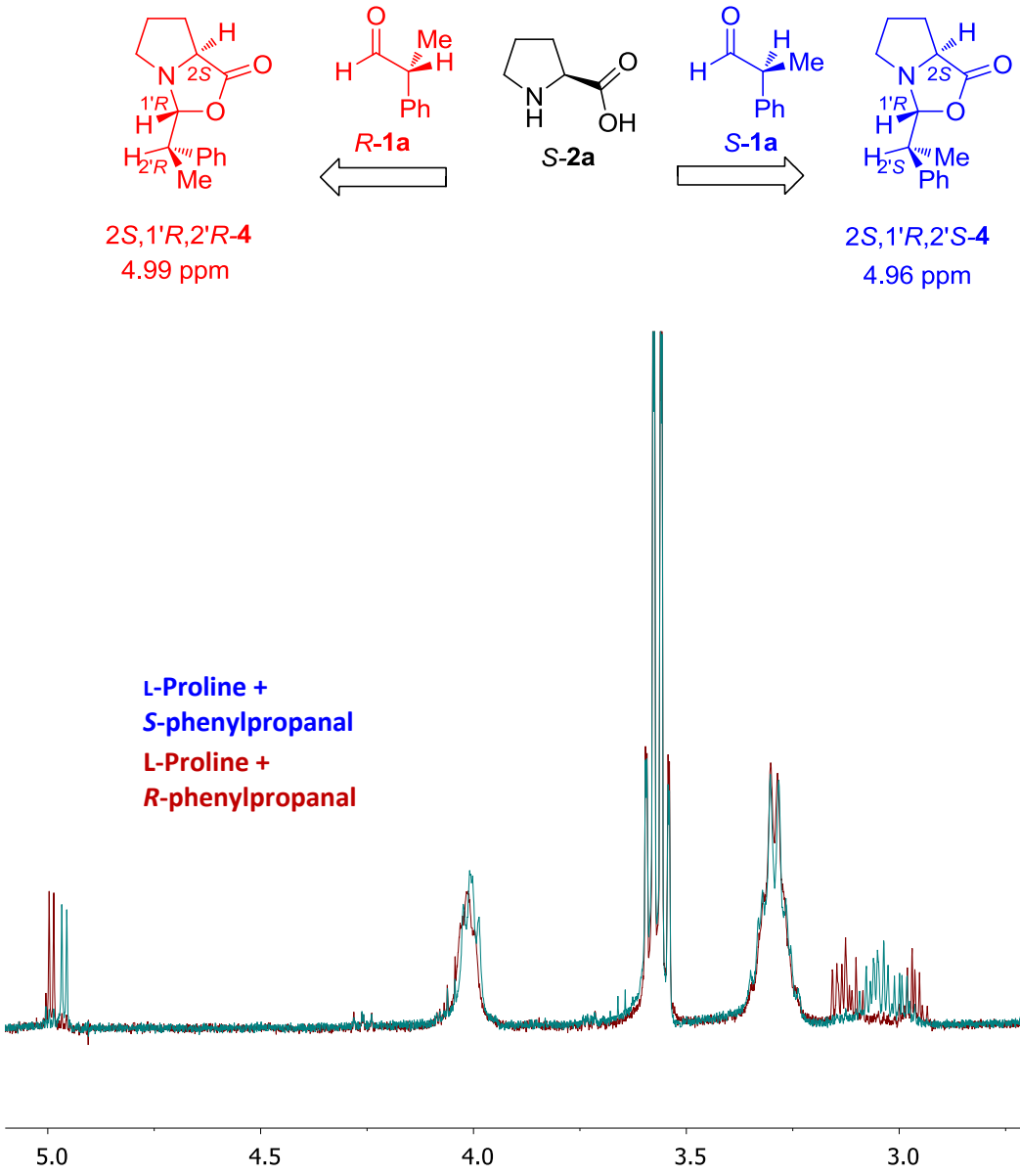
8. Effect of AcOH to the enamines formation of 2-phenylpropanal with 1,8-diazobicycloundec-7-ene (L)-prolinate

The addition of acetic acid to enamine of DBUprolinate decreases the enamine percentage and increases the oxazolidinone percentage. In addition, the acetic acid accelerates the equilibration between *E* and *Z* enamines and the first *E*/*Z* ratio observed in these conditions is already the thermodynamic ratio (*E*/*Z*=8.6).

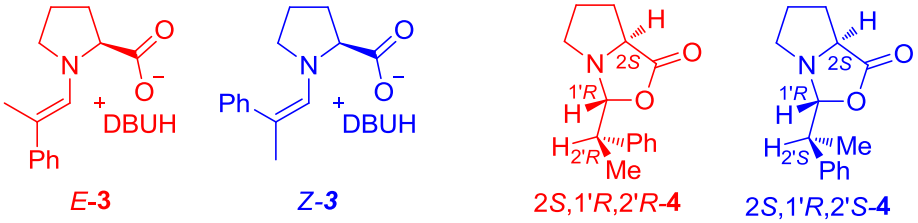


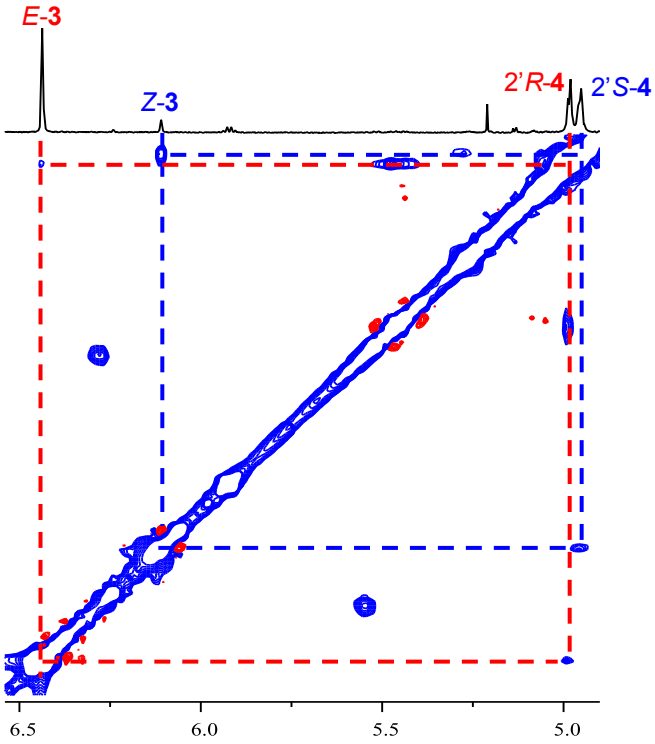
9. Correlation between enamines and oxazolidinones of L-proline with 2-phenylpropanal

In the thermodynamic equilibrium of racemic 2-phenylpropanal with proline/DBU and one equivalent of acid, it is possible to observe two enamines and two oxazolidinones. Both enamines were characterized by nOe contacts as the *E*-**3** and *Z*-**3** enamines in the *s-trans* conformation (see section 3.2). To assign the two oxazolidinones we prepared the corresponding ones from *S*-phenylpropanal (*S*-**1a**) and *R*-phenylpropanal (*R*-**1a**) with L-proline (*S*-**2a**). Each enantiomerically pure aldehyde yielded only one oxazolidinone. The L-proline (*S*-**2a**) with *R*-phenylpropanal (*R*-**1a**) yielded the oxazolidinone diastereomer which has the signal of the proton of C(1') downfield (4.99 ppm) and with *S*-phenylpropanal (*S*-**1a**) yielded the oxazolidinone diastereomer which has the signal of the proton of C(1') upfield (4.96 ppm).

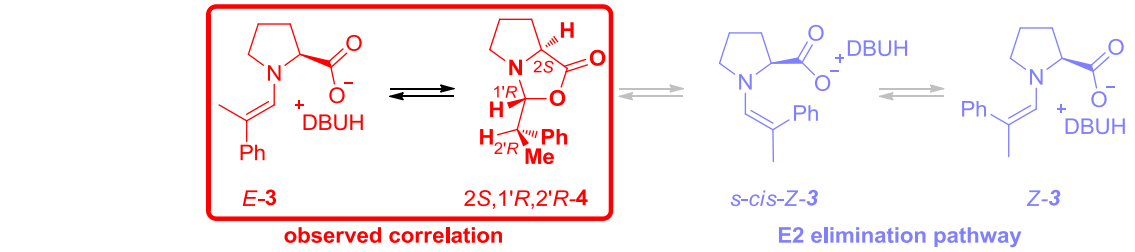


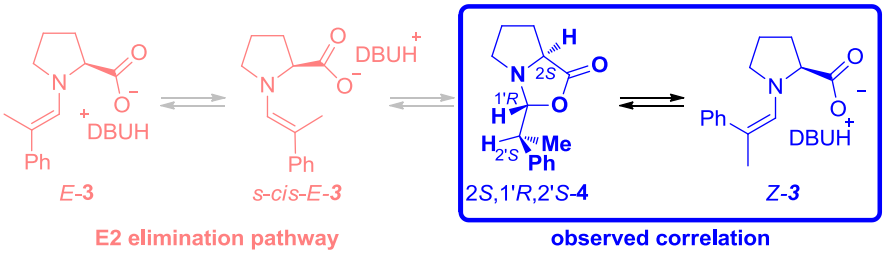
The 2D-ROESY experiment of the equilibrated mixture of racemic 2-phenylpropanal with L-proline/DBU and one equivalent of acetic acid shows more intense EXSY cross-peaks for each of the enamines with each of the oxazolidinones. The enamine *E*-**3** correlates preferentially with the 1*S*,1'*R*,2'*R*-**4** oxazolidinone and the enamine *Z*-**3** with the 1*S*,1'*R*,2'*S*-**4** oxazolidinone.





We may discount the E2-elimination route based on the relationship observed between the enamine and oxazolidinone. For the 2*S*,1'*R*,2'*R*-**4** case that gives the major *s-trans E*-3 enamine, the E2 elimination pathway would yield the *Z*-**3** enamine. Identical logic applies to the 2*S*,1'*R*,2'*S*-**4** oxazolidinone, which correlates with the minor enamine *Z*-**3**.





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