A Mechanistic Rationalization of Unusual Kinetic Behavior in Proline-Mediated Reactions - Supporting Information

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A. General experimental procedure for reactions in Omnical CRC90 or SuperCRC reaction calorimeter

The experiments were performed as described previously.[1,2] Reactions were carried out in an Omnical Super CRC reaction calorimeter, which allows continuously monitoring of the instantaneous enthalpy balance around the vessel. The sample vessel is a 4 or 16 mL septum-cap vial equipped with a shaft and stirring blade. The system operates as a differential scanning calorimeter by comparing the heat released or consumed in a sample vessel compared with that from a reference compartment at intervals of 2-6 seconds over the course of the reaction.

An energy balance around the vessel for the case of a single reaction occurring demonstrates that reaction heat flow, q, is proportional to the reaction rate, r, where ΔH_{rxn} is the heat of the reaction and V is the reaction volume. The observed heat flow profiles may also be used to obtain the fractional conversion of substrate by calculation of the fractional area under the temporal heat flow curve as given below, where the numerator represents the area under the heat flow curve to any time point *t* and the denominator represents the total area under the heat flow curve to reaction completion at time t_f.

$$q = \Delta H_{rxn} \cdot vol \cdot rate$$

$$fraction\ conversion = f_{final} \cdot \frac{\int_0^t q(t)dt}{\int_0^{t_{end}} q(t)dt}$$

Conversion determined from heat flow was compared in all cases to conversion by GC measurement and in some cases also to FTIR spectroscopic monitoring to confirm that the observed heat flow represents an accurate measure of rate of the reaction under study (Figure S-1).

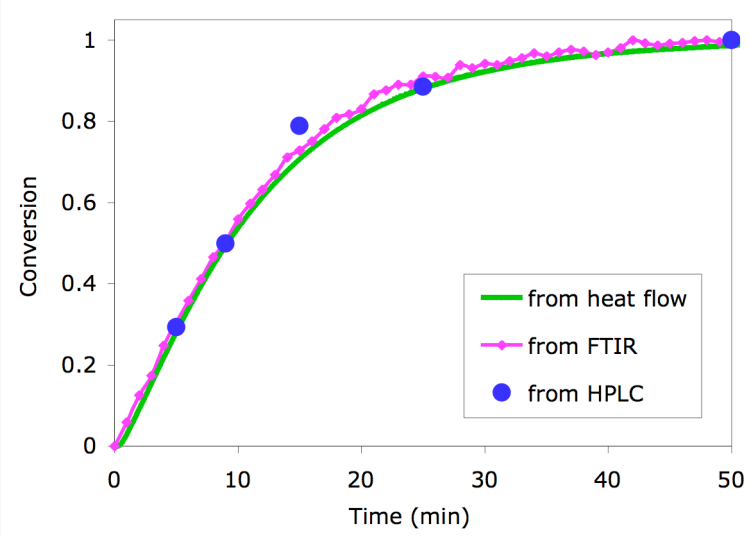


Figure S-1. Comparison of conversion vs. time for different methods of monitoring the aldol reaction of Scheme 2 carried out in DMSO.

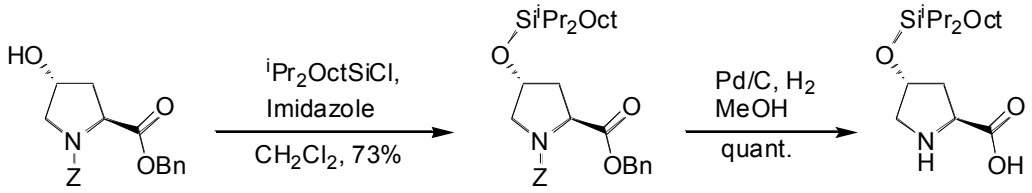
B. Reaction procedure for the α-amination kinetic studies

L-Proline (Lancaster) was added to the reaction vessel with dichloromethane (Aldrich). After addition of diethylazodicarboxylate (DEAD, Lancaster), this vessel was placed in the calorimeter and stirred until thermal equilibration was reached (ca. 40-60 minutes). A syringe containing a known amount of propionaldehyde (Aldrich) was placed in the sample injection port of the calorimeter and was allowed to reach thermal equilibrium. Once thermal equilibrium was reached, reaction was initiated by injecting propionaldehyde into the reaction mixture. Reaction work up and analysis were performed according to a literature procedure.[1]

C. Reaction procedure for the aminoxylation kinetic studies

L-Proline (Lancaster) was weighed along with nitrosobenzene (Aldrich) in the reaction vessel and chloroform (Aldrich) was added. This vessel was placed in the calorimeter and stirred until thermal equilibration was reached (ca. 40-60 minutes). A syringe containing known amount of propionaldehyde (Aldrich) was placed in the sample injection port of the calorimeter and was allowed to reach thermal equilibrium. Once thermal equilibrium was reached, reaction was initiated by injecting propionaldehyde into the reaction mixture. The details of the reaction work up and analysis were similar to that reported earlier (see above).[2]

D. Synthesis of (4*S*)-4-diisopropyloctylsilyloxy-L-proline

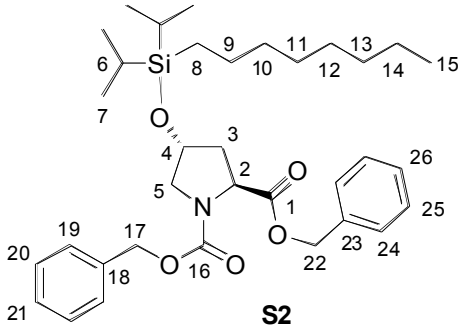


S1 **S2** **8**

(a) General

NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer. The chemical shifts are reported in ppm downfield of internal tetramethylsilane for ^{1}H NMR and relative to the residual solvent signal for ^{13}C NMR. Infra-red spectra were recorded on a Perkin-Elmer RX FT-IR spectrometer, spectra were analysed as thin films between NaCl or KBr plates. Elemental analysis was performed at London Metropolitan University. Abbreviations: Bn: Benzyl, Z: Benzyloxycarbonyl

(b) *N*-Z-4(*S*)-diisopropyloctylsilyloxy-L-proline S2



S2

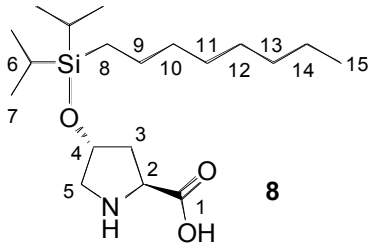
In a round bottom flask, 0.67g (1.89mmol, 1.0eq.) *N*-Z-4-*trans*-L-hydroxyproline benzyl ester **S1**[4] and 0.29g (4.27mmol, 2.3eq.) imidazol were dissolved in 5ml of CH_2Cl_2, 0.55g (2.08mmol, 1.1eq.) diisopropyloctylsilyl chloride were added and the mixture stirred at room temperature for 3.5 hours until full conversion was achieved according to TLC (hexane:ethyl acetate 3:1). The mixture was washed with sat. $NaHCO_3$, two times with sat. NH_4Cl and finally with brine. Drying over $MgSO_4$, removal of the solvent in vacuum and purification by flash column chromatography (hexanes:ethyl acetate 5:1) yielded 1.02g (93%) of **S2** as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.41-7.13 (m, 10H, Ar-H), 5.25-4.9 (m, 4H, $H^{17, 22}$), 4.60-4.38 (m, 2$H^{2,4}$), 3.74-3.60 (m, 1H^{5}), 3.56-3.38 (m, 1$H^{5'}$), 2.30-2.14 (m, 1H^{3}), 2.11-1.95 (m, 1$H^{3'}$), 1.40-1.15 (m, 12H^{9-14}), 1.06-0.80 (m, 17$H^{6,7,15}$), 0.66-0.52 (m, 2H, H^{8}) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.7 + 172.54 (C^{1}); 155.1 + 154.4 (C^{16}); 136.7 + 136.5, 135.7 + 135.5 ($C^{18, 23}$); 128.6, 128.51, 128.46, 128.4, 128.3, 128.25, 128.2, 128.01, 127.99, 127.9 ($C^{19-21, 24-26}$); 70.5 + 69.8 ($C^{2 \text{ or } 4}$); 67.1 + 66.9 + 66.8 ($C^{17, 22}$); 58.3 + 58.1 ($C^{2 \text{ or } 4}$); 55.3 + 54.9 (C^{5}); 40.1 + 39.1 (C^{3}); 34.1; 32.0; 29.35; 29.25; 23.4; 22.8; 17.6 (C^{7}); 14.2 (C^{15}); 12.5 (C^{6}); 10.8 (C^{8}) ppm.

EI-MS ($C_{34}H_{51}NO_5Si$) m/z: 91 (Bn^+, 100), 581 (M, 0.04), ν_{max}: 1749, 1715 cm^{-1}, **Elemental analysis**: calculated: C 70.18%, H 8.83%, N 2.41%; found: C 70.07%, H 8.90%, N 2.31%.

(d) 4*O*-diisopropyloctylsilyl-4-*trans*-L-hydroxyproline 8



8

In a round bottom flask, 2.37g (4.07mmol) **S2** was dissolved in 24ml methanol and 87mg (0.04mmol, 1.0mol%) Pd/C (5w%) were added under an atmosphere of nitrogen. The atmosphere was changed to hydrogen, a hydrogen filled balloon was added and the mixture stirred at room temperature for seven hours. Filtration of the catalyst and removal of the solvent in vacuum yielded 1.41g (97%) of **8** as a colourless waxy solid which was stored at 4°C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.3 (s, $1H^1$), 4.48 (m, $1H^4$), 4.16 (dd like t, $^3J_{H,H}$ = 7.4Hz, $1H^2$), 3.47 (m, $1H^{5'}$), 3.20 (m, $1H^{5'}$), 2.34-2.04 (m, $2H^3$), 1.40-1.17 (m, $12H^{9-14}$), 1.06-0.93 (m, $14H^{6,7}$), 0.89 (t, $^3J_{H,H}$ = 6.4Hz, $3H^{15}$), 0.67-0.54 (m, $2H^8$) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.8 (C^1), 70.9 (C^4), 59.9 (C^2), 52.5 (C^5), 39.2 (C^3), 34.1, 32.0, 29.3, 29.2, 23.4, 22.7, 17.6 (C^7), 14.2 (C^{15}), 12.4 (C^6), 10.8 (C^8) ppm.

FAB$^+$-MS ($C_{19}H_{39}NO_3Si$) m/z: 285 (100), 358 ($M+H^+$, 14), 380 ($M+Na^+$, 17). ν_{max}: 3400, 2925, 2866, 1631 cm^{-1}. **Elemental analysis** calculated: C 63.81%, H 10.99%, N 3.92%; found: C 63.88%, H 11.14%, N 3.81%.

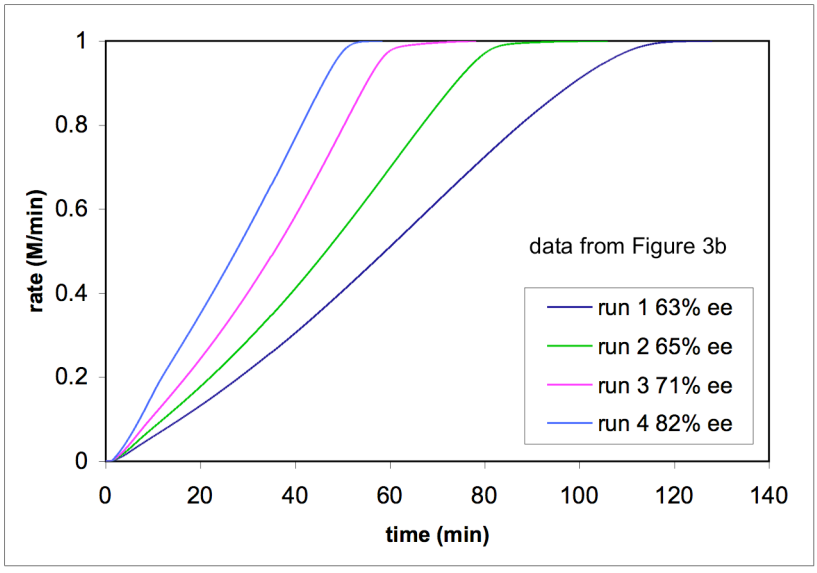
E. Conditions for Reactions in Figures 1 - 3.

Figure 1. Reaction carried out in DMF. α-amination: $[\mathbf{1}]_0$ = 1.9 M; $[\mathbf{2b}]_0$ = 0.6 M; 17 mol% **4**;; T = 10 ˚C. Product ee = 56%. Aldol: $[\mathbf{5}]_0$ = 2.5 M; $[\mathbf{6}]_0$ = 0.5 M; 20 mol% **4**; T = 25 ˚C. Product ee = 76%. Conversion complete in both cases.

Figure 2.. Reaction conditions in $CHCl_3$: α-aminoxylation: $[\mathbf{1}]_0$ = 2.0 M; $[\mathbf{2a}]_0$ = 0.7 M; T = 5 ˚C; 2 mol% **8**; Product ee = 98%. Aldol: $[\mathbf{5}]_0$ = 2.5 M; $[\mathbf{6}]_0$ = 0.6 M; T = 25 ˚C; 8.5 mol% **8**; Product ee = 75%. Full conversion in both cases.

Figure 3. Concentrations of reactants in each experiment as shown on plots. a) α-aminoxylation carried out at 5 C in $CHCl_3$ using 0.07 M proline. b) α-amination carried out at 10 C in CH_2Cl_2 using 0.14 M proline. Conversion was complete in all cases. Product enantioselectivity was 97-98 %ee for the reactions in Figure 3a and ranged from 82-63 %ee for the reactions in Figure 3b. Low aldehyde concentration and longer reaction times both have an adverse effect on enantioselectivity for the α-amination reaction.

Temporal view of data from Figure 3b:



run no.	$[\mathbf{1}]_0$ (M)	$[\mathbf{2b}]_0$ (M)
1	0.86	0.69
2	1.01	0.69
3	1.24	0.69
4	1.1	0.45

F. Theoretical calculations:

The electrostatic potential near the van der Waals surface in Figure 4 was created from energy scans of proline. Only the electronic energy at 0 K is computed and plotted. Input files for each scan are listed below in Gaussian 03 input format:

Gaussian 03, Revision C.02,
M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.

The Gaussian input file for the configuration in Figure 4a is listed below.

```
------------a_proline.gjf-----------------------------------------
%chk=a_proline.chk
%nproc=1
# B3LYP/6-31G(D)
# opt

Proline
energy check -401.1546691

0 1
N 0.6263173626 -1.0931143833 0.5733189372
C 1.9403148785 -0.799020544 -0.0474285248
C -0.1245121633 0.1779092086 0.7528622225
H 2.2409418156 -1.6161204804 -0.7115394204
H 2.72695208 -0.6736858415 0.7119576894
C 1.7019661829 0.523748113 -0.7844297367
C 0.7911982951 1.288137833 0.1898307432
H -0.3759397984 0.3625383693 1.8029977095
C -1.4660205291 0.1077738079 -0.0126661814
H 1.1807636813 0.3396569212 -1.7316464232
H 2.6338166173 1.0501633432 -1.0101243448
H 0.2114633684 2.0900619277 -0.2725512876
H 1.3881587093 1.7240740811 0.9993235239
O -2.2457868062 1.0319869259 -0.0413213622
O -1.6699454931 -1.0606595099 -0.6344385199
H -0.8464073226 -1.5821302818 -0.4296611351
H 0.7242077215 -1.6046671957 1.4450790504

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```

The Gaussian input file for the configuration in Figure 4b is listed below.

```
------------b_proline.gjf-----------------------------------------
%chk=b_proline.chk
%nproc=1
# B3LYP/6-31G(D)
# opt

activated proline
energy check -401.1396335

0 1
N 0.5669561225 1.2625405648 -0.1619137373
C -0.1241283109 0.0860363975 -0.7413606364
C 0.931067111 -1.0479191204 -0.6949323234
C 2.1737662746 -0.4141513739 -0.0279778459
C 1.5814831226 0.7489211044 0.7713782882
C -1.3700579879 -0.2491869626 0.0937876788
O -1.3915272722 -1.0017232908 1.0369321542
O -2.4862313755 0.4694078537 -0.2242777524
H 2.8630239204 -0.0260649757 -0.7853767448
H 0.5423365015 -1.868240086 -0.0867362408
H 1.145560772 -1.435591914 -1.6945695653
H 2.309489097 1.5354005805 0.9981050767
H 1.1564757226 0.3842047249 1.7209645236
H 2.7196887739 -1.124043797 0.6001392496
H -0.4296387989 0.3195335343 -1.7723916405
H -0.0783120268 1.9131778708 0.2824715194
H -2.3280288942 0.9801633366 -1.0358162001
```

G. Supplementary References

(1) Iwamura, H.; Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 11770-11771.

(2) Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem. Int. Ed.* **2004**, *43*, 3317-3321.

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(4) Tamaki, M.; Han, G.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1038-1042.