5-(Pyrrolidine-2-yl)tetrazole: Rationale for the Increased Reactivity of the Tetrazole Analogue of Proline in Organocatalyzed Aldol Reactions

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5-[(2*S*)-Pyrrolidine-2-yl]-1*H*-tetrazole (**1**), i.e. the tetrazolic acid analogue of proline, has been found to be significant more reactive than L-proline (**2**) in various organocatalyzed reactions. In the organocatalyzed direct asymmetric aldol reaction, acetone was reacted with aromatic and aliphatic aldehydes to afford the resulting β-hydroxy ketones in good yields and moderate to high enantiomeric excesses. The increased reactivity of **1**, as compared to **2**, has been rationalized through a combined computational and NMR spectroscopic study. It was found that catalyst **2** was almost completely engaged in oxazolidinone formation with the aldehyde whereas **1** did not take part in such parasitic equilibrium. This finding, together with the improved solubility of the tetrazole analogue, is proposed to account for the observed reactivity.

Introduction

The aldol reaction is one of the most important carbon–carbon bond-forming reactions; therefore, the widespread interest in developing asymmetric variants of this reaction is not surprising. The asymmetric aldol reactions reported today rely on: the use of chiral auxiliaries, catalysts that facilitate reaction between preformed enolates and aldehydes, and catalysts capable of inducing reaction between unmodified ketones and aldehydes.[1,2]

Catalysts facilitating the direct asymmetric addition reaction between unmodified ketones and aldehydes has been developed by Shibasaki and Trost using heterobimetallic catalysts,[3–4] whereas Lerner and others have used more naturally inspired catalytic systems consisting of aldolase enzymes and catalytic antibodies.[5–6] An organocatalytic approach utilizing L-proline as catalyst for an intramolecular aldol cyclization, also termed the Hajos–Parrish–Eder–Sauer–Wichert reaction, was reported some thirty years ago.[7] Recently List et al. demonstrated that L-proline also could mediate the intermolecular aldol reaction using unmodified ketones and aldehydes.[8] This report has sparked a tremendous renewed interest in the area of asymmetric catalysis by small organic molecules, e.g. organocatalysis, with both proline[9] and other molecular entities.[10]

Although proline is an ideal catalyst in terms of price and availability, often-encountered drawbacks relates to low reactivity and low solubility of the catalyst. Second-generation catalysts, in which the carboxylic acid function of proline is replaced by known bio-isosteres such as tetrazolic acids or *N*-sulfonylamides[11] have therefore recently emerged, and have been proven to show dramatically improved reactivity and/or selectivity for many organocatalyzed reactions. Other novel organocatalysts, based on tripeptides[12] have also been developed.

After the initial discovery by Ley,[13] Yamamoto,[14] and ourselves,[15] the use of the catalyst 5-[(2*S*)-pyrrolidine-2-yl]-1*H*-tetrazole (**1**), i.e. the tetrazolic acid analogue of proline **2**, has expanded to organocatalyzed variants of enantioselective aldol condensations,[16] *O*-nitroso aldol/Michael reaction,[17] and addition to nitro olefins.[18] Lately, Barbas and co-workers employed tetrazole **1** as a highly active catalyst for the creation of a quaternary stereocenter in a total synthesis of LFA-1 antagonist BIRT-377.[19]

The direct asymmetric aldol condensation between unmodified ketones and aldehydes relies on activation of the ketone partner through formation of the corresponding enamine as an intermediate through condensation with the secondary amine function of the catalyst, Scheme 1. The reactive enamine then attacks the aldehyde via an ordered Zimmerman–Traxler like transition state. A high concentration of acetone is used to suppress formation of by-products and in order to drive the reaction equilibrium towards product.

In our initial report on catalyst **1** we reasoned that part of the increased reactivity was due to a greater charge-stabilization in the aldol reaction transition state by the tetrazolic acid function, in comparison to the carboxylic acid in **2**. However, in this full account of our studies of **1** we find that the main reason for the increased reactivity of **1**

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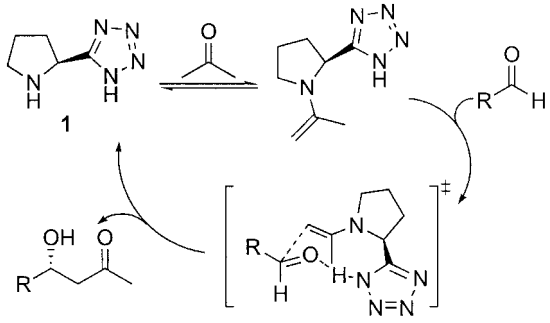


Scheme 1.

over **2** in the organocatalyzed aldol reaction, and most likely also in other organocatalyzed reactions, is mainly attributed to the lack of parasitic bicyclo-oxazolidinone formation between the aldehyde and catalyst **1**.

Results and Discussion

Synthesis

The new organocatalyst **1** was synthesized from commercially available L-proline (**2**) according to Scheme 2.

The synthesis commenced with Cbz protection of L-proline[20a] **2** to yield **3**, which was subsequently transformed to amide **4**, utilizing in situ activation of the carboxylic acid.[20b] Subsequent dehydration furnished the corresponding nitrile **5** in high yield,[20c–d] which was further transformed into the protected tetrazole **6** utilizing the "click chemistry" protocol developed in the Sharpless laboratory.[20e–20f]

The target compound **1**, which can be represented by the two tautomers **1-*1H*** and **1-*2H***, was obtained after catalytic hydrogenation and purification by a solid-phase catch and release procedure. This highly efficient synthesis furnished the desired product in 75% overall yield, without any detectable racemization.[20g]

Asymmetric Aldol Reaction

The new tetrazole catalyst was assessed in the direct asymmetric aldol condensation in order to investigate the effect upon substitution of the carboxylic acid to the tetrazolic acid in terms of reactivity and selectivity. Initially, the reaction between acetone and the three aldol acceptors 4-nitrobenzaldehyde (**7**), 2,2-dimethylpropionaldehyde (**8**), and 4-methoxybenzaldehyde (**9**) was evaluated. A large excess of acetone (20% of the solvent volume) was used in order to drive the equilibrium towards products. The reaction was followed directly by performing the reaction in an NMR tube using [D_6]DMSO as solvent and suppression of the acetone signal by the WET-pulse sequence.[21]

The results presented in Figure 1 clearly show that **1** is significantly more reactive than **2**, especially when the less reactive substrates like 4-methoxybenzaldehyde and 2,2-dimethylpropionaldehyde is used as substrates.

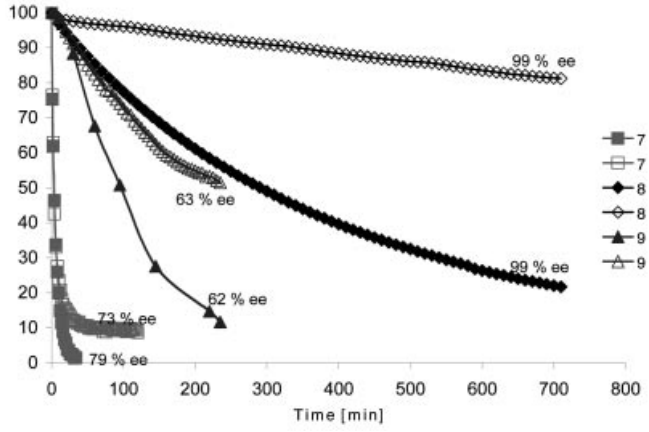
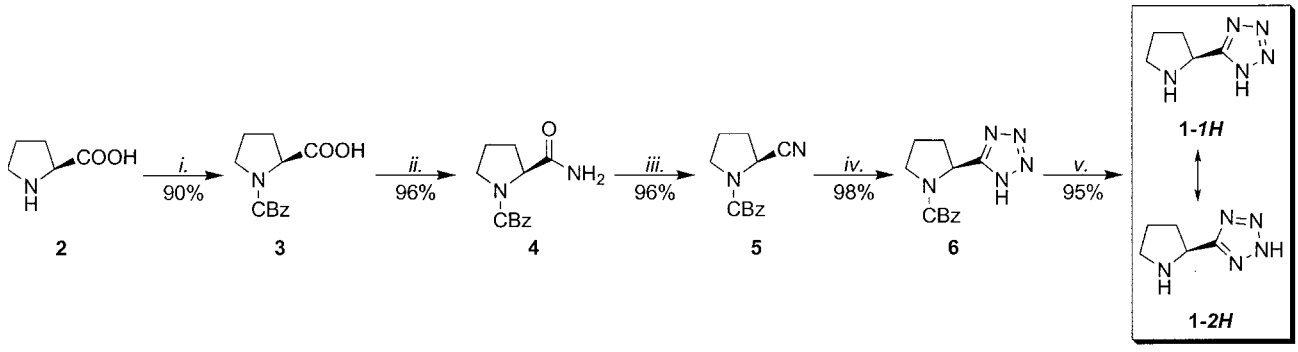


Figure 1. Graph showing the conversion of starting material into product as a function of time during the direct organocatalyzed asymmetric aldol reaction between acetone and aldehydes 4-nitrobenzaldehyde (**7**), 2,2-dimethylpropionaldehyde (**8**), and 4-methoxybenzaldehyde (**9**) using catalyst **1** (solid markers) and catalyst **2** (empty markers).

It should also be noted that proline was far more active in the archetypal reaction between acetone and 4-nitrobenzaldehyde than previously reported, giving the aldol product in 76% isolated yield after only thirty minutes.

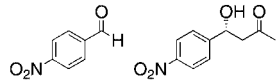
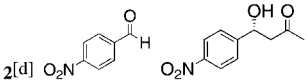
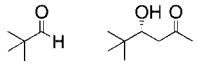
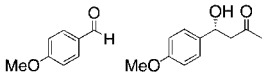
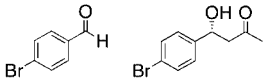
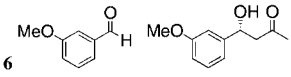
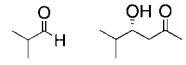
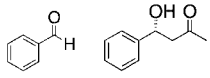
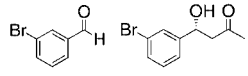
Having established the higher reactivity of **1**, as compared to **2**, we next evaluated the potential of **1** as a catalyst for the direct asymmetric aldol reaction between acetone and a selection of aliphatic and aromatic aldehydes. Ini-



Scheme 2. Synthesis of **1**. (*i*) Cbz-Cl, NaOH, 5 °C; (*ii*) $(Boc)_2O$, NH_4HCO_3, CH_3CN, cat. pyridine; (*iii*) Cyanuric chloride, DMF; (*iv*) NaN_3, $ZnBr_2$, water/2-propanol; (*v*) H_2O, AcOH, H_2, Pd/C.

tially, all reactions were run at small scale and monitored by NMR as described above, to find the optimal reaction time for each substrate (see the supporting information for graphs of conversion vs. time). Next, the reactions were run on larger scale to afford the isolated products **7**–**14** reported in Table 1.

Table 1. Direct asymmetric aldol reaction between acetone and the listed aldehydes catalyzed by **1** in DMSO at room temperature.

Entry	Substrate	Product		Time [min]	Yield[a] [%]	*ee*[b] [%]
1			**7**	10	82	79
2[d]			**7**	2400	77	74
3			**8**	800	69	99[c]
4			**9**	400	65	62
5			**10**	140	67	66
6			**11**	400	62	62
7			**12**	800	79	99[c]
8			**13**	240	69	65
9			**14**	140	69	63

[a] Isolated yield after column chromatography. [b] Enantiomeric excess determined by chiral HPLC analysis (Chiralpak AS and Chiralpak AS-H). [c] Enantiomeric excess determined by chiral HPLC analysis (Chiralpak AD). [d] Catalyst loading 5 mol% and reaction time 40 h.

As seen from the optimized reaction times in Table 1, aliphatic aldehydes as a substance class are less reactive than the aromatic aldehydes investigated. Nevertheless, the high catalytic activity of the tetrazole catalyst allows all aliphatic aldehydes to be transformed to chiral β-hydroxy ketones with high enantioselectivity and fair yields within 12 hours.

The increased reactivity if **1** suggests that it should be possible to lower the catalyst loading from the 20% typically used when proline is employed as catalyst. Indeed, as seen in Table 1 (entry 2) and in Figure 2, the catalyst loading could be lowered by 300%, and still provides a turnover which match the reactivity of **2** at higher loading.

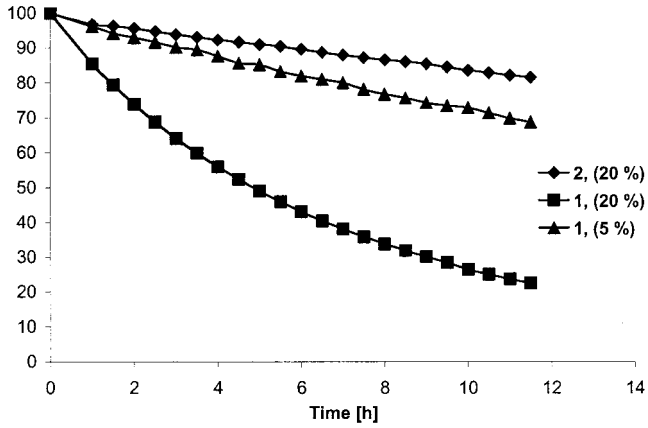


Figure 2. Graph showing the conversion of 2,2-dimethylpropionaldehyde (**8**) into the product (*R*)-4-hydroxy-5,5-dimethylhexane-2-one as a function of time during the organocatalyzed direct asymmetric aldol reaction with acetone using catalyst **1** (20 mol%, and 5 mol%) and **2** (20 mol%).

As reported in our initial study,[15] the solubility of catalyst **1** allows it to be used in other solvents than DMSO, with maintained, or slightly lowered, performance. Dioxane, dimethylformamide, and tetrahydrofuran were found to be suitable solvents for the direct asymmetric aldol reaction with catalyst **1**. Especially dimethylformamide was interesting, as this solvent allowed the reaction temperature to be decreased with only a small reduction in conversion, but a substantial increase in enantioselectivity (Table 2).

Table 2. Selected solvents from previous solvent study.

Entry	Solvent	*T*[a] [°C]	Conv.[b] [%]	Yield[c] [%]	*ee*[d] [%]	*ee*[e] [%]
1	DMF	23	99	93	70	69
2	DMF	5	96	80	80	81
3	DMF	–50	99[g]	77	82	86
4	dioxane	23	99	87	66	64
5	dioxane	5	84	78	67	67
6	DMF/ H_2O[f]	23	99	89	76	76
7	DMF/ H_2O[f]	5	75	73	77	81
8	THF	23	99	88	51	53
9	THF	5	95	77	62	65
10	THF	–50	99[g]	76	72	72

[a] Temperature was held constant with aid of a thermostat. [b] Reaction time was 4 hours and conversions were determined on crude products by means of HPLC analysis. [c] Yields after column chromatography. [d] Enantiomeric excess was determined by chiral HPLC analysis on crude products. [e] Enantiomeric excess was determined on aldol adducts purified by column chromatography. [f] Mixture of (9:1) (DMF/water) was employed as solvent. [g] Reaction time was eight hours.

Earlier reports have stated that the proline-catalyzed asymmetric aldol reaction was highly sensitive towards water.[22a–22b] The results at hand indicate that catalyst **1** (Table 2, entry 7–8) tolerates the presence of 10% of water without affecting the enantioselectivity, conversions, or isolated yield.

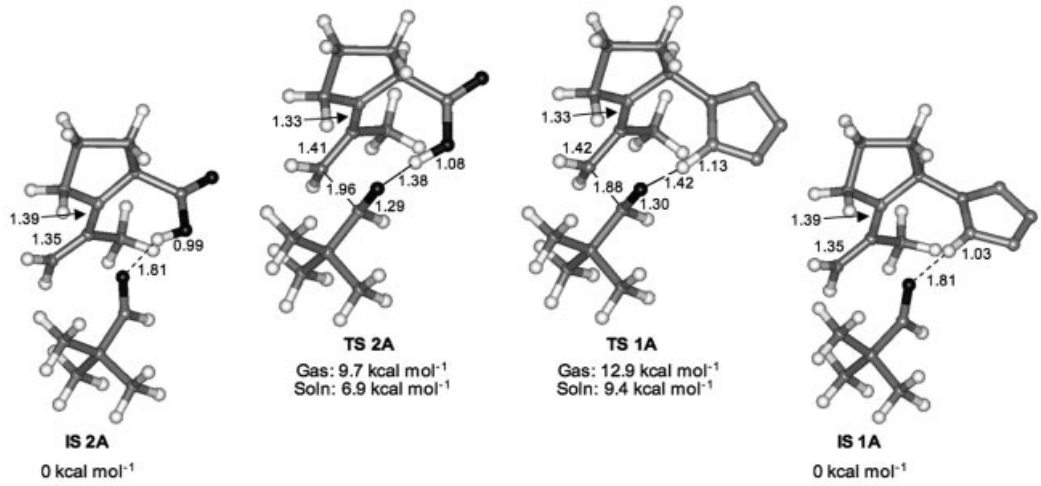


Figure 3. Geometry-optimized structures of the initial state and transition state of the proline (**IS2A** and **TS2A**) and tetrazole-catalyzed (**IS1A** and **TS1A**) asymmetric aldol reaction between acetone and 2,2-dimethylpropionaldehyde. Geometries are optimized at B3LYP/6-31G(d,p) level of theory and ZPE corrected. Energies in solution refers to single point B3LYP/6-311+G(d,p) calculations in DMSO using a self-consistent reaction field method and are ZPE corrected.

Theoretical Studies

In order to provide a plausible explanation for the increased reactivity of the tetrazole catalyst, as compared to proline, we decided to study the reaction between 2,2-dimethylpropionaldehyde and acetone computationally. Several recent studies have addressed both the intramolecular[23a] as well as the intermolecular[23b] proline-catalyzed asymmetric aldol reaction by computational means. Houk et al. first rationalized the observed stereoselectvity for the intermolecular reaction,[24a] while Boyd[24b] later presented a detailed study on most parts of the possible reaction path, and suggested that the rate-determining step in the gas phase is the initial condensation between proline and the ketone, while calculations incorporating solvation effects suggested the rate-determining step to be the carbon–carbon bond forming step, as previously proposed by List et al.[24c] An identical activation energy for the enamine formation and the carbon–carbon bond formation was recently reported by Houk et al. in new calculations[24d] on the intramolecular reaction.

Based on the many detailed theoretical studies addressing the stereoselectivity of the proline-catalyzed reactions, we restricted ourselves to a comparison between the proline and the tetrazole catalyst in terms of the proposed rate-determining steps. In our case, we did not limit ourselves to study a model system, but instead performed all calculation on the full system involving the condensation of acetone with 2,2-dimethylpropionaldehyde. Figure 3 shows the B3LYP/6-31G(d,p)-optimized structures of the initial states and the transition states for the previously established lowest energy route leading to the product with experimentally verified stereochemistry.

Surprisingly, the initial calculation in gas-phase suggested that the proline-catalyzed reaction has a lower activation energy than the tetrazole catalyst. As solvation has been shown to play a vital role on previous theoretical studies on this reaction, we next performed single point B3LYP/6-311+G(d,p) calculations in DMSO using a self-consistent reaction field method.[25] Again, the activation energy for the proline mediated reaction was found to be lower than the aldol reaction catalyzed by the tetrazole catalyst. Thus, none of the calculations done on the C–C bond formation step rationalize the much higher reactivity of the tetrazole catalyst observed experimentally.

We therefore next examined the enamine formation step, which has been suggested to have comparable activation energy as the carbon–carbon bond formation (vide supra), to see if we could detect a larger difference for the two catalysts in this step.

As can be seen in Figure 4, the activation energy for this step is clearly different for the two catalysts. In the gas-phase, catalyst **2** needs 7.2 kcal mol^{-1} for the enamin formation, while the corresponding energy for catalyst **1** is only 2.1 kcal mol^{-1}. However, upon including solvation effects in the calculations, both catalysts experience a dramatic increase in activation energy, due to the stabilizing effect of the solvent on the charged initial states for these reactions. Consequently, according to these calculations, the enamine formation now becomes the rate-determining step instead of the carbon–carbon bond formation for both these catalysts. A similar activation energy for the enamine formation and the aldol reaction step was also noted in Houk's most recent calculations on the intramolecular reaction.[23b]

In attempt to find a lower energy route for the enamine formation, we also investigated a water-mediated process. One molecule of water is liberated upon forming the iminium ion from the catalyst and acetone; this water molecule is suitably located for assisting the transformation of then imine to the enamine. However, upon investigating the barrier for this, previously neglected, pathway an even higher activation enthalpy was found. Figure 5 shows the water-

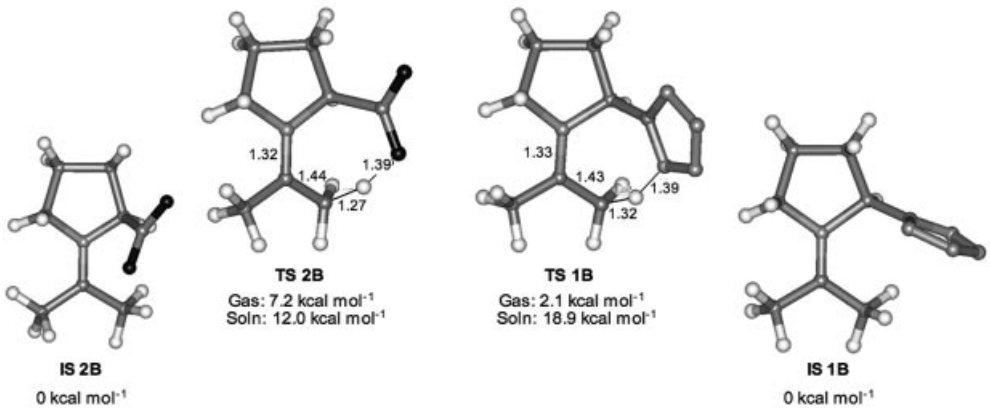


Figure 4. Geometry-optimized structures of the initial state and transition state of the proline (**IS2B** and **TS2B**) and tetrazole (**IS1B** and **TS1B**) mediated enamine formation. Geometries are optimized at B3LYP/6-31G(d,p) level of theory and ZPE corrected. Energies in solution refers to single point B3LYP/6-311+G(d,p) calculations in DMSO using a self-consistent reaction field method and are ZPE corrected.

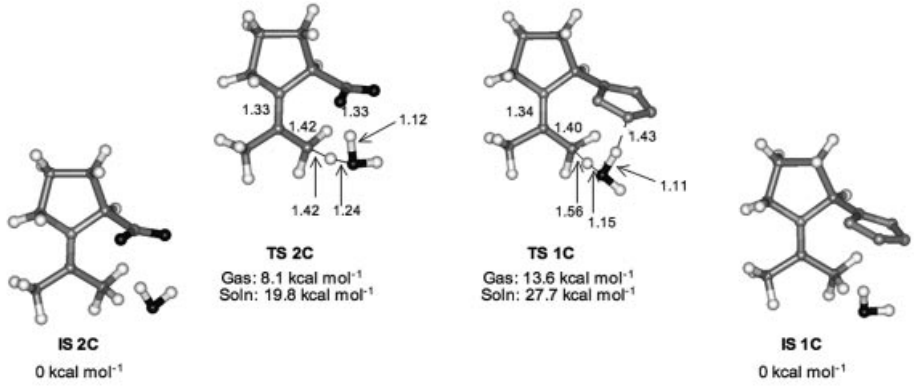


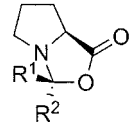
Figure 5. Geometry-optimized structures of the initial state and transition state of the proline- (**IS2C** and **TS2C**) and tetrazole-mediated (**IS1C** and **TS1C**) enamine formation occurring through the active participation of one water molecule. Geometries are optimized at B3LYP/6-31G(d,p) level of theory and ZPE corrected. Energies in solution refers to single point B3LYP/6-311+G(d,p) calculations in DMSO using a self-consistent reaction field method and are ZPE corrected.

mediated enamine formation, shown to be substantially higher in energy, as compared to the process not mediated by water .

No matter which step is actually rate limiting in the real situation, none of our computational studies showed a lower activation enthalphy in solution for the tetrazole catalyst, as compared to proline. Thus, after the computational study was completed it was clear that we needed to find an alternative explanation for the increased activity of catalyst **1** in the asymmetric aldol reaction found experimentally.

NMR Spectroscopic Studies

In order to find additional reasons for the increased reactivity of the tetrazole catalyst, we next turned to NMR spectroscopic studies. Several reports have highlighted the importance of bicyclic oxazolidinones of type **15** and **16** formed between the proline and the aldehyde or ketone.[26a–26b]



15 R^1 = H, R^2 = *t*Bu
16 R^1 = R^2 = Me

List et al. have established that such oxazolidinone formation leads to a parasitic consumption of the catalyst for the aldol reaction in DMSO, while Blackmond et al. showed that bicyclic oxazolidinone formation in the proline-catalyzed α-aminoxylation and α-amination reactions may actually make the catalyst more active by increasing the solubility of proline or itself participate as a catalyst in the reaction.[27a–c]

To us, it appeared reasonable that the carboxylic acid in proline and the tetrazolic acid in **1** should have different reactivity towards aldehydes and ketones. To establish this, we performed a reaction between 2,2-dimethylpropionaldehyde and catalysts **1** and **2,** respectively**,** in the absence of acetone. The bicyclic oxazolidinone adduct thus expected

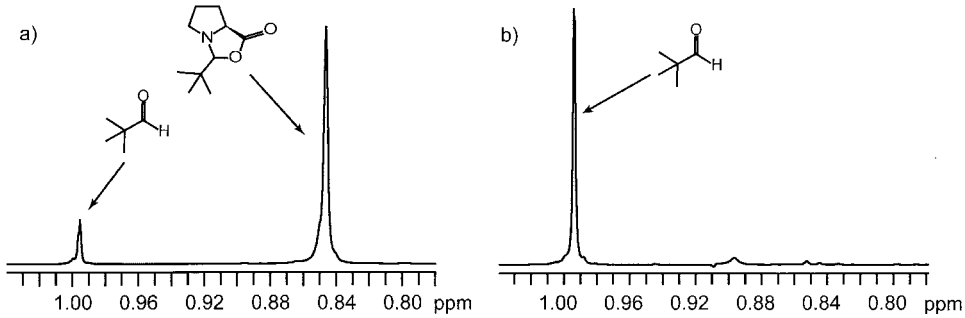


Figure 6. Expansion of ^{1}H NMR spectra of a mixture of 2,2-dimethylpropionaldehyde and **2** (a) or **1** (b) in [D_6]DMSO. The spectra show almost quantitative formation of bicyclic oxazolidinone with **2** while **1** does not take part in such equilibrium. Spectra recorded in [D_6]DMSO at $C_{cat.}$ = 0.196 M, $C_{aldehyde}$ = 0.196 M.

i.e. **15**, has been described earlier.[26b,28] An NMR spectroscopic investigation showed that whereas **2** almost quantitatively existed as the corresponding bicyclic oxazolidinone (Figure 6, a) the corresponding tetrazole analogue **1** existed completely free i.e. no cyclic structure was identified by ^{1}H NMR spectroscopy, Figure 6, b. Formation of the oxazolidinone causes the *tert*-butyl group protons (singlet) to be shifted to higher field, as seen in Figure 6.

The same experiment was performed using a large excess of acetone. Although several species, including what appears to be the product of acetone self condensation, were seen, none of them could be assigned to the tricyclic tetrazole analogue of oxazolidinone **16** previously described to form between acetone and proline.[26a]

Conclusions

We have demonstrated that replacement of the carboxy group in L-proline by the corresponding tetrazolic acid leads to a new organocatalyst. This catalyst has been widely employed in the literature and is known to have better solubility than proline in most solvents. The tetrazole-based catalyst **1** has also been shown to be more reactive and sometimes yield higher stereoselectivities, as compared to proline, when employed as catalyst in organocatalyzed reactions. In this account we have tried to rationalize the increased reactivity of **1** in the direct asymmetric aldol reaction between acetone and various aldehydes. A computational investigation of the transition states involved failed to provide any evidence for the underlying reason for the increased activity. However, an NMR spectroscopic investigation of a mixture of the catalyst and the aldehyde showed that proline easily engage in parasitic bicyclic oxazolidinone formation, while catalyst **1** does not. Consequently, more catalyst is available for forming the enamine intermediate in the aldol reaction in the case of catalyst **1** than when proline is used. We suggest that his is the main reason for the increased reactivity of **1** in DMSO solution, while factors related to solubility may also contribute in other solvent systems.

Experimental Section

Chemicals and solvents were either purchased puris p.A. from commercial suppliers or purified by standard techniques. For thin layer chromatography (TLC), precoated 0.25 mm silica plates (Macherey–Nagel 60 Alugram® Sil G/UV_{254}) were used and spots were visualized either with UV light, ethanolic phosphomolybdic acid followed by heating, by 0.5% 2,4-dinitrophenylhydrazine in 2 M HCl followed by heating or by a solution composed of *p*-anisaldehyde (23 mL), concentrated H_2SO_4 (35 mL), acetic acid (10 mL) and 900 mL ethanol followed by heating. Column chromatography was performed on silica gel (Matrex™ 60A, 37–70 μm). Macroporous polystyrene-sulfonic acid (MP-TsOH) was purchased from Argonaut. ^{1}H NMR 500 MHz spectra was recorded on a Varian Unity 500 MHz and ^{13}C NMR 100 MHz spectra were recorded on a Varian Unity 400 MHz spectrometer at ambient temperature using deuturated chloroform, water or dimethylsulfoxide as solvent. Chemical shifts (δ) in ppm are reported using residual chloroform, water or dimethylsulfoxide as internal reference (^{1}H δ = 7.26, ^{13}C δ = 77.0 ppm), (^{1}H δ = 4.2 ppm) or (^{1}H 2.49, ^{13}C δ = 77.0 ppm) and coupling constants (*J*) in Hz. High pressure liquid chromatography (HPLC) was done on a Gilson system consisting of a Gilson 322 pump, Gilson 233 XL autosampler, Gilson UV/Vis 152 detector or an evaporative light scattering detector (Sedere, Sedex75).

Analytical HPLC runs were done in the straight phase mode Chiralpak AS, Chiralpak AS-H and Chiralpak AD (5μ, 4.6×250 mm) with hexane/2-propanol as mobile phase (isocratic 70:30, isocratic 90:10, isocratic 97:3, 1.0 mL/min and 0.7 mL/min) for enantioselectivity determination. Reverse phase HPLC was done using a Kromasil C18 (5 μ, 4.0×150 mm) column (for purity determination) with acetonitrile/water (both containing 0.1% TFA) as mobile phase (Gradient: 5–50% acetonitrile, flow 1.5 mL/min) and a Chirobiotic T (5 μ, 4.6×250 mm) column (for enantiomeric excess determination) of the amino acid derivative **1** with water as mobile phase (isocratic 100% water, 2.5 mL/min).

Gas chromatography coupled with mass spectra detection was done with a Finnigan MAT GCQ PLUS system equipped with an AS2000 auto injector from CE, and a n.v. rescom SE54 (30 m×250 μm) column using nitrogen as carrier gas and electron impact ionization (EI, 70 eV). GC program: 100 °C, hold 4 min then 100–250 °C (20 °C/min). Mass spectra recorded by means of direct infusion technique were performed on a Finnigan MAT GCQ PLUS system using electron impact ionization (EI, 70 eV) and chemical ionization using methane gas. Infrared spectra were recorded on a Perkin–Elmer 1760 FT-IR spectrometer. Melting point determination was done with a melting point apparatus, SMP3 from Stuart

Scientific. A thermostat was used to maintain a constant temperature in the reaction (25 °C and 0 °C) supplied by Grant. For the run at –50 °C a chloroform/liquid nitrogen bath was employed.

***N*-(Benzyloxycarbonyl)-L-proline (3):** To a cold solution (5 °C) of (*S*)-proline **2** (15 g; 0.13 mol) in 60 mL of 2 M sodium hydroxide was added under vigorous stirring alternatingly benzyl chloroformate (90 g; 0.17 mol) and 47 mL of a 4 M sodium hydroxide solution. The mixture was stirred for an additional two hours at 5 °C after which the mixture was washed with 2 × 40 mL of diethyl ether. The aqueous layer was acidified to pH 1, saturated with sodium chloride and then extracted with ethyl acetate 3 × 50 mL. The combined extracts were dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give (29.2 g; 90%) of a pale yellow oil which was considered sufficiently pure for further use. ^{1}H NMR and ^{13}C NMR were identical to earlier reports.[29] Direct infusion MS (CI) *m*/*z* (rel. intensity): 250.2 ([M + H]$^+$, 54), 206.3 (60), 160.3 (92), 114.2 (18), 91.4 (96), 70.5 (100).

***N*-(Benzyloxycarbonyl)-L-prolinamide (4):** To a round-bottomed flask was added *N*-(benzyloxycarbonyl)-L-proline (**3**) (28 g; 0.11 mol), di-*tert*-butyl pyrocarbonate (37 g; 0.17 mol), ammonium hydrogen carbonate (13 g; 0.166 mol) and acetonitrile 500 mL. The reaction flask was flushed with nitrogen and sealed. Pyridine (6 ml; 80 mmol) was slowly added to the mixture and the resulting mixture was left stirring 68 hours. To the mixture was added 50 mL water and the volume was reduced under vacuum to approximately 50 mL. The mixture was extracted with dichloromethane (3 × 50 mL) and the combined extracts were washed with saturated $NaHCO_3$ (3 × 50 mL), 0.2 M HCl (3 × 50 mL) and brine (50 mL). The solution was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound as yellow oil (26.8 g; 96%). The ^{1}H NMR and ^{13}C NMR was identical to the previously reported data.[30] Direct infusion MS (CI) *m*/*z* (rel. intensity): 249.0 ([M + H]$^+$,10), 204.0 (50), 160.3 (90), 91.4 (100), 65.6 (18).

***N*-(Benzyloxycarbonyl)-L-prolinenitrile (5):** To a 500-mL round-bottomed flask was added *N*-(benzyloxycarbonyl)-L-prolinamide (**4**) (25.6 g; 0.10 mol) and dimethylformamide 330 mL. The flask was capped with a drying tube ($CaCl_2$). The solution was chilled in an ice bath and cyanuric chloride (14 g; 74.7 mmol) was added in one shot where after the solution was allowed to slowly reach room temperature and stirring was continued for 79 hours. The reaction was quenched with 650 mL water and the solution was extracted with ethyl acetate (2 × 500 mL). The organic phase was washed with water (4 × 250 mL), dried with magnesium sulfate, filtered, and concentrated under reduced pressure to give a pale yellow oil (22.8 g; 96%) which was considered sufficiently pure for further use. The ^{1}H NMR and ^{13}C NMR was identical to the previously reported data.[20g] Direct infusion MS (CI) *m*/*z* (rel. intensity): 231.0 ([M + H]$^+$, 8), 204.0 (100), 160.2 (50), 91.4 (50), 70.5 (100).

5-[(2*S*)-1-(Benzyloxycarbonyl)pyrrolidin-2-yl]tetrazole (6): *N*-(Benzyloxycarbonyl)-L-prolinenitrile (**5**) (11.5 g; 50 mmol), sodium azide (6.5 g; 0.10 mol), zinc bromide (5.5; 24 mmol), 75 mL 2-propanol and 150 mL water was added to a 500-mL round-bottomed flask. The reaction mixture was stirred at reflux for 24 hours. To the reaction was added 3 M HCl (100 mL). Stirring was continued until no solid was present and the solution was clear. The organic layer was isolated and the aqueous layer was extracted with ethyl acetate (2 × 150 mL). The combined organic layers were washed with brine (200 mL) and evaporated to give the title compound as a pale yellow oil. The oil was triturated with petroleum ether and evaporated to give a white, semi-crystalline rest (13.4 g; 98%). The ^{1}H NMR and ^{13}C NMR was identical to the previously reported data.[20e] Direct infusion MS (CI) *m*/*z* (rel. intensity): 274.1 ([M + H]$^+$,70), 230.3 (74), 160.3 (28), 91.5 (100), 70.5 (60).

5-[(2*S*)-Pyrrolidine-2-yl]-1*H*-tetrazole (1): 5-[(2*S*)-1-(Benzyloxycarbonyl)pyrrolidin-2-yl]tetrazole (**6**) (2.3 g; 8.7 mmol) was dissolved in 100 mL (9:1) (acetic acid/water). To this homogeneous solution was added (0.23 g; 10 wt.-%) palladium on carbon. The flask was placed under a hydrogen atmosphere and stirred for 72 h. The solution was filtered and concentrated under reduced pressure to give a colourless oil 1.3 g. The oil was dissolved in 20 mL methanol and 10 g of a macroporous polystyrene-sulfonic acid (MP-TsOH) was added to the homogeneous solution. The solution was stirred for one hour. The resin was washed with three times 40 mL methanol and then the compound was released with 8 × 30 mL of a solution of sat. ammonia in methanol. The solution was concentrated under reduced pressure to give the title compound as an off-white solid; yield 1.1 g (95%); m.p. 269–271 °C. $[\alpha]_D^{rt}$ = –1.1 (*c* = 1, CH_3OH). IR (KBr): $\tilde{\nu}$ = 3380 cm^{-1} (br., m), 2930 (s), 2535 (br., s), 1980 (br., m). ^{1}H NMR (500 MHz; [D$_6$]DMSO): δ = 9.1 (br. s, 1 H), 4.8 (m, 1 H), 2.5–2.4 (m, 1 H), 3.4–3.2 (m, 3 H), 2.4–2.2 (m, 1 H), 2.15–1.9 (m, 3 H) ppm. ^{13}C NMR (100 MHz; [D$_6$]DMSO): δ = 158.9, 54.6, 45.8, 29.7, 23.6 ppm. ESI-MS, *m*/*z* (rel. intensity): 140.0 (MH$^+$, 100); HPLC-ELSD on both reversed phase (Kromasil C18) and a chiral column (Chirobiotic T) showed only one peak which confirmed the purity and the stereochemical integrity of the obtained material.

General Procedure (GP1) for Direct Asymmetric Aldol Reaction: To a solution of 5-[(2*S*)-pyrrolidine-2-yl]-1*H*-tetrazole in solvent/acetone (4:1 v/v, 2.72 M) was added the aldehyde. The solution was stirred for the required time and then quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was dried with sodium sulfate, filtered, and concentrated to give pure aldol products after column chromatography.

4-Hydroxy-4-(4′-nitrophenyl)butan-2-one (7): Synthesized according to GP1. 5-[(2*S*)-pyrrolidine-2-yl]-1*H*-tetrazole (0.02 mmol), DMSO/acetone (1 mL), and 4-nitrobenzaldehyde (15.1 mg, 0.1 mmol). Column chromatography (pentane/ethyl acetate, 5:4); yield 17.2 mg (82%); R_f = 0.43; direct infusion MS (EI) *m*/*z* (rel. intensity): 209.3 (M$^+$,12), 192.3 (18), 174.3 (100), 144.3 (60). ^{1}H NMR and ^{13}C NMR are identical to earlier published results.[31] Enantiomeric excess determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane, 30:70), UV 254 nm, flow rate 1.0 mL/min. (*R*) isomer, t_r = 11.2 min and (*S*) isomer, t_r = 14.3 min.

4-Hydroxy-5,5-dimethylhexane-2-one (8): Synthesized according to GP1. 5-[(2*S*)-pyrrolidine-2-yl]-1*H*-tetrazole (0.12 mmol), DMSO/acetone (6 mL), 2,2-dimethylpropionaldehyde (51.6 mg, 0.6 mmol), the mixture was stirred for 12 h. Column chromatography (pentane/ethyl acetate, 4:1); yield 59.5 mg (69%) of a colorless oil; R_f = 0.31; direct infusion MS (CI) *m*/*z* (rel. intensity): 145.2 (M+1, 100), 127.2 (80), 109.2 (78), 87.1 (10). GC-MS analysis (GC Column: n.v. rescom SE54), t_R = 6.85 min (CI) *m*/*z* (rel. intensity): 145.2 (M+1, 100), 127.2 (80), 109.2 (78), 87 (10). ^{1}H NMR spectroscopic data were identical to earlier published results.[31] ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.6 (3 C), 34.1 (1 C), 45.1 (1 C), 74,8 (1 C), 210 (1 C) ppm. Enantiomeric excess was determined by HPLC (Daicel Chiralpak AD, *i*PrOH/hexane, 3:97), UV 280 nm, flow rate 0.7 mL/min. (*R*) isomer, t_r = 12.7 min and (*S*) isomer, t_r = 14.3.

4-Hydroxy-4-(4′-methoxyphenyl)butan-2-one (9): Synthesized according to GP1. 5-[(2*S*)-pyrrolidine-2-yl]-1*H*-tetrazole (80 mg; 0.12 mmol), DMSO/acetone (6 mL), 4-methoxybenzaldehyde (80 mg, 0.59 mmol), the mixture was stirred for 360 minutes. Column chromatography (pentane/ethyl acetate, 3:2); yield 70 mg (62%); R_f

= 0.44; direct infusion MS (CI) *m*/*z* (rel. intensity): 194.9 ([M + 1], 6), 177.1 (76), 137.3 (100), 109.5 (32), 94.3 (22). ^{1}H NMR and ^{13}C NMR spectroscopic data were identical to earlier published results.[32] Enantiomeric excess was determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane, 10:90), UV 254 nm, flow rate 1.0 mL/min. (*R*) isomer, t_r = 15.4 min and (*S*) isomer, t_r = 19.8 min.

4-(4′-Bromophenyl)-4-hydroxybutan-2-one (10): Synthesized according to GP1. 5-[(2*S*)-pyrrolidine-2-yl]-1*H*-tetrazole (0.08 mmol), DMSO/acetone 4 mL, 4-bromobenzaldehyde (74 mg, 0.4 mmol), the mixture was stirred for 150 minutes. Column chromatography (pentane/ethyl acetate, 8:3); yield 65 mg (67%); R_f = 0.45; direct infusion MS (CI) *m*/*z* (rel. intensity): 244.9 (M+1, 8), 226.0 (10), 185.2 (34), 145.4 (100), 117.4 (22), 78.7 (68). ^{1}H NMR spectroscopic data were identical to earlier published results.[31] ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.7 (1 C), 51.7 (1 C), 69.2 (1 C), 121 (1 C), 127 (2 C), 131 (2 C), 142 (1 C), 209 (1 C) ppm. Enantiomeric excess was determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane, 15:85), UV 220 nm, flow rate 1.0 mL/min. (*R*) isomer, t_r = 11.1 min and (*S*) isomer, t_r = 13.6 min.

4-(3′-Bromophenyl)-4-hydroxybutan-2-one (11): Synthesized according to GP1. 5-[(2*S*)-pyrrolidine-2-yl]-1*H*-tetrazole (0.04 mmol), DMSO/acetone 4 mL, 3-bromobenzaldehyde (74 mg, 0.1 mmol), the mixture was stirred for 140 minutes. Column chromatography (pentane/ethyl acetate, 8:3); yield 61 mg (64%); R_f = 0.45; direct infusion MS (CI) *m*/*z* (rel. intensity): 244.9 (M+1, 8), 226.0 (10), 185.2 (34), 145.4 (100), 117.4 (22), 78.7 (68). ^{1}H NMR spectroscopic data were identical to earlier published results.[31] ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.7 (1 C), 51.7 (1 C), 69.1 (1 C), 123 (1 C), 124 (1 C), 128 (1 C), 130 (1 C), 131 (1 C), 145 (1 C), 208 (1 C) ppm. Enantiomeric excess was determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane, 10:90), UV 220 nm, flow rate 0.7 mL/min. (*R*) isomer, t_r = 20.74 min and (*S*) isomer, t_r = 22.6 min.

4-Hydroxy-4-methylhexan-2-one (12): Synthesized according to GP1. 5-[(2*S*)-pyrrolidine-2-yl]-1*H*-tetrazole (16.8 mg; 0.12 mmol), DMSO/acetone (6 mL), 2-methylpropionaldehyde (43.3 mg, 0.6 mmol), the mixture was stirred for 12 h. Column chromatography (pentane/ethyl acetate, 4:1); yield 61.3 mg (79%); R_f = 0.32. ^{1}H NMR spectroscopic data were identical to earlier published results.[31] ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7 (1 C), 18.3 (1 C), 30.8 (1 C), 33.0 (1 C), 46.9 (1 C), 72.2 (1 C), 210 (1 C) ppm. Enantiomeric excess was determined by HPLC (Daicel Chiralpak AD, *i*PrOH/hexane, 3:97), UV 280 nm, flow rate 0.7 mL/min. (*R*) isomer, t_r = 16.3 min and (*S*) Isomer, t_r = 17.2.

4-Hydroxy-4-(3′-methoxyphenyl)butan-2-one (13): Synthesized according to GP1. 5-[(2*S*)-pyrrolidine-2-yl]-1*H*-tetrazole (16 mg; 0.118 mmol), DMSO/acetone (5.9 mL), 3-methoxybenzaldehyde (80 mg, 0.59 mmol), the mixture was stirred for 240 minutes. Column chromatography (pentane/ethyl acetate, 3:2); yield 79 mg (69%); R_f = 0.44; direct infusion MS (CI) *m*/*z* (rel. intensity): 194.9 ([M + 1], 6), 177.1 (32), 137.3 (100), 109.5 (80), 94.3 (46), 78.3 (58). ^{1}H NMR (500 MHz. $CDCl_3$): δ = 2.2 (s, 3 H), 2.9 (m, 2 H), 3.4 (br. s, 1 H), 3.8 (s, 3 H), 5.2 (m, 1 H), 6.8 (ddd, *J* = 8.3, 2.6, 1.1, 1 H), 6.9 (m, 1 H), 7.2 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.7 (1 C), 52 (1 C), 55 (1 C), 69.7 (1 C), 111 (1 C), 113 (1 C), 118 (1 C), 130 (1 C), 144 (1 C), 160 (1 C), 209 (1 C) ppm. Enantiomeric excess was determined by HPLC (Daicel Chiralpak AS, *i*PrOH/hexane, 10:90), UV 254 nm, flow rate 0.7 mL/min. (*R*) isomer, t_r = 18.9 min and (*S*) isomer, t_r = 24.1 min.

4-Hydroxy-4-phenylbutan-2-one (14): Synthesized according to GP1. 5-[(2*S*)-pyrrolidine-2-yl]-1*H*-tetrazole (16 mg; 0.118 mmol), DMSO/acetone (5.9 mL), benzaldehyde (66 mg, 0.59 mmol), the mixture was stirred for 240 minutes. Column chromatography (pentane/ethyl acetate, 3:2); yield 63 mg (67%); R_f = 0.56; direct infusion MS (CI) *m*/*z* (rel. intensity): 165.0 ([M + 1], 2), 145.3 (82), 103.4 (48), 77.31 (100). ^{1}H NMR spectroscopic data were identical to earlier published results.[33] ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.7 (1 C), 51.9 (1 C), 69.8 (1 C), 126 (1 C), 127 (2 C), 128 (2 C), 142 (1 C), 209 (1 C) ppm. Enantiomeric excess was determined by HPLC (Daicel Chiralpak AS, *i*PrOH/hexane, 10:90), UV 257 nm, flow rate 1.0 mL/min. (*R*) isomer, t_r = 15.5 min and (*S*) isomer, t_r = 19.8 min.

Computational Details: Density functional calculations were done using Jaguar 5.5[34] on a PC equipped with dual Intel Xeon processors running Linux RedHat 9. Geometries were optimized at the B3LYP/6-31G(d,p)[35] level of theory, and the vibrational frequencies calculated to verify that all optimized structures represented minima or transition stated on the potential energy surface. Single point energies in solution were computed using the B3LYP/6-311+G(d,p) optimized structures at B3LYP/6-31+G(d,p) level of theory using the self-consistent reaction field method as implemented in Jaguar.

NMR Spectroscopic Studies: The NMR spectroscopic studies were performed by mixing L-proline (23.1 mg; 0.2 mmol) or 5-[(2*S*)-pyrrolidine-2-yl]-1*H*-tetrazole (27.8 mg; 0.2 mmol) and 1.0 mL dry [D_6]DMSO in an oven dried 10 mL round bottomed flask. The mixtures were stirred for ca 10 h under argon atmosphere. To these mixtures was added (17.3 mg; 21.72 μL; 0.2 mmol) of freshly distilled 2,2-dimethylpropionaldehyde. The mixtures were stirred for 2 h and 0.7 mL of the clear solution was transferred to a dry NMR tube via a dry syringe. ^{1}H NMR was recorded on both samples showing extensive formation of the bicyclic oxazolidinone {3-*tert*-butyl-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-1-one} in the former case while no equivalent structure in the latter case. Another NMR spectroscopic study was performed by mixing 5-[(2*S*)-pyrrolidine-2-yl]-1*H*-tetrazole (2.5 mg; 0.018 mmol) and 1.0 mL dry [D_6]DMSO in an oven-dried 2-mL round-bottomed flask. The mixture was stirred for ca 10 h under argon atmosphere. From this mixture was transferred 0.6 mL to a dry NMR tube. To the sample was added 0.11 mL of dried acetone via syringe. ^{1}H NMR spectra using suppression through the WET pulse sequence[21] was recorded and did not indicate any formation of bicyclic oxazolidinone.

Supporting Information Available: HPLC traces, ^{1}H NMR, ^{13}C NMR spectra for key compounds and experiments together with absolute energies and coordinates for the calculated structures (see also the footnote on the first page of this article).

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