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Rational design of asymmetric organocatalysts—increased reactivity and solvent scope with a tetrazolic acid

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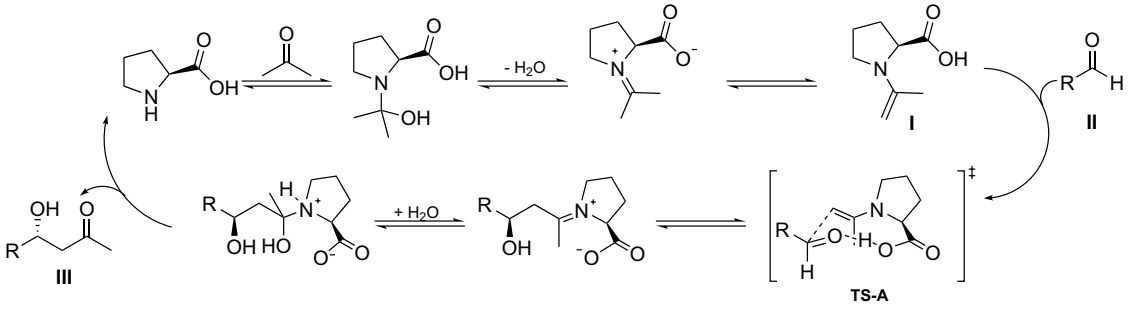
Abstract—Replacement of the carboxylic acid functionality in the widely used organocatalyst proline with a tetrazolic acid leads to a catalyst with increased reactivity and solvent scope, as demonstrated in the direct catalytic asymmetric aldol reaction.

Catalysis of asymmetric reactions by simple metal-free organic molecules is currently receiving immense interest.[1] The seminal work by List, Lerner, Barbas and others on the intermolecular adaptation[2] of the proline catalyzed direct asymmetric aldol reactions (Hajos–Parrish–Eder–Saur–Wiechert reaction)[3] nicely illustrates the advantages of this methodology, which is characterized by operational simplicity, high efficiency, and a biomimetic 'green' approach. Further studies, primarily by the groups of List and Barbas, have demonstrated the use of enamine intermediates also in other important reactions, for example, Mannich,[4] Michael,[5] and electrophilic α-amination.[6] Surprisingly, the parent amino acid proline is often found to be the most efficient catalyst for these enamine mediated processes, yielding high stereoselectivity and yield for various substrates in several different reaction types.[7] Still, the reaction rates for several of these transformations are slow, a frequently encountered disadvantage of organocatalyzed reactions.

With this in mind, we set out to design a more reactive catalyst for the direct asymmetric aldol reaction. Both experimental and theoretical studies support that the rate-determining step of this reaction in solution is the reaction between enamine intermediate **I**, initially formed after condensation of proline with the ketone component, with the aldehyde component **II** proceeding through transition state A **TS-A** and leading to product **III**, Scheme 1.[8]

Several theoretical studies have highlighted the importance of the carboxylic acid functionality of proline in this reaction. The role of the carboxylic acid is



Scheme 1. Proposed mechanism for the proline catalyzed asymmetric aldol reaction.

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dual: First, it orients the incoming aldehyde through a hydrogen bond, which ensures that the reaction proceeds on only one face of the pyrrolidine ring. The second, and most important, role of the carboxylic acid function is to lower the activation barrier of the reaction by charge stabilization along the C–C bond-formation by means of the intramolecular hydrogen bond shown in **TS-A**. Theoretical studies have suggested that this stabilization could lower the activation barrier for the aldol reaction with up to 18 kcal/mol;[8b] this is also supported by experiment showing that the carboxamide of proline is unreactive.[2c] Based on the suggested mechanism, we reasoned that a stronger hydrogen bond donor should lower the energy of the transition state further, and thus lead to increased reactivity.

We figured, that a suitable catalyst could be obtained by replacing the carboxylic acid functionality in proline with a tetrazolic acid, that is yielding 5-pyrrolidine-2-yltetrazole **1**.[9] Compound **1** was readily prepared by catalytic hydrogenation of the CBz-protected analogue, which in turn was synthesized through Sharpless' recently developed 'click'-methodology, Scheme 2.[10]

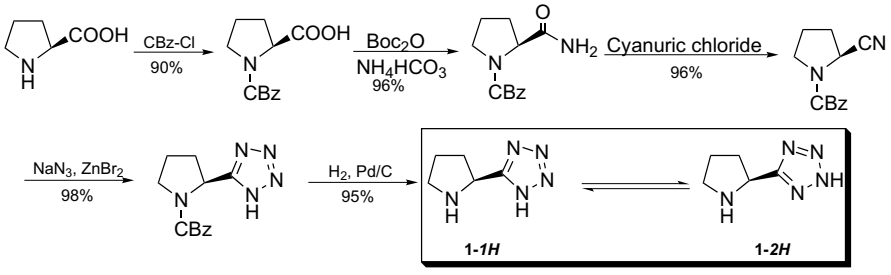
Tetrazoles and carboxylic acids have similar structural requirements and aqueous pK_a values; however, the tetrazole group has increased lipophilicity and metabolic stability.[11] These properties have led to a widespread use of tetrazoles as carboxylic acid replacements in medicinal chemistry, but catalysts containing a tetrazole functionality have only been reported very recently.[12] Although the pK_a of a tetrazole and its corresponding carboxylic acid is very similar in aqueous solution, the pK_a difference in organic solvents can be markedly different as evidenced for acetic acid (pK_a(H_2O) = 4.75, pK_a(DMSO) = 12.3) and tetrazole (pK_a(H_2O) = 4.86, pK_a(DMSO) = 8.2).[13] Since DMSO is the most commonly employed solvent for the proline catalyzed aldol condensation we thought that proline tetrazole might show increased reactivity as compared to proline. Further, the use of DMSO is expected to promote the formation of a Zimmerman–Traxler type of TS, as the required *1H*-tautomer of the tetrazole functionality is known to be predominant in polar aprotic media like DMSO. Catalyst **1** is also expected to stabilize the developing negative charge in **TS-A** better than proline, due to charge delocalization over the whole tetrazole ring.

Direct catalytic aldol reactions between acetone and the 'benchmark' substrate *p*-nitrobenzaldehyde **2**, to yield (*R*)-4-hydroxy-4-(*p*-nitrophenyl)-butan-2-one **3**, were set up to assess the effect on rate and selectivity upon substitution of the carboxylic acid to tetrazolic acid. ^{1}H NMR spectroscopy was used to monitor the progress of the reaction.[14] As seen in Figure 1a, the reactivity difference between **1** and proline is small for this highly reactive aldehyde. However, it should be noted that **1** repeatable gives full conversion of the substrate, while the reaction with proline at 20% catalyst loading often slows down considerably after about 70% conversion. The short reaction times needed to get >90% conversions with this substrate are notable. Previous studies with proline as catalyst typically report reaction times of 24–48 h. Thus, also the proline catalyzed process appears faster than previously noted.

The practical significance of the increased reactivity of the tetrazole derivative over proline gets more apparent when less reactive aldehydes are employed as aldol acceptors. A large difference in reaction rate is seen for the reaction of *p*-methoxybenzaldehyde **4** to yield (*R*)-4-hydroxy-4-(*p*-methoxyphenyl)-butan-2-one **5** (Fig. 1b), and for the transformation of the aliphatic aldehyde trimethylacetaldehyde **6** into (*R*)-4-hydroxy-5,5-dimethyl-hexan-2-one **7** (Fig. 1c).

Regarding the enantioselectivity, no large differences were seen between the two catalysts, as might be expected by the similar three-dimensional (flat) structure of the carboxylic- and tetrazolic acid function.

Another rationale for the tetrazolic acid replacement was the increased lipophilicity of this group as compared to the carboxylic acid. Catalyst **1** would be expected to have a larger solvent scope than proline. To investigate this proposal, we performed the aldol reaction between acetone and **2** in various solvents (Table 1, entries 1–12). The tetrazole catalyst **1** was shown to be more reactive than proline in all solvents investigated. In addition, it was found that the reaction could be performed in less polar solvents than those normally employed for the reaction. The reactivity and selectivity of **1** in DMF was comparable to that obtained in DMSO, suggesting that DMF is the solvent of choice for the direct asymmetric aldol reaction with this catalyst. In contrast to what was observed in DMSO, addition of up to 10% water to the DMF leads to a small increase in enantioselectivity (cf. entries 3, 4, and 13). The use of DMF, instead of



Scheme 2. Synthesis of 5-pyrrolidine-2-yltetrazole **1**. Compound **1** exists as a mixture of tautomers **1-*1H*** and **1-*2H***.

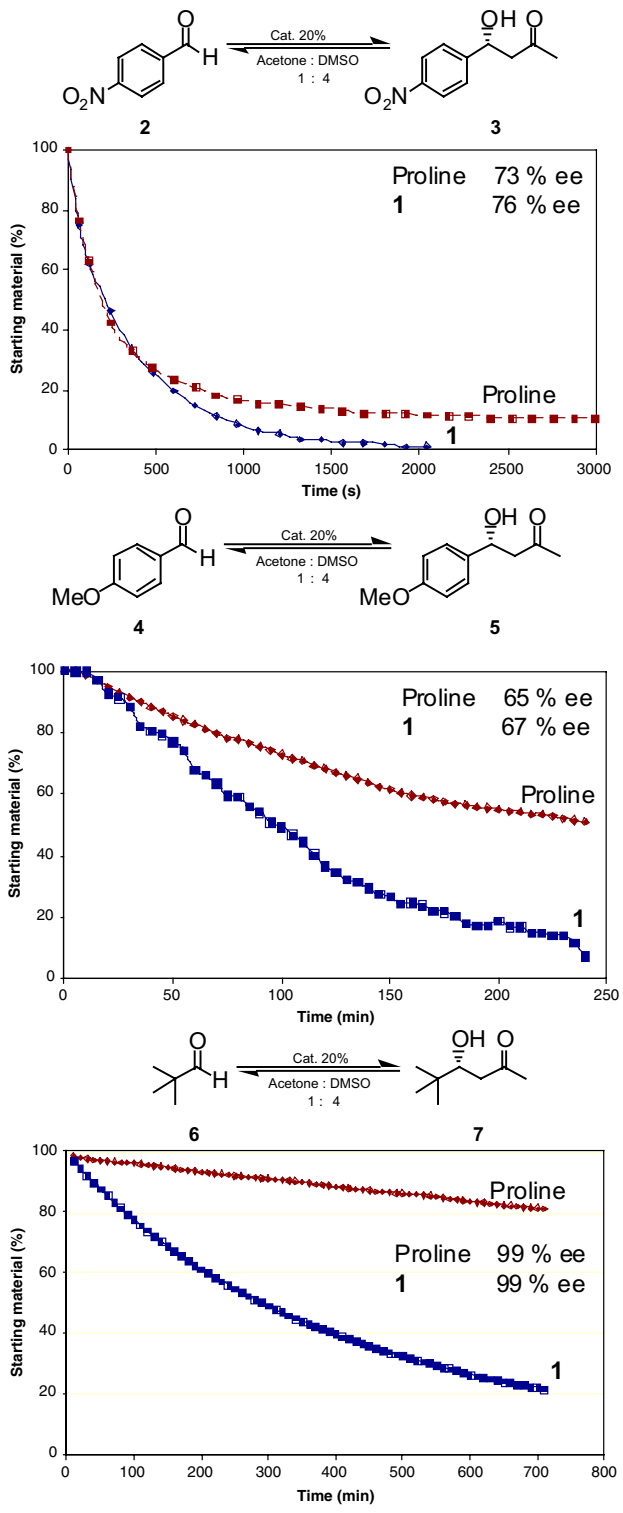


Figure 1. Graphs showing the conversion of starting aldehyde as a function of time during catalyzed direct asymmetric aldol reaction with acetone at 25 °C. As seen, the reaction with the tetrazole catalyst **1** is considerably faster with proline, especially for more unreactive substrates. Typical experimental procedures are described.[14]

DMSO, also allows the reaction temperature to be lowered. As expected, a lower reaction temperature leads to an increase in enantioselectivity, while the reactivity in this case is surprisingly well maintained (entries 11, 14, and 15).

Table 1. Direct catalytic asymmetric aldol reaction between acetone and *p*-nitrobenzaldehyde **2** in various solvents

Entry	Solvent	Catalyst	Temp (°C)	Yield[a] (%)	Ee[b] (%)
1	DMSO	**1**	25	93	76
2	DMSO	Proline	25	75	73
3	DMSO/H_2O[c]	**1**	25	76	71
4	DMSO/H_2O[c]	Proline	25	36	63
5	Dioxane	**1**	25	88	66
6	Dioxane	Proline	25	55	44
7	Toluene	**1**	25	70	61
8	Toluene	Proline	25	45	54
9	PBS[d]	**1**	25	85	0
10	PBS[d]	Proline	25	83	0
11	DMF	**1**	25	93	70
12	DMF	Proline	25	50	70
13	DMF/H_2O[c]	**1**	25	89	76
14	DMF	**1**	5	80	81
15	DMF	**1**	−50	77	86

All reactions were performed with 20 mol% catalyst.[14] The reaction time was 4 h.
[a] Isolated yield after chromatography.
[b] Enantiomeric excess of (*R*)-**4**.
[c] 10% water added.
[d] PBS buffer at pH 7.4.

To summarize, we have presented an efficient synthetic route to the tetrazolic acid analogue of proline, and shown that this catalyst has markedly increased reactivity, as compared to proline, in the direct asymmetric aldol reaction. In addition to increased reactivity, this new catalyst also shows expanded solvent scope. The wide use of proline in organocatalyzed processes, and the fact that organocatalyzed reactions often depend on essential hydrogen bond stabilization of the transition state, suggest that **1** and other tetrazole derivatives will be useful new entities for organocatalyst design.

Acknowledgements

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14. General procedure: L-proline or **1** (0.02 mmol) was stirred in a mixture of the solvent and acetone (4:1, 1 mL) for 15 min. Thereafter, the aldehyde acceptor (0.1 mmol) was added and the homogenous mixture stirred for the reported time. The mixture was quenched with 1 mL of satd aq NH_4Cl solution and extracted with EtOAc. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give the aldol products after column chromatography. Conversions were determined directly by performing the reaction in an NMR tube using DMSO-d_6 and solvent suppression of the acetone signal. The enantioselectivity was determined after chromatography using Daicel Chiralpak AS (**3** and **5**) or Chiralpak AD (**7**) as reported in Ref. 2d.