5-Pyrrolidin-2-yltetrazole: A New, Catalytic, More Soluble Alternative to Proline in an Organocatalytic Asymmetric Mannich-type Reaction

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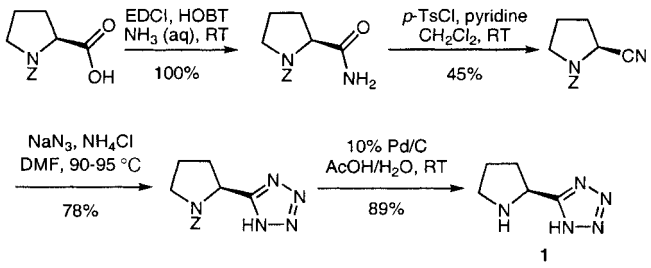
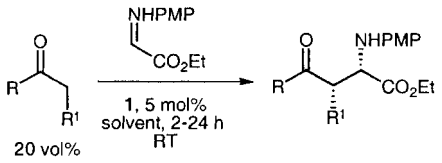
Abstract: A Mannich-type addition of ketones to *N*-PMP protected α-imino ethyl glyoxalate is catalyzed by a new proline analogue, 5-pyrrolidin-2-yltetrazole **1**. The new organocatalyst has significant advantage over its parent in that it can be used in non-polar solvents without loss of enantioselectivity.

Key words: asymmetric, Mannich, organocatalysis, proline, tetrazole



Scheme 1



Scheme 2 General scheme for the addition of ketones into *N*-PMP-protected α-imino ethyl glyoxalate.

Catalytic asymmetric synthesis, which avoids the use of metals to co-ordinate a stereogenic environment is of great interest.[1] There are many advantages that organocatalysts have over their metal-mediated counterparts. They can often be used under aerobic conditions, are cheap to use, and in most cases only a small molecule is required to affect a high enantioselectivity. Furthermore, attachment of such compounds to a solid-phase would allow easier scale up and recycling of the catalyst. An organocatalytic system that has been studied extensively[2] is an enantioselective proline-based one which accelerates a range of transformations such as aldol reactions,[3] Robinson annulations[4] and Mannich reactions.[5] Although these reactions are highly enantioselective, they all rely on fairly polar solvents such as DMSO due to the insoluble nature of proline itself.

A proline alternative with greater solubility in conventional solvents, which would not affect enantioselectivity would be highly desirable and ideally it would have a greater turnover number.

Tetrazoles are generally used in medicinal chemistry as bioisosteres for carboxylic acids to increase the solubility of the drug whilst retaining the properties of the acid. Tetrazole **1** was synthesized in order to capitalize on the improved solubility using a slight modification of the literature procedure[6] (Scheme 1) in the hope that this would provide the extra solubility required in catalytic reactions.

In order to test the efficacy of this new catalyst against proline itself, the Mannich-type addition of a carbonyl-containing compound (in a large excess) to *N*-PMP-protected α-imino ethyl glyoxalate was selected (Scheme 2). This reaction has been investigated recently by Barbas and co-workers, using proline as a catalyst[5a] and therefore serves as an excellent comparison with the new tetrazole catalyst.

Dichloromethane, wet acetonitrile and wet tetrahydrofuran were all screened in the reaction of cyclohexanone to the imine in order to determine the best solvent (Table 1). The highest yielding reaction was found to be that carried out in dichloromethane, with tetrazole **1** being used at a level of 5 mol%. In this system, the catalyst appeared insoluble at first, though after time (ca. 1 h) partial solubilization was achieved which presumably aided the course of the reaction.[7] It is interesting to note that the same reaction conditions with L-proline gave no observable product after the same amount of time, indicating that organocatalyst solubility is key in this reaction. This was emphasized when further optimization showed that tetrazole **1**, at extended reaction times, could be used at the level of 1 mol% (where it appeared to dissolve completely) without compromising enantioselectivity. These catalytic amounts are very significant; proline is routinely used at levels of 20 mol%.[2] Furthermore, organocatalyst **1** appears to give more rapid reaction in dichloromethane than DL-proline does in DMSO as visualized by thin layer chromatography.

The lower yields obtained where a small amount of water was present is possibly due to hydrolysis of the imine, although this did not appear to affect the high enantio-

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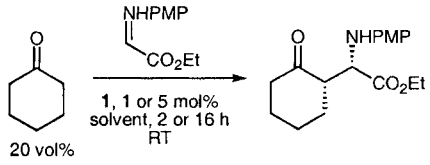
Table 1 Experimental Data



	Catalyst (mol%)	Solvent	Reaction time (h)	Yield (%)[a]	dr *syn*:*anti*[b]	ee (%)[c]
1	**1** (5)	CH_2Cl_2	2	65[8]	>19: 1	>99
2	L-Proline (5)	CH_2Cl_2	2	0	–	–
3	**1** (5)	Wet MeCN	2	49	>19: 1	>99
4	**1** (5)	Wet THF	2	37	>19: 1	>99
5	**1** (1)	CH_2Cl_2	16	70	>19: 1	>99

[a] Based on isolated product.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by chiral HPLC.

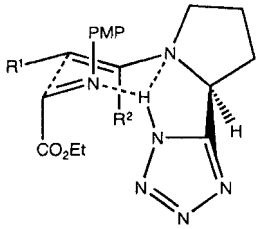


Figure 1 Transition state of the tetrazole organocatalyzed Mannich reaction.[9] The PMP group on the imine sits axially to avoid clash with the tetrazole, thereby forcing the *E*-enamine (which is preferred) to produce the *syn*-product.

selectivities. These reactions are thought to proceed via a hydrogen bonded transition state similar to that suggested by Houk and Bahmanyar (Figure 1).[9]

Encouraged by the observation that this reaction proceeded in dichloromethane where L-proline did not, a range of different carbonyl-containing compounds was screened (Table 2) using tetrazole **1**. Reactions were performed at a level of 5 mol% for practical reasons and also to ensure complete saturation of the system.

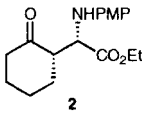
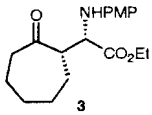
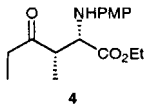
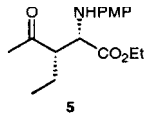
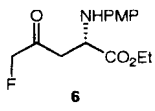
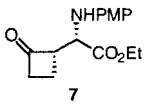
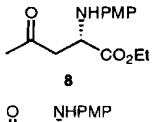
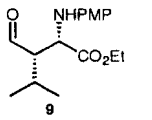
Pleasingly, the catalyst performed very well, giving generally good yields and excellent diastereoselectivities and enantioselectivities. Cyclic compounds **2**, **3** and **7** were produced in excellent enantiomeric excess, as were acyclic compounds **4**, **5** (the thermodynamic product) and **8**. The reaction to form compound **8** was performed in neat acetone and hence purification just required evaporation of the solvent and filtration of the residue through a plug of silica.

In all but one case, the reactions using tetrazole **1** were just as or more efficient than the corresponding L-proline reaction (for example the yield of compound **4** represents an improvement on that previously described of the same reaction using L-proline in DMSO[5a] and compound **5** was only produced in a 51% yield using DL-proline at 5 mol% in DMSO compared to 72% yield using **1**). Compound **6** was produced at a slower rate due to the formation of a biphasic mixture between the dichloromethane and a fluorous phase. It was also observed to proceed in high regioselectivity and reduced enantioselectivity (this is ascribed to disruption of the hydrogen bonding within the transition state) as reported previously.[5a]

Aldehyde **9** was also synthesized[5d,e] and reduced to its lactone in order to analyze the ee by HPLC.[11]

In summary, tetrazole catalyst **1** has been made and catalyzes the Mannich-type addition of a carbonyl-containing compound to *N*-PMP-protected α-imino ethyl glyoxalate in non-polar solvents. This represents an attractive alter-

Table 2 Carbonyl-Containing Products

Product	Reaction time (h)	Yield (%)[a]	Dr *syn*:*anti*[b]	Ee (%)[c]
 **2**	2	65	>19: 1	>99
 **3**	8	59	>19: 1	>99
 **4**	16	63	>19: 1	>99
 **5**	8	72	>19: 1	>99
 **6**	24[d]	31	–	14
 **7**	24	74	>19: 1	94
 **8**	8	99[e]	–	>99
 **9**	24	75	7: 1[f]	95[g]

[a] Based on isolated product.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by chiral HPLC.[10]
[d] Reaction stopped after 24 h at 55% conversion.
[e] Reaction performed in acetone.
[f] Epimerization on the silica column led to a deterioration of dr.[5d,e]
[g] Ee measured on corresponding lactone.[11]

native to L-proline, particularly as it avoids the use of solvents such as DMSO and can also be used in smaller quantities without compromising on enantioselectivity. Further uses of this catalyst will be reported in due course.

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(7) The tetrazole is not soluble in neat ketone.

(8) **General Procedure**: *N*-PMP-protected α-imino ethyl glyoxalate (93.5 mg, 0.5 mmol) was dissolved in anhydrous CH_2Cl_2 (4 mL). Carbonyl-containing compound (1 mL, 20 vol%) was added to this solution followed by 5-pyrrolidin-2-yltetrazole (3.5 mg, 5 mol%) and the resulting mixture stirred under argon for 2–24 h. After this time, the mixture was quenched with sat. NH_4Cl solution (10 mL) and the aqueous layer extracted with EtOAc (2 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a residue which was further purified by column chromatography using varying mixtures of EtOAc and petroleum ether 40–60 as eluent.

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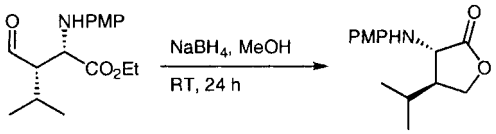
(10) Determined by chiral HPLC (**3**): Chiralcel AS 0.7 mLmin^{-1}, 6% 2-propanol: 94% hexane; t_R(major) = 18 min, t_R(minor) = 24 min. **5**: Chiralcel AS 0.7 mLmin^{-1} 94% hexane: 6% 2-propanol; t_R(major) = 14 min, t_R(minor) = 16 min. **6**: Chiralcel AS 1 mLmin^{-1} 85% hexane: 15% 2-propanol; t_R(major) = 16 min, t_R(minor) = 22 min. **7**: Chiralcel OD 1 mLmin^{-1}, 5% 2-propanol: 95% hexane; t_R(major) = 13.5 min, t_R(minor) = 19 min. **9** (lactone): Chiralcel AS 0.7 mLmin^{-1} 94% hexane: 6% 2-propanol; t_R(minor) = 43 min, t_R(major) = 57 min. For retention times of **2**, **4** and **8** see ref. 5a

(11) In order to obtain separation on HPLC, the aldehyde was converted to the lactone by reduction with sodium borohydride (Scheme 3) before chromatography to avoid epimerization. This represents a good route to enantiopure functionalized 1-amino-2-alkyl-δ-lactones.



Scheme 3