A Homo-Proline Tetrazole as an Improved Organocatalyst for the Asymmetric Michael Addition of Carbonyl Compounds to Nitro-Olefins

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Abstract: A new homo-proline tetrazole derivative **7** has been prepared and shown to have improved properties for achieving asymmetric Michael addition of carbonyl compounds to nitro-olefins.

Key words: asymmetric, nitro-Michael, organocatalysis, homo-proline, tetrazole

The last few years have witnessed major advances in new catalytic methods based on organic molecules.[1] The reactions can usually be performed under an aerobic atmosphere with wet solvents and the catalysts are generally inexpensive and air stable. Probably the most extensively studied asymmetric organocatalytic system is based on proline **1** (Figure 1),[2] which accelerates a range of transformations such as the aldol[3] and Mannich reactions[4,6] together with other α-functionalisations of ketones.[5] Although these reactions are generally highly enantioselective, they usually require polar solvents such as DMSO due to the insoluble nature of proline itself in many standard organic solvents.

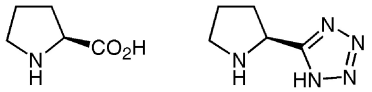


Figure 1

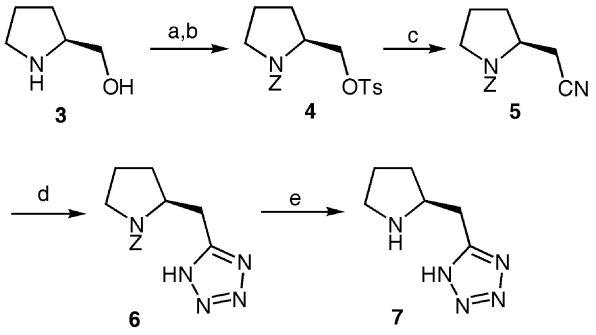
We and others have reported on the tetrazole analogue of proline **2** as a more soluble and effective catalyst in a variety of transformations.[6,7] The tetrazole ring is commonly used as a bioisostere for a carboxylic acid due to its similar pK_a.

We have since reported on the use of this organocatalyst in the far more challenging 1,4-addition of a ketone into a nitro-Michael acceptor.[7] Again, we showed that this organocatalyst outperformed proline, particularly in the context of enantioselectivity.

Considerable effort has been devoted to this area and many improvements to this reaction have been made.[8,11] We realised that our previous enantioselectivities (32–70% ee) using tetrazole **1**, while better than proline, were still only modest. Accordingly, the preparation of a new organocatalyst **7** was undertaken (the rationale for which is discussed later in this article) and its reactions as a catalyst investigated (Scheme 1).

Initial investigations were extremely encouraging: treatment of cyclohexanone and β-nitrostyrene with catalyst **7** provided a 43% yield and 80% ee (Table 1, entry 1). Optimisation studies were then carried out, and the effect of solvent, concentration and reaction time were all investigated (Table 1).[9]

Pleasingly, these investigations showed the new organocatalyst **7** gave improved enantioselectivities in this reaction when compared to catalyst **2**.



Scheme 1 *Reagents and conditions*: (a) Cbz-Cl, Et_3N, CH_2Cl_2; (b) Ts-Cl, pyridine, 20 °C, 77% overall; (c) NaCN, 50 °C, 93%; (d) NaN_3, NH_4Cl, 150 °C, 73%; (e) 10% Pd/C, H_2 (1 atm), HOAc–H_2O (9:1), 55%.

The study showed again that the previous optimal solvent system, IPA (propan-2-ol)–EtOH (1:1) is especially successful. It can be seen that lowering the catalyst loading deteriorates the yield (Table 1, entry 9) and increasing the concentration leads to an increase in reaction rate (as indicated by precipitation of product) but not to an increase in conversion (Table 1, entries 3, 6, 7).

Perhaps most interesting is the observation that the reaction works well using a relatively small amount of ketone. In previous work in this area, reactions were generally performed with between 10 and 20 equivalents of ketone.

Thus, these general conditions (Table 1, entry 5) were applied to all subsequent examples. The very good performance of tetrazole **7**, particularly when compared to other organocatalysts under these conditions for the same reaction is clear (Table 2). Interestingly, homo-proline itself gives no reaction under these conditions and even with DMSO as a solvent, only 5% conversion was observed.

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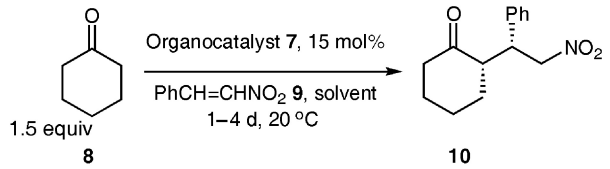
Table 1 Initial Optimisation Study of Organocatalyst **7**



Entry	Solvent	Concentration (M)	Time (d)	Yield (%)[a,b]	ee (%)[c]
1	DMSO	0.13	2	43	80
2	MeOH	0.13	2	35	85
3	IPA–EtOH, 1:1	0.13	2	77	90
4	IPA–EtOH, 1:1	0.13	4	78	89
5	IPA–EtOH, 1:1	0.25	1	88	91
6	IPA–EtOH, 1:1	0.25	2	76	88
7	IPA–EtOH, 1:1	0.5	2	78	89
8	IPA–EtOH, 1:1[d]	0.25	1	84	90
9	IPA–EtOH, 1:1[e]	0.25	2	26	92
10	IPA–EtOH, 1:1[f]	0.25	1	74	90
11	CH_2Cl_2[g]	0.25	1	<20	N.d.

[a] Based on isolated product.
[b] All diastereomeric ratios (dr) determined by ^{1}H NMR spectroscopy and >19:1. Relative stereochemistry was confirmed by comparison with literature data.
[c] Determined by chiral HPLC (Daicel Chiralpak AD-H).
[d] 1 Equiv H_2O added.
[e] Using 5 mol% catalyst.
[f] 20 Equiv ketone used.
[g] Based on conversion as seen by ^{1}H NMR spectroscopy.

Having demonstrated the superiority of this organocatalyst over its predecessors **1** and **2**, we set about testing a range of ketones and a range of nitro-Michael acceptors (Table 3).

In order to discuss these results, it is first necessary to examine the possible transition states. We postulate two potential models for the stereochemical outcome of this reaction, in line with what has been proposed previously for analogous systems.[8e,10] Both propose an electrostatic interaction between the nitro group and the nitrogen of the pyrrolidine ring. One of these suggests that there may be an extended hydrogen-bonded transition state **18**;[10] the other proposes that there is a facial bias, induced by the steric hindrance of the tetrazole and it is this which determines the selectivity as shown in **19** (Figure 2).[8e]

We believed that, should model **18** apply, the transition state would be less crowded for the homo-tetrazole **7** than the tetrazole **2**. Similarly, should the steric model **19** apply, then the homo-tetrazole side chain should be more bulky, due to increased freedom of rotation. In both cases this should lead to an improvement in the enantioselectivity, as was indeed observed.

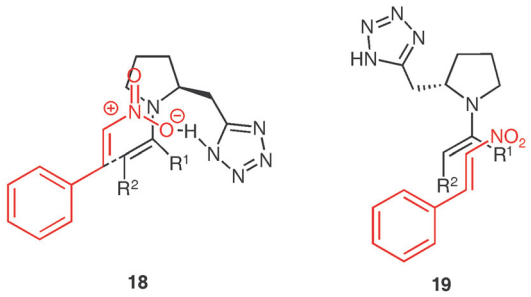


Figure 2

The enantioselectivities found in this reaction with our new catalyst **7** are generally very good, and particularly with cyclohexanone where they are consistently high. This consistency suggests that the nature of the nitro-Michael acceptor has less effect on the stereoselective outcome of the reaction than the ketone. This observation supports the second model **19** for the enantioselectivity, since any electronic change of the nitrostyrene could lead to a significant change in the interaction of model **18**. However, both mechanisms are still plausible, and further work is underway to develop catalysts, which might support this conclusion.

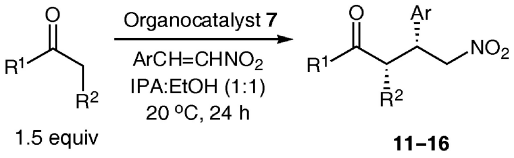
The addition of acetic acid in an attempt to facilitate enamine formation and hence increase yield does not give consistent results. In the case of products **11** and **13**, it

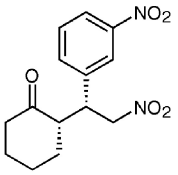
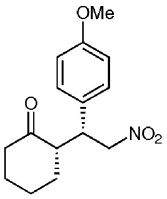
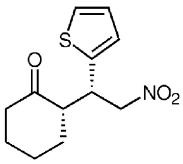
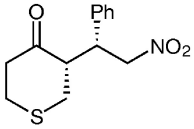
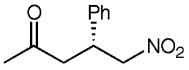
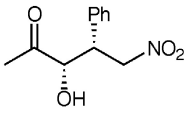
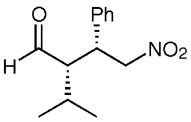
Table 2 Comparison of Organocatalysts under Optimised Conditions

Entry	Catalyst	Solvent	Yield (%)[a]	dr, *syn*:*anti*[b]	ee (%)[c]
1	**1**	IPA–EtOH, 1:1	52	>19:1	51
2	**2**	IPA–EtOH, 1:1	80	>19:1	62
3	Homo-proline	DMSO[d]	<5	N.d.	N.d.
4	**7**	IPA–EtOH, 1:1	88	>19:1	91

[a] Based on isolated product.
[b] All dr determined by ^{1}H NMR spectroscopy. Relative stereochemistry was confirmed by comparison with literature data.
[c] Determined by chiral HPLC (Daicel Chiralpak AD-H column).
[d] No reaction at all in IPA–EtOH, 1:1.

Table 3 Enantioselective 1,4-Nitro-Michael Addition Using Tetrazole Catalyst **7**



Entry	Product	Conditions[a]	Yield (%)[b]	dr, (*syn*:*anti*)[c]	ee (%)[d]
1		A	59	>19:1	93
2		B	69	>19:1	92
3		C	71	>19:1	90
4		D	<20[e]	N.d.	N.d.
	11				
5		A	74	–[e]	93
6		B	68	–[e]	92
	12				
7		A	51	>19:1	90
8		B	66	>19:1	91
	13				
9		A	61	>19:1	90
10		B	34	17:1	90
	14				
11		A	68	–	42
12		B	53	–	39
	15				
13		A	52	2.5:1	52 (1)
14		B	37	2:1	36 (2)
	16				
15		A	39	>19:1	37
16		B	40	>19:1	0
	17				

[a] Conditions: (A) as described; (B) 0.7 equiv HOAc added; (C) reaction performed at 30 °C; (D) 0.15 equiv *p*-TsOH added.
[b] Based on isolated yield.
[c] Determined by ^{1}H NMR spectroscopy. Relative stereochemistry was confirmed by comparison with literature data.
[d] Determined by chiral HPLC.
[e] *Anti* product not observed by ^{1}H NMR spectroscopy.

leads to increased yields with no significant change in enantioselectivity. In other cases, it leads to a decrease in yield (Table 3, entries 5, 6). This suggests that enamine formation may not be the rate determining step in all cases. In the case of the aldehyde, use of acetic acid leads to a complete erosion of enantioselectivity (Table 3, entry 16); possibly due to a significant increase in the uncatalysed reaction rate. However, the use of a very strong acid suppressed the reaction completely (Table 3, entry 4).

Finally, and perhaps most interestingly, the selectivity of the reaction with the aldehyde to give **17**, although consistent with the other substrates in Table 3, is the reverse of that normally found for this example in literature; selectivity with aldehydes has been reported to be opposite to that observed for ketones.[8b,e,i,11,12] The reason for the switch of enantioselectivity in literature is not completely understood, but it has been proposed that there is a switch from *anti*- to *syn*-enamine formation which would lead to formation of the opposite enantiomer.[11]

In conclusion, an improved catalyst **7** for the asymmetric addition of a ketone to nitro-olefins has been developed, giving enantiomeric excesses of up to 93% for a wide range of ketones and nitro-olefins.

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Catalyst synthesis details on request.

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(9) **Typical Experimental Procedure.**
To a suspension of catalyst (15 mol%) and nitro-olefin (0.5 mmol) in an *i*-PrOH–EtOH mix (1:1, 2 mL) was added ketone (0.75 mmol, 1.5 equiv) and the resulting mixture stirred at 20 °C for 24 h. After this time the reaction was quenched with sat. NH_4Cl (2 × 20 mL) and the aqueous phase extracted with EtOAc (2 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give a residue which was further purified by flash column chromatography using EtOAc and petroleum ether 40–60 as eluent.
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(11) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611.
(12) This was proven by comparison of chiral HPLC retention times and also by an inversion of sign in the optical rotation as compared to literature.