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Novel Imidazolidine-Tetrazole Organocatalyst for Asymmetric Conjugate Addition of Nitroalkanes

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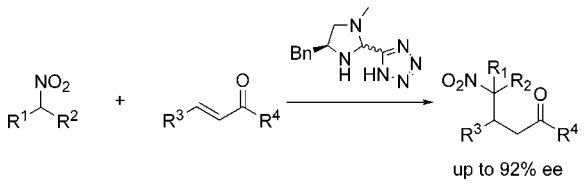
ABSTRACT



The Michael addition of nitroalkanes to α,β-unsaturated enones catalyzed by a novel chiral imidazolidine-2-yltetrazole organocatalyst has been investigated. The new more soluble organocatalyst decreases reaction times and improves enantioselectivities compared to other catalysts. The Michael addition adducts were obtained with up to 92% ee.

The catalytic asymmetric conjugate addition of stabilized carbanions to α,β-unsaturated carbonyl compounds is a well-documented and fundamental synthetic procedure for carbon−carbon bond formation in organic chemistry.[1] Nitroalkanes are a valuable source of stabilized carbanions since the high electron-withdrawing properties of the nitro group provide an outstanding enhancement of the hydrogen acidity at the α-position.[2] The products of 1,4-addition of nitroalkanes to enones[3] are useful precursors for a variety of structures such as aminocarbonyl compounds, aminoalkanes, and pyrrolidines. As a result, the development of new methods to achieve asymmetric conjugate addition of nitroalkanes to α,β-unsaturated ketones in the presence of catalytic quantities of, e.g., chiral bases, Lewis acids, and amines continues to be the subject of intense developments.[3−7] Good results have been achieved by Shibasaki et al.[5] using a lanthanum tris-binaphthoxide catalyst and Soós et al.[4] using a bifunctional cinchona catalyst, although in both cases only the reaction of chalcones with nitromethane was explored. Recently, Jacobsen et al. reported a high-yielding and versatile Al-salen-catalyzed Michael addition to α,β-unsaturated ketones, affording Michael adducts with excellent enantioselectivities.[6]

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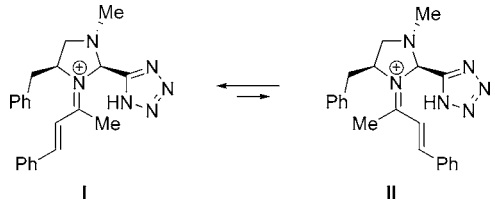
We have previously reported the environmentally benign imidazolidine-catalyzed Michael reaction of nitroalkanes to acyclic α,β-unsaturated enones with moderate to good enantioselectivity.[7] Due to the importance of the optically active products obtained in this reaction, we decided to try to develop a new catalyst that could lead to improved reaction rates as well as increased enantioselectivity in the reaction.

The phenylalanine-derived imidazolidine catalyst[7] **2** (vide infra) has proved to be a powerful catalyst for the catalytic asymmetric Michael reaction of α,β-unsaturated ketones with various Michael donors.[8] However, because of its low solubility, long reaction times are often required for the reaction to go completion. Therefore, an alternative catalyst with greater solubility, which would lead to shorter reaction times and improved enantioselectivities, would be highly desirable.

Tetrazoles are generally used as carboxylic acid replacements in medicinal chemistry to increase solubility of a drug while retaining the properties of the acid. These properties of the tetrazole moiety have also been exploited in organocatalysis to improve yield and enantioselectivity in a number of proline-catalyzed reactions.[9] Furthermore, for the present reaction we hypothesized that the increased steric bulk of the tetrazole moiety compared to the carboxylic acid would lead to a more sterically well-defined iminium ion intermediate. This would be achieved by control of the ratio of iminium ion intermediates **I**:**II** by favoring iminium ion **I** even more compared to **II** (see Scheme 1). If further control

Scheme 1. Increased Control of the Intermediate Iminium Ion Geometry

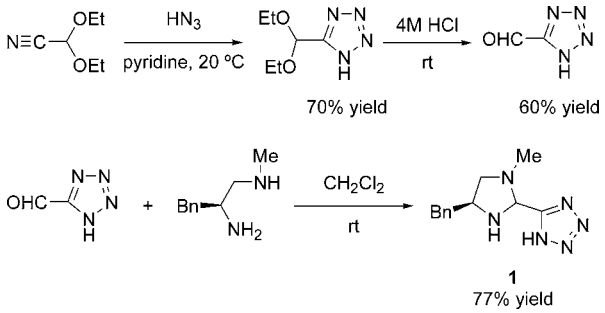


of the iminium ion geometry could be achieved, higher asymmetric induction in the reaction might be expected, as iminium intermediates **I** and **II** obviously lead to opposite enantiomers of the product.

Herein, we present a novel imidazolidine-2-yltetrazole-derived catalyst **1** for the catalytic asymmetric conjugate addition of various nitroalkanes to acyclic and cyclic enones. The synthesis of catalyst **1** is reported as well as its improved properties in terms of catalytic activity and ability to induce enantioselectivity compared to previous imidazolidine catalysts.

Catalyst **1** can easily be prepared using a slight modification of the synthesis of 1*H*-tetrazole-5-carbaldehyde[10] (CAUTION: hydrazoic acid formed in the reaction is extremely toxic) followed by condensation with *N*-methyl-3-phenylpropane-1,2-diamine[7] (Scheme 2).

Scheme 2. Synthesis of 5-(4-Benzyl-1-methyl-imidazolidine-2-yl)-1*H*-tetrazole



To our delight, we found that catalyst **1** was formed as a single stereoisomer in the reaction as determined by ^{1}H NMR spectroscopy. Unfortunately, we have not been able to determine the relative stereochemistry so far, as we have been unable to grow suitable crystals for X-ray analysis. On the basis of previous reports with imidazolidinone[11] and imidazolidine[7] catalysts, a cis relationship of the 5-benzyl and 2-tetrazole substituents is presumed, as this exposes the lone pair of the N^1-atom for nucleophilic attack onto the substrate carbonyl group (see Scheme 1). On the other hand, a 2,5-trans relationship of the two bulky substituents would effectively shield the lone pair of the N^1-atom, decreasing the nucleophilicity of the catalyst and thus rendering it ineffective. Furthermore, calculations at the PM3-level[12] indicate that a trans relationship between the 2-tetrazole and N^3-methyl (see Scheme 1) substituents for steric reasons is favored by >2 kcal/mol compared to the corresponding 2,3-cis relationship.

To test the efficiency of **1** against imidazolidine catalyst **2**, which previously afforded the best results in this reaction,[7] we selected 2-nitropropane as the nitroalkane for the 1,4-addition to a series of different α,β-unsaturated enones. Results are summarized in Table 1.

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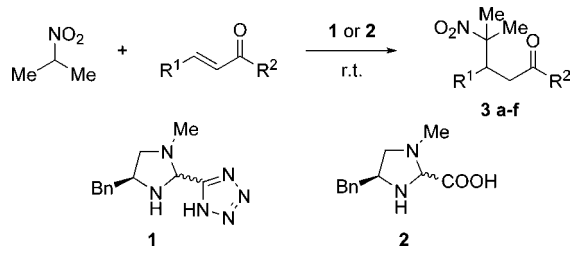
(12) Performed using the ChemDraw3D program.

Table 1. Catalytic Enantioselective Addition of 2-Nitropropane to Various α,β-Unsaturated Enones Catalyzed by **1** and **2**



entry	R^1	R^2	catalyst	reaction time (h)	isolated yield (%)	ee[a] (%)
1	Ph	Me	**1**	78	**3a**, 97	87 (*S*)
2	Ph	Me	**2**	240	**3a**, 95	79 (*S*)
3	Ph	Et	**1**	170	**3b**, 94	89 (*S*)
4	Ph	Et	**2**	300	**3b**, 64	83 (*S*)
5	*p*-ClC_6H_4	Me	**1**	72	**3c**, 83	87 (*S*)
6	*p*-ClC_6H_4	Me	**2**	130	**3c**, 82	75 (*S*)
7	*p*-OHC_6H_4	Me	**1**	70	**3d**, 83	89 (*S*)
8	*p*-OHC_6H_4	Me	**2**	180	**3d**, 81	75 (*S*)
9	*p*-$NO_2C_6H_4$	Me	**1**	100	**3e**, 96	64 (*S*)
10	*p*-$NO_2C_6H_4$	Me	**2**	130	**3e**, 90	65 (*S*)
11	2-furyl[b]	Me	**1**	200	**3f**, 87	83 (*R*)
12	2-furyl[b]	Me	**2**	200	**3f**, 64	70 (*R*)

[a] Determined by chiral stationary phase GC or HPLC. Absolute configuration determined by X-ray analysis of the *p*-ClC_6H_4 adduct[7] and others assigned by analogy. [b] Mixture of (*E*)- and (*Z*)-isomers. Reaction conditions: In an ordinary test tube equipped with a magnetic stirring bar, 0.5 mmol of the enone was added to 1.0 mL of the nitroalkane, and then the catalyst (0.1 mmol) was added. The test tube was closed with a rubber stopper and the reaction mixture stirred at ambient temperature for the time indicated in the table. The crude mixture was purified by FC on silica gel after evaporation of the nitroalkane (see Supporting Information).

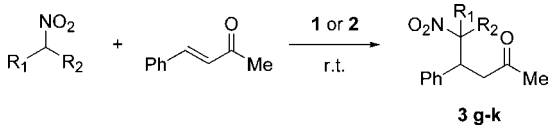
As expected, not only was the addition of 2-nitropropane catalyzed by **1** with different aromatic enones significantly faster compared to reactions catalyzed by **2** but also a substantial improvement of the asymmetric induction was observed. The faster reaction might be due to the tetrazole unit having a different acidity compared to a carboxylic acid. It is important to note that when catalyst **1** was used, full conversions were in all cases obtained for the time shown in Table 1, while for reactions catalyzed by **2** this was rarely achieved.

The most significant improvement was observed for reactions with benzylideneacetone: the reaction time decreased from 240 to 78 h, and the enantioselectivity was improved from 79 to 87% ee (Table 1, entries 1 and 2). In the case of *p*-hydroxybenzylideneacetone, we observed that the enantioselectivity improved from 75 to 89% ee (Table 1, entries 7 and 8). However, for *p*-nitrobenzylideneacetone, no improvement of the enantioselectivity was observed, although the reaction time decreased by 30 h (Table 1, entries 9 and 10). For the furyl derivative, increases in enantiomeric excess and yield of 13 and 23%, respectively, were observed (Table 1, entries 11 and 12).

To further expand the scope of the reaction, various nitroalkanes were tested in the reacion with benzylideneacetone.

For the addition of nitromethane (Table 2, entries 1 and 2), catalyst **1** was found to be a significant improvement over

Table 2. Catalytic Enantioselective Addition of Various Nitroalkanes to Benzylideneacetone Catalyzed by **1** and **2**



entry	R^1	R^2	catalyst	reaction time (h)	isolated yield (%)	ee (%)[a]
1	H	H	**1**	240	**3g**, 90	92
2	H	H	**2**	150	**3g**, 48	73
3	H	Me	**1**	100	**3h**, 83[e]	89/89
4	H	Me	**2**	130	**3h**, 75	71/73
5	H	CO_2Et	**1**	60	**3i**, 85[b]	86[c]
6	H	CO_2Et	**2**	110	**3i**, 84[d]	79[c]
7	$(CH_2)_4$		**1**	120	**3j**, 90	80
8	$(CH_2)_4$		**2**	100	**3j**, 93	77
9	$(CH_2)_5$		**1**	300	**3k**, 82	85
10	$(CH_2)_5$		**2**	275	**3k**, 60	71

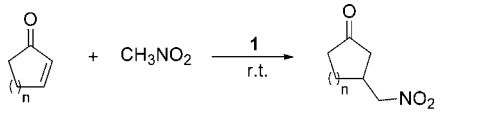
[a] Determined by chiral stationary phase GC or HPLC. [b] Diastereomeric ratio was 1:0.6 as measured by ^1H NMR spectroscopy. [c] Measured after decarboxylation. [d] Diastereomeric ratio was 1:1 as measured by ^1H NMR spectroscopy. [e] Diastereomeric ratio was 1:0.9. For reaction conditions, see Table 1.

catalyst **2**, both in terms of reaction rate and asymmetric induction, as the yield was almost doubled and the enantioselectivity was increased to 92% ee. Use of nitroethane produced a less marked effect, as the yield increased to 83%, and both diastereomers were obtained with 89% ee (Table 2, entries 3 and 4).

Nitroacetate afforded a 1:0.6 mixture of diastereomers with catalyst **1**; on the other hand, catalyst **2** gave a 1:1 mixture, and the optical purity was improved to 86% ee (Table 2, entries 5 and 6). Cyclic nitroalkanes could also be added to benzylideneacetone with improved enantioselectivity, and for nitrocyclohexane 85% ee of the Michael adduct was observed (Table 2, entries 7−10).

We then extended our studies to the addition of nitromethane to cyclic enones in the presence of catalyst **1**. The results are shown in Scheme 3. The Michael addition of nitromethane to cyclopentenone and cyclohexenone proceeded with full conversion after 215 and 260 h, respectively.

Scheme 3. Catalytic Enantioselective Addition of Nitromethane to Cyclic Enones Catalyzed by **1**



3l, n = 1: 75% yield, 61% ee
3m, n = 2: 70% yield, 77% ee

In both cases, yields were better and enantioselectivies comparable to those reported in the literature (Scheme 3).[3d]

The absolute configuration of the Michael adducts obtained using catalyst **1** was determinated by comparison of GC, and HPLC traces as well as optical rotation were found to be the same as those for reactions catalyzed by **2**.[7] This is in agreement with *si*-face attack on iminium ion **I** as previously proposed for catalyst **2**.[7]

In summary, we hypothesized that a new imidazolidine-2-yltetrazole catalyst **1** would lead to improved reaction rates and asymmetric induction for the Michael addition of nitroalkanes to α,β-unsaturated ketones. The catalyst was synthesized in good yield and successfully employed in the reaction, affording Michael adduct with up to 92% ee, thereby proving our hypothesis. The results represent an improvement of previously reported organocatalytic nitro-Michael reactions of α,β-unsaturated ketones.

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Supporting Information Available: Complete experimental procedures and HPLC separation conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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