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Asymmetric Michael addition of α-nitro-ketones using catalytic peptides

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Abstract—Peptide-based catalysts have been developed that promote the asymmetric Michael addition of nitroalkanes. The most effective peptides contain a β-turn structural element as well as a basic histidine and an arylsulfonamide-protected arginine. Excellent yields with enantioselectivities of up to 74% ee have been observed.

Nitroalkanes are valuable synthetic building blocks for the formation of new carbon–carbon bonds, as well as precursors to numerous other functional groups.[1] The electron-withdrawing nature of the nitro group facilitates removal of the alpha proton under mild conditions, and the resulting conjugate base can serve as a nucleophile in a variety of transformations, such as nitroaldol (Henry) reactions and Michael additions. Reduction of the nitro groups to amines or hydrolysis to carbonyl derivatives can provide access to a wide variety of synthetic products.

Hydrogen-bonding interactions have previously been shown to modulate the regiochemistry of nitroalkane alkylation.[2] There is a growing body of literature that suggests that these interactions can also orchestrate efficient enantioselectivity in a variety of catalytic reactions.[3] Enantioselectivity in the reactions of nitroalkane nucleophiles has been demonstrated using hydrogen-bonding receptors[4] and *Cinchona* alkaloids.[5] High levels of selectivity have also been observed with proline derivatives,[6] and a variety of metal-based catalysts.[7]

We sought to employ small peptides as catalysts in these reactions, with the hypothesis that hydrogen-bonding amino acid side chains could aid in transition state organization.[8,9] Peptides have proven to be effective catalysts for a range of chemical reactions, and provide quick access to libraries that can be tailored to individual synthetic transformations.[10] A related peptide-catalyzed conjugate addition of azide ion[11] likely takes advantage of hydrogen-bonding in the transition state.[12]

The search for peptide-based catalysts capable of promoting the Michael addition of nitroalkanes began with a targeted design strategy. Pentapeptides with a propensity for β-turn nucleation were utilized to provide the structural rigidity necessary to control facial selectivity.[13] A histidine residue was incorporated to serve as a mild base to deprotonate the nitroalkane. Additional hydrogen-bonding functionality was included to provide potential binding sites that might lead to transition state stabilization. A series of peptides were screened using the Michael addition shown in Eq. 1 ($R^1 = Ph$, $R^2 = R^3 = Me$). The catalysts were prepared through Fmoc-solid-phase peptide synthesis, and were screened directly after cleavage from the resin, without further purification. Systematic variations were introduced in an effort to explore their impact on selectivity and to probe mechanistic issues. The most selective peptide **1** was found to

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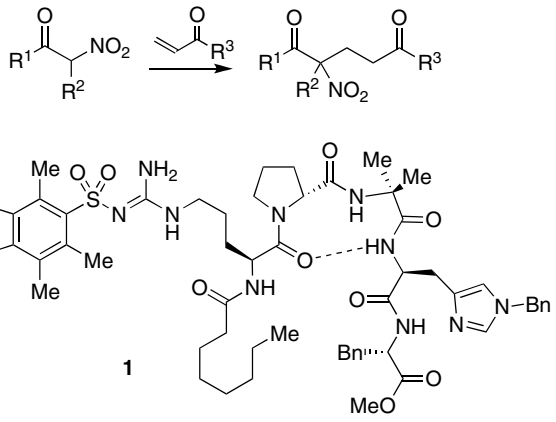
include a D-Pro-Aib turn element, a benzyl-histidine, and an Pbf-protected arginine.



(1)

Analysis of select members of the peptide library provided insight into those aspects of the catalyst that are important for selectivity and the mechanistic role played by each residue (Table 1). The first two peptides differed only in the stereochemistry of the proline residue (entries 1, 2), and while both show selectivity in the Michael addition, each favors a different stereoisomer.[14,15] Further modification of the turn elements only reduced selectivity. A significant structural change was introduced by transposing the arginine and histidine residues.[16] This exchange of residues led to an increase in selectivity for the D-proline peptide **1**, but produced racemic products for the L-isomer (entry 3). Also of note was the observation that the direction of the selectivity for peptide **1** was reversed in comparison with entry 2, where the residues were transposed. This suggests a direct structural role for one or both residues in the organization of the transition state.

The role of the arginine residue was explored through either its deletion, or variation of its position in the catalyst sequence. Replacement of the arginine with a phenylalanine produced only racemic products as expected.

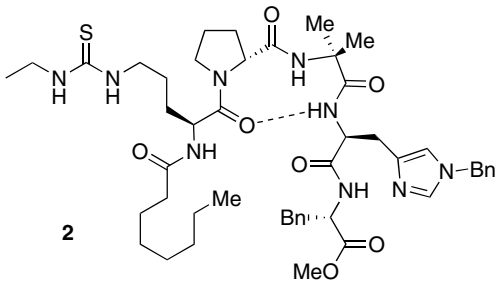
Table 1. Selected peptide catalysts and selectivity observed for the Michael addition shown in Eq. 1 ($R^1 = Ph$, $R^2 = R^3 = Me$)

Entry	Catalyst	ee
1	Ac-His(Bn)-L-ProAib-Arg(Pbf)-Gly-OMe	12
2	Ac-His(Bn)-D-ProAib-Arg(Pbf)-Gly-OMe	−6
3	Oct-Arg(Pbf)-L-Pro-Aib-His(Bn)-Phe-OM	0
4	Oct-Arg(Pbf)-D-Pro-Aib-His(Bn)-Phe-OMe (**1**)	24
5	Oct-Arg(H+)-D-Pro-Aib-His(Bn)-Phe-OMe	0
6	Oct-Arg(NO_2)-D-Pro-Aib-His(Bn)-Phe-OMe	0
7	Oct-Arg(Boc)$_2$-D-Pro-Aib-His(Bn)-Phe-OMe	0
8	Oct-hArg(Pmc)-D-Pro-Aib-His(Bn)-Phe-OMe	0
9	Oct-Orn(CONHEt)-D-Pro-Aib-His(Bn)-Phe-OMe	0
10	Oct-Orn(CSNHEt)-D-Pro-Aib-His(Bn)-Phe-OMe (**2**)	14
11	Oct-Arg(Pbf)-D-Pro-Aib-Ala-Phe-OMe + NMI	0
12	Oct-Arg(Pbf)-D-Pro-Aib-His(Trt)-Phe-OMe	0
13	Boc-His(π-Me)-D-ProAib-Arg(Pbf)-Gly-OMe	−4
14	Boc-Ala(3-pyridyl)-D-ProAib-Arg(Pbf)-Gly-OMe	−6

All reactions were conducted at 4 °C. Selectivity was determined by chiral HPLC.

However, other modifications indicated the subtlety of transition state organization required for maximal effect. Deprotection of the arginine side chain to produce a peptide with a cationic arginine guanidinium (entry 5; as the BF_4 salt) produced only racemic products. While one would expect the deprotected functional group to exhibit stronger binding to the intermediate nitronate than the neutral guanidine of peptide **1**,[2] it is possible that strong complexation with the side chain competes with effects of other parts of the peptide. Other more subtle variations of the protecting group on the arginine side chain also led to an elimination of selectivity. Replacement of the (Pbf) with the analogous (Pmc) showed similar activity, but nitro and bis(Boc)-protected arginines both produced racemic products (entries 6, 7). It is currently unclear if this is due to changes in the hydrogen-bonding capacity of the side-chain guanidine or if the aromatic sulfonamide plays a role in selectivity. Elongation of the side chain by one methylene using homoarginine (entry 8) produced racemic products as well.

Other hydrogen-bonding side chains were employed in an attempt to clarify the role of hydrogen bonds in selectivity. Urea and thiourea are analogs of the arginine side-chain guanidine, but should differ in their hydrogen-bonding strength.[17,18] Their incorporation into peptides with the same spacing as peptide **1** was accomplished through modification of an ornithine side chain with an isocyanate and isothiocyanate, respectively. The urea peptide (entry 9) showed no selectivity, while the thiourea peptide **2** (entry 10) produced products with 14% ee. Although this is no advance on the 24% ee realized with peptide **1**, the greater selectivity of thiourea over urea is consistent with stronger association to oxyanions.[17] This result may indicate that hydrogen bond strength plays an important role in the transition state.



Histidine was included in the peptide design to initiate the chemical reaction, but it appears to play a role in determining selectivity as well. To test the role of histidine, a peptide was created that was identical to peptide **1** except that the histidine was replaced by an alanine. Without the basic imidazole only starting materials were recovered. Addition of equal amounts (0.02 mol equiv) of this control peptide and *N*-methyl imidazole (NMI) led to complete conversion to products, but with no observed selectivity (entry 11). This suggests that the histidine residue does not merely deprotonate the nitroalkane, but also plays a role in the selectivity of the subsequent nucleophilic addition. It seems likely that

this is accomplished through association with the intermediate nitro-enolate anion. The benzyl side chain on the histidine is not thought to play a significant role since peptides that contain a π-methyl-histidine or even a 3-pyridylalanine showed selectivities similar to their τ-benzyl-histidine analogs, although the increased bulk of a trityl histidine led to racemic products (entries 12–14).[19]

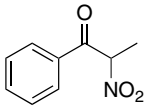
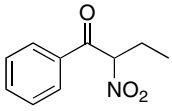
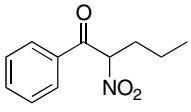
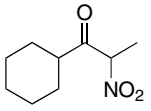
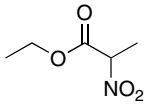
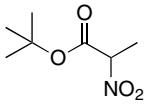
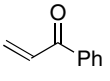
The selectivity of peptide **1** can be modified by optimizing reaction conditions. Lowering substrate concentrations to 100 mM or below indeed had a positive effect, but the expense of reactivity, so 100 mM was used for all subsequent experiments. Toluene was the best solvent with a self-consistent comparison producing 40% ee, while benzene (30% ee), diethyl ether (18% ee) and hexanes (racemic with peptide precipitation) showed reduced selectivity. The peptides are minimally soluble in toluene, thus the catalysts were introduced into the reaction medium as dichloromethane solutions. The final concentration did not exceed 3% v/v dichloromethane in toluene. Maximal selectivities were observed at 4 °C.

The selectivity and synthetic flexibility of peptide **1** was further probed by exploring substrates with differing functional groups and steric bulk (Table 2). Nitroketone derivatives were synthesized from acyl imidazoles and nitronate salts,[20] while nitroester derivatives were obtained by nitration of the alpha-bromoesters.[21] All aspects of the substrates were found to result in changes in selectivity. An increase in the size of the alpha-side chain (R^2) from methyl to ethyl (entries 1, 2) showed greater selectivity, but further increasing the steric bulk provided a less selective reaction (entry 3). A cyclic nitroketone analog, 2-nitroindanone, showed nearly racemic products in comparison with the acyclic version, suggesting that the ideal conformation is *s*-trans. Replacement of the phenyl group with the cyclohexyl analog (entry 4) or an ethyl ester (entry 5) resulted in complete loss of selectivity. The peptide catalyst was, however, capable of performing selective reactions of *t*-butyl 2-nitropropionate with phenyl vinyl ketone as the electrophile (entry 6). Phenyl vinyl ketone was the most effective electrophile with nitroesters, but reaction with nitroketones produced only racemic products. Phenylketone substrates demonstrated reduced synthetic yields with increasing alkyl chain length, while more reactive nitroesters and cyclohexylketone showed excellent yields.

Electronic effects were investigated by comparing 2-nitropropiophenone with *para*-methoxy and *para*-nitro derivatives at 250 mM substrate. (At lower concentrations, the nitrophenylketone failed to react.) Under these conditions, the methoxyphenylketone produced 10% ee, the phenylketone 24% ee, and the nitrophenylketone 40% ee. These results suggest that it is the nucleophilic attack that is responsible for selectivity.

Kinetic analysis for several substrates all showed that the peptide-catalyzed reaction was >10 times faster than with *N*-methyl imidazole (Fig. 1). This peptide-catalyzed rate acceleration could result from various effects. The deprotonated anion could be stabilized by interactions

Table 2. Selectivity and isolated yields observed with various nitrocarbonyls using peptide **1** (2 mol %) as a catalyst

Entry	Substrate	Electrophile	Yield (%)	ee (%)
1			82	52
2			64	74
3			29	60
4			99	0
5			96	0
6			85	50

All reactions were conducted at 4 °C. Selectivity was determined by chiral HPLC.

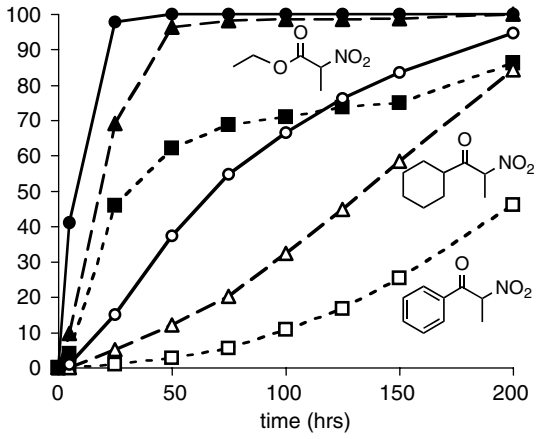


Figure 1. Kinetic comparison of select substrates with either peptide **1** (closed symbols) or *N*-methylimidazole (open symbols). Substrates include ethyl ester (●, ○), cyclohexyl ketone (▲, △), and phenyl ketone (■, □). All reactions were performed at 4 °C.

with the peptide, but the results above suggest that nucleophilic attack is rate determining. Two possibilities that are consistent with rate acceleration are direct activation of the electrophile, or assembly of the transition state on the peptide catalyst. Additionally, the rate of reaction for nitroesters (entry 5) and cyclohexylketones (entry 4) is faster than the analogous phenylketone (entry 1), suggesting that the greater selectivity of entry 1 may be correlated with reduced starting material reactivity.

Synthetic and kinetic data suggest a mechanistic role for peptide side chains in catalytic selectivity. Both arginine and histidine must be part of the peptide and their transposition changes the direction of the observed selectivity, suggesting interactions with both side chains in the transition state. Greatest selectivity is observed for the D-Pro-Aib turn element, which promotes a β-turn and orients the amide NH oriented towards the same face as the histidine and arginine side chains.[22] Rate accelerations are consistent with the preorganization of nucleophile and electrophile on the peptide. The low selectivity of the cyclic nitroindanone and reduced yields for increased alkyl chain length (R^2) suggest that the nucleophile could interact with the peptide optimally when the carbonyl and nitro groups are in an *s*-trans configuration. One possibility is the accumulation of hydrogen-bonding interactions between the peptide and anionic intermediate (Fig. 2), and our ability to fully understand and control these interactions will provide the key to maximizing selectivity in this and other reactions.

In summary, catalytic peptides have been developed that promote the asymmetric Michael addition of nitrocarbonyl compounds. Methodologically, this approach provides a mild, asymmetric method for the creation of new carbon–carbon bonds that may be complementary to other organocatalytic and metal-based approaches. These results also demonstrate a mechanism-driven catalytic design predicated on bifunctional catalysis. These studies set the stage for further design of catalytic peptides for other important carbon-bond forming reactions.

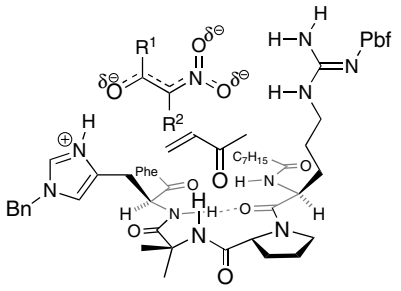


Figure 2. A possible assignment of side chain roles.

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Supplementary data

Experimental procedures and product characterizations for all new compounds synthesized. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.073.

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