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Asymmetric Catalytic Mannich Reactions Catalyzed by Urea Derivatives: Enantioselective Synthesis of β-Aryl-β-Amino Acids

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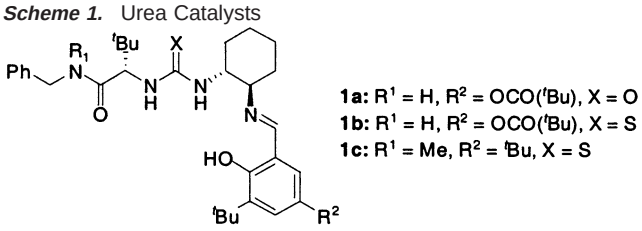
β-Amino acid derivatives have proven utility as building blocks for the preparation of pharmaceutical targets,[1] natural products,[2] and peptidic materials with unique structural properties.[3] Of the methods available for their synthesis,[1,4−6] the addition of ester enolate equivalents to imines (the Mannich reaction) is especially attractive as it involves the convergent assembly of two units of similar complexity with concomitant formation of a carbon−carbon bond. Various chiral auxiliary[7] and reagent-based[8] approaches to Mannich reactions have been reported for the enantioselective synthesis of β-amino acids. The development of a catalytic, enantioselective version of this reaction,[4,5] however, has proven challenging: the catalyst must be capable of activating imines toward nucleophilic attack, yet be resistant to inhibition by the strongly Lewis-basic amine products. Significant advances have been made recently in the discovery of chiral zirconium-based catalysts for the Mannich reaction.[5a,b] These systems, however, are restricted to imine substrates bearing *N*-aryl substituents with a pendant chelating group for two-point binding to the catalyst. This requirement imposes several practical limitations, including the need for strong oxidative or reductive conditions for product amine deprotection. Herein, we describe a highly efficient route to *N*-*tert*-butoxycarbonyl- (*N*-Boc) protected β-amino acids via the enantioselective addition of silyl ketene acetals to *N*-Boc-aldimines catalyzed by thiourea catalyst **1c** (Scheme 1).

Scheme 1. Urea Catalysts



1a: R^1 = H, R^2 = OCO(ᵗBu), X = O
1b: R^1 = H, R^2 = OCO(ᵗBu), X = S
1c: R^1 = Me, R^2 = ᵗBu, X = S

Urea derivatives of general structure **1** have emerged as useful catalysts for the asymmetric hydrocyanation of *N*-allyl or *N*-benzyl aldimines[9a,b] and ketoimines.[9c] Kinetic and structural studies carried out with **1a** revealed the mechanism of catalysis to involve imine activation via hydrogen bonding to the urea component of the catalyst.[9d] These results prompted us to investigate **1a** for the activation of imines toward other interesting carbon-based nucleophiles, and enolate equivalents in particular. Initial studies on the reaction of *N*-allyl and *N*-benzyl benzaldimines with trimethylsilyl ketene acetal derivatives proved unsuccessful, however, presumably as a result of the poor reactivity of the imine substrates. In contrast, the more electrophilic benzaldehyde *N*-Boc imine **3a**[7a] (eq 1) underwent reaction with trimethylsilyl ketene acetal **2** (3 equiv) in the presence of **1a** (10 mol %) to afford the desired Mannich adduct in 47% ee (eq 1).[10] The rate of the uncatalyzed racemic reaction was found to be significant (roughly 45% conversion in the absence of catalyst under the same reaction conditions), indicating that the pathway catalyzed by **1a** proceeded with very high enantioselectivity.

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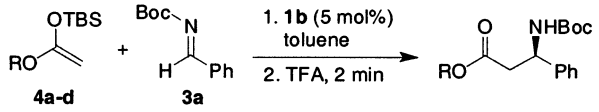
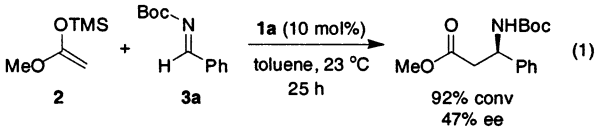
Table 1. Optimization of the Silyl Ketene Acetal in the Mannich Reaction of **3a**[a]



entry	silyl acetal	R	temp (°C)	time (h)	conv(%)[b]	ee (%)[c]
1	**4a**	Me	23	5.5	90	54
2	**4b**	Et	23	3.5	90	63
3	**4c**	ⁱPr	23	2.0	93	68
4	**4c**	ⁱPr	−40	48.0	90	**91**
5	**4d**	ᵗBu	23	21.5	91	51

[a] Reactions were carried out with 0.25 mmol of imine and 0.5 mmol of silyl ketene acetal in 125 μL of toluene. [b] Determined via GC relative to dodecane as an internal standard. [c] See Supporting Information.



Several factors were found to increase the rate of the catalyzed pathway relative to the background reaction. In particular, variation of catalyst structure, the silyl ketene acetal substrate, and reaction temperature led to pronounced effects and provided the basis for reaction optimization.[11] Replacement of the urea moiety in **1a** (X = O) with a thiourea group as in **1b** (X = S) resulted in a substantial increase in reactivity. For example, subjection of **1b** to the reaction conditions outlined in eq 1 led to formation of the Mannich product in 90% conversion and 70% ee after 8 h at ambient temperature.[12]

Variation of the silyl and alkoxy groups of the silyl ketene acetal nucleophile led to additional rate enhancement. Use of *tert*-butyldimethylsilyl ketene acetals, which can be prepared cleanly with 100% *O*-silylation,[13] afforded best results and allowed the use of lower catalyst loadings (Table 1). An additional accelerating effect was observed with larger alkoxy substituents (Table 1, entries 1−3), although the trend was reversed in the case of the *tert*-butoxy derivative (**4d**, entry 5).

Rate enhancements achieved through the catalyst and nucleophile optimizations outlined above permitted the use of lower temperatures with maintenance of useful reaction rates (Table 1, entry 4). Selective suppression of a racemic background pathway occurred at reduced temperature. For example, reaction of **3a** with **4c** at 23 °C proceeded to 30% conversion in the absence of catalyst

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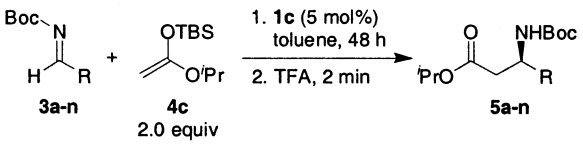
Table 2. Mannich Reactions Catalyzed by **1c**



entry	imine	R	temp (°C)	yield (%)[a]	ee (%)[b]
1	**3a**	Ph	−40	95	97
2	**3b**	*o*-$CH_3C_6H_4$	−30	88	91
3	**3c**	*m*-$CH_3C_6H_4$	−30	98	94
4	**3d**	*p*-$CH_3C_6H_4$	−30	87	96
5	**3e**	*p*-$OMeC_6H_4$	4	91	86
6	**3f**	*p*-FC_6H_4	−30	88	93
7	**3g**	*m*-BrC_6H_4	−30	96	92
8	**3h**	*p*-BrC_6H_4	−30	93	94
9	**3i**	1-naphthyl	−30	93	87
10	**3j**	2-naphthyl	−30	88	96
11	**3k**	2-furyl	−40	84	91
12	**3l**	2-thienyl	−30	95	92
13	**3m**	3-quinolinyl	−30	99	96
14	**3n**	3-pyridyl	−30	99	98

[a] Isolated yield after silica gel chromatography. [b] Absolute stereochemistry determined via correlation to authentic material[17] and literature values.[18]

within 2 h, but no uncatalyzed reaction was observed at −40 °C over 48 h.

Further catalyst optimization was achieved through the construction of a small, parallel library of 22 compounds, with systematic variation of salicylaldimine, diamine, amino acid, and amide components.[14] Enantioselectivity in the Mannich reaction remained invariant with changes in the para substituent of the salicylaldimine ring. Accordingly, commercially available di-*tert*-butylsalicylaldehyde was used for the preparation of subsequent catalysts. In contrast, replacement of the secondary amide with a tertiary amide derivative, as in catalyst **1c**, resulted in a significant improvement in enantioselectivity (e.g., **5a** was obtained in 95% yield and 97% ee, Table 2, entry 1). The presence of the tertiary amide also served to prevent undesired formation of thiohydantoin byproducts during catalyst preparation.[15] This allowed the preparation of catalyst **1c** in five steps from commercially available starting materials in 86% overall yield with only a single chromatographic purification step.

The scope of the reaction of **4c** with *N*-Boc arylimine derivatives is summarized in Table 2. Ortho-, meta-, and para-substituted arylimines underwent addition with generally high enantioselectivity and in excellent yield. One of the attractive features of this methodology is the remarkable tolerance for Lewis basic substrates, enabling the highly enantioselective synthesis of thienyl-, furyl-, pyridyl-, and quinolinyl-substituted 3-amino propionic esters (entries 11−14). Indeed, all *N*-Boc imines screened to date have proven to be excellent substrates with respect to both enantioselectivity and yield.[16] Reactions were carried out using 2 equiv of **4c** relative to the imine, as this was found to have a beneficial effect on rate, particularly with electron-rich substrates. Electron-deficient imines proved more reactive, however, and their efficient conversion could be achieved with 1.2 equiv of nucleophile. For example, when 3-pyridinecarboxaldimine **3n** was combined with 1.2 equiv of **4c** in the presence of **1c**, **5n** was obtained in 99% yield and 98% ee within 48 h. This and similar reactions have been carried out on scales as high as 10 mmol with no detrimental effect on yield or enantioselectivity. The resulting Boc-protected, β-amino acid derivatives are readily deprotected under mildly acidic conditions and are well suited for direct use in peptide synthesis.[17]

In summary, urea derivatives of general structure **1** serve as highly effective catalysts for the asymmetric addition of silyl ketene acetal derivatives to aldimines. From a steric and electronic standpoint, the *N*-Boc imine substrates utilized in this reaction are fundamentally different from the *N*-alkyl derivatives employed in the Strecker reaction. This raises the interesting possibility that the mechanism of substrate activation may be different in the two reactions, thereby suggesting great promise for the application of this catalyst class to an even broader range of asymmetric reactions.

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Supporting Information Available: Detailed experimental procedures and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Other imine protecting groups examined under the same reaction conditions: *N*-Cbz benzaldimine, 26% ee; *N*-tosyl benzaldimine, 0% ee.

(11) The enantioselectivity of this reaction is relatively insensitive to dilution, stoichiometry, and rate of nucleophile addition. No change in enantioselectivity was observed with solvents of low polarity, while strongly polar aprotic solvents led to dramatically poorer ee's. Use of protic solvents resulted in rapid decomposition of the imine.

(12) Thiourea catalysts also display enhanced enantioselectivity relative to their urea counterparts in the case of the Strecker reaction.[9d]

(13) While HMPA has traditionally been used as a cosolvent for *tert*-butyldimethylsilylation of lithium enolates, both DMPU or 1-methyl-2-pyrrolidinone (NMP) are effective alternatives.

(14) Full details of catalyst structure/enantioselectivity profiles for both the Mannich and the Strecker reactions will be reported in due course.

(15) Thiohydantoin formation proved problematic in the preparation of thiourea derivatives bearing secondary amides. Detailed experimental procedures are provided as Supporting Information.

(16) Aliphatic *N*-Boc imines have as yet not been investigated because no useful method currently exists for their synthesis.

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