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Catalysis of highly stereoselective Mannich-type reactions of ketones with α-imino esters by a pyrrolidine-sulfonamide. Synthesis of unnatural α-amino acids

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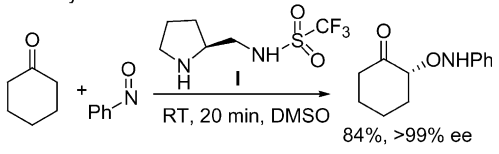
Abstract—The novel pyrrolidine-sulfonamide **I** has been prepared and used successfully to catalyze Mannich-type reactions between ketones and α-imino esters. The process is used to efficiently synthesize functionalized α-amino acid derivatives with excellent levels of regio-, diastereo-, and enantio-selectivity.

Asymmetric synthesis of optically active natural and unnatural α-amino acids has been of long-standing interest to organic chemists since these substances are versatile synthetic building blocks for the preparation of an assortment of biologically important molecules.[1] In this regard, the enantioselective Mannich-type reactions of enolates or enolate equivalents with α-imino esters constitutes a powerful approach to the synthesis of novel functionalized γ-keto-α-amino acid derivatives.[2] Over the past few years, catalytic, enantioselective versions of this process has received great attention with a major emphasis being given to the development of organometallic catalysis.[3–6] These metal-based catalysis methods rely on the use of preformed enolates or enolate equivalents. An effective, atom-economic asymmetric version of this reaction, employing unmodified carbonyl compounds would be more attractive. Examples of Mannich reactions catalyzed by organometallic-based chiral catalysts have been described by Shibasaki and co-workers,[7] Trost and Terrell,[8] and Jørgensen and co-workers.[9]

The development of metal-free organocatalysts has emerged as a new frontier in asymmetric catalysis,[10] pioneered by List et al.[11] and MacMillan and co-workers.[12] Several catalytic systems including L-proline,[13,14] peptides,[15] and small organic molecules[16,17] have been reported for the Mannich reactions. L-Proline and its derivative pyrrolidine tetrazole catalyzed process have been reported for promoting direct Mannich-type reactions of ketones and aldehydes with α-imino esters.[14,16] As part of a program aimed at developing new and broadly useful organocatalysts for asymmetric synthesis, we recently uncovered a pyrrolidine-sulfonamide organocatalyst **I**, which promotes direct α-aminoxylation reactions of ketones and aldehydes with nitrosobenzene in a highly enantio- and regioselective manner (Eq. 1).[18] To our knowledge, this is the first example of the use of an amine sulfonamide organocatalyst for catalysis of organic transformations.

We envisioned that enamines formed from ketones and **I** would also add to electrophilic α-imino ester in Mannich-type reactions to provide novel functionalized γ-keto-α-amino acids (Eq. 2). Studies testing this proposal have demonstrated that pyrrolidine-sulfonamide **I** catalyzes reactions of unmodified ketones with α-imino esters in a highly efficient manner with excellent levels of regio-, diastereo-, and enantio-selectivity.

Pyrrolidine-sulfonamide **I** catalyzed the direct α-aminooxylation reactions



(1)

Keywords: Asymmetric catalysis; Ketones; Mannich reaction; Amino acids; Pyrrolidine-sulfonamide.
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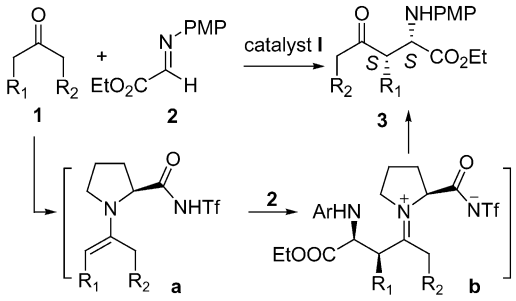
Pyrrolidine-sulfonamide **I** catalyzed the Mannich-type reactions

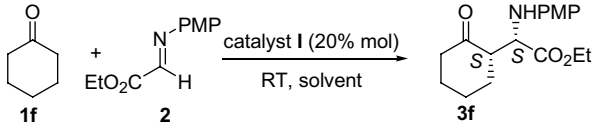


(2)

An exploratory study was conducted to evaluate the proposed enantioselective Mannich-type reactions catalyzed by **I**. Initial studies of the reaction of cyclohexanone **1f** with the *N*-PMP (*p*-methoxyphenyl) protected α-imino ethyl glyoxylate **2** in the presence of 20 mol% of **I** in DMSO (Table 1, entry 1) revealed that the Mannich-type reaction took place rapidly (2 h) at room temperature and with excellent enantioselectivity (>99% ee). Catalyst **I** displayed a higher level of catalytic activity and higher yield (90% vs 81%) than L-proline. Significantly, ^{1}H NMR analysis of the product mixture showed that the *syn*-diastereomer was formed predominantly (dr >95:5). The observed stereochemical outcome, that is, **3f** with (*S*,*S*) configuration, matched that of proline-catalyzed Mannich-type reactions, presumably a consequence of the energetic similarities of their diastereomeric transition states (Eq. 2).[17]

Solvent effects on this process were examined next (Table 1). In a similar manner to enantioselective α-aminooxylations of ketones with nitrosobenzene catalyzed by **I**,[18] a variety of solvents can be employed for the Mannich-type process. The catalyst exhibited high activities in all solvents explored; in every case, good to high yields (76–90%), high levels of enantioselectivities (95% to >99% ee), and high diastereoselectivities (≥95:5 *syn*/*anti*) were observed. Based on this study, DMSO was selected as the solvent used for the further examination of this process.

Table 1. Effect of solvent on the Mannich reaction of cyclohexanone **1f** with α-imino ethyl **2**[a]



Entry	Solvent	Reaction time (h)	% Yield[b]	% ee[c]	dr[d]
1	DMSO	2.0	90	>99	>95:5
2	$CHCl_3$	7.0	86	95	>95:5
3	DMF	2.5	82	97	>95:5
4	THF	4.5	89	97	>95:5
5	CH_3CN	3.5	88	98	>95:5
6	EtOAc	5.5	84	98	>95:5
7	CH_3NO_2	5.5	76	98	>95:5
8	1,4-Dioxane	2.0	89	97	>95:5

[a] Reaction conditions: a solution of cyclohexanone **1f**:α-imino ethyl ester **2**:catalyst **I** = 10:1:0.2 (mole ratio) in a solvent (table) was run 2.0–7.0 h.
[b] Isolated yields.
[c] Enantiomeric excess (ee) determined by chiral HPLC analysis (Chiralpak AS-H).
[d] dr = *syn*/*anti* As determined by ^{1}H NMR after column chromatography.

Table 2. Effect of catalyst loadings on the Mannich-type reaction between **1f** and **2**

Entry	Mol% **I**	Reaction time (h)	% Yield[a]	% ee[b]	dr[c]
1	20	2.0	90	>99	>95:5
2	10	3.5	90	96	>95:5
3	5	14	86	96	>95:5
4	2	50	81	91	>95:5

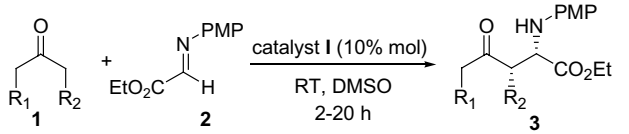
[a] Isolated yields.
[b] Determined by chiral HPLC analysis (Chiralpak AS-H).
[c] dr = *syn*/*anti* As determined by ^{1}H NMR.

The effect of catalyst loading on the reaction efficiency was probed. A variety of catalyst loadings (2–20 mol%) were employed to catalyze reaction of cyclohexanone **1f** with α-imino ethyl ester **2** in DMSO (Table 2). As expected, the time to bring about complete reaction increased with a decrease in catalyst loading. However, the reaction yields (81–90%) and enantio- and diastereoselectivities remained high or only slightly decrease (91% to >99% ee, and >95:5 dr) when the amount of catalyst was lowered. From an operational perspective, use of 10 mol% of catalyst **I** is optimal to ensure high levels of enantio- and stereoselectivities (96% ee, >95:5 dr) and efficiency (90% yield) while maintaining a reasonable reaction time (3.5 h, Table 2, entry 2).

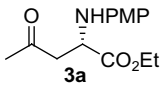
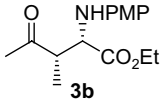
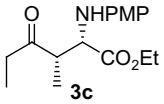
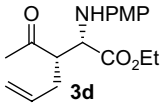
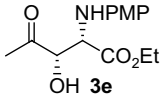
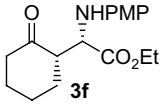
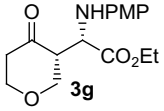
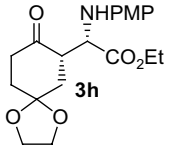
Having established optimal reaction conditions, we next explored the scope of the organocatalytic Mannich-type reactions between α-imino ester **2** and various ketones (Table 3). Significantly, we observed that pyrrolidine-sulfonamide **I** catalyzed Mannich-type reactions occurred with both acyclic (entries 1–5) and cyclic ketones (entries 6–8), affording adducts **3** in good yields (74–91%) with high *syn* diastereo- and enantioselectivities (>95:5 dr and 96% to >99% ee). In the case of ketones **2**–**8** (Table 3, entries 2–8), two adjacent stereogenic centers were generated simultaneously with complete (*S*,*S*)-stereocontrol. More importantly, reactions of unsymmetric ketones (entries 2, 4, and 5) resulted in the highly regioselective production of adducts **3b**,**d**,**e** resulting from reaction at the more substituted α-sites with excellent stereoselectivities as well (≥96% ee and ≥95/5 dr *syn*/*anti*). Studies with differently α-substituted carbonyl substrates (entries 2, 4, and 5) reveal that methyl, allyl, and hydroxyl substituents provided the greatest degree of stereochemical control (96% to >99% ee and dr ≥95:5 (*syn*/*anti*)). Finally, changes in the electronic properties of ketones (Table 3, entries 5, 7, and 8) had only a small effect on the process.

In summary, the study described above has uncovered a novel pyrrolidine-sulfonamide catalyst **I** that can be

Table 3. Catalyst **I** catalyzed the reactions of various ketones **1** with α-imino ester **2**



1 **2** **3**

Entry	Product	% Yield[a]	% ee[b]	dr[c]
1	 **3a**	91	>99	—
2	 **3b**	84	97	>95:5
3	 **3c**	83	97	>95:5
4	 **3d**	88	96	>95:5
5	 **3e**	74	>99	>95:5
6	 **3f**	90	96	>95:5
7	 **3g**	83	>99	>95:5
8	 **3h**	78	96	>95:5

[a] Isolated yields.
[b] Determined by chiral HPLC analysis (Chiralpak AS-H).
[c] dr = *syn*/*anti* As determined by ^{1}H NMR.

used to promote highly efficient, direct, asymmetric Mannich-type reactions of ketones with α-imino esters to produce functionalized α-amino acid esters. In this process, **I** exhibits high catalytic activity and excellent levels of regio-, diastereo-, and enantio-selectivity. Further applications of this catalyst to other synthetically useful transformations are currently being investigated.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.08.032.

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