Organocatalysis in Ionic Liquids: Highly Efficient L-Proline-Catalyzed Direct Asymmetric Mannich Reactions Involving Ketone and Aldehyde Nucleophiles

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Abstract: Proline-catalyzed direct asymmetric Mannich reactions of *N*-PMP protected α -imino ethyl glyoxylate with various aldehydes and ketones in ionic liquids afforded both α - and β -amino acid derivatives with excellent yields and enantioselectivities, providing facile product isolation, catalyst recycling, and significantly improved reaction rates, ca 4- to 50-fold. Three component Mannich reactions involving other imines also worked well in ionic liquids. Significant advantages and limitations of ionic liquid solvents in this reaction have been revealed.

Key words: proline, enamine, Mannich reaction, ionic liquids, green chemistry

In the 91 years since its invention, the Mannich reaction has established itself as one of the most important carboncarbon bond-forming reaction in organic synthesis.¹ During this time, substantial efforts have been devoted to optimizing this reaction since the β -amino ketones and aldehydes it provides are key intermediates in the synthesis of natural products and bioactive products in medicinal chemistry. Of late, particular emphasis has been devoted to the development of asymmetric versions of this type of transformation. These studies have culminated in the development of approaches that affect the direct catalytic addition of unmodified ketones² and most recently aldehydes.³ In considering the optimization of a reaction, attention must also be paid to the practical aspects of the reaction that go beyond the products themselves; i.e. solvent, apparatus, and recycling of non-consumed materials. Ideally such optimization takes into account environmental safety as an important element of the overall economy of the process.⁴ In 1997 we initiated comparative studies of aldolase antibodies with proline⁵ and this research effort has led to the development of a number of organocatalytic reactions as well as additional catalysts. The reactions include asymmetric aldol, Michael, Mannich, Diels-Alder and related reactions based on exploiting enamines and imines generated in a catalytic fashion.^{2c,d,3,6} Organocatalysis of direct asymmetric Mannich reactions involving ketone nucleophiles and, more significantly, aldehyde nucleophiles promises to have an impact on the practice of this important reaction.

SYNLETT 2003, No. 12, pp 1906–1909 Advanced online publication: 19.09.2003 DOI: 10.1055/s-2003-41483; Art ID: Y00403ST © Georg Thieme Verlag Stuttgart · New York In recent years, ionic liquids have attracted a great deal of attention from synthetic chemists as novel green reaction media.⁷ This is mainly due to their nonvolatile nature, tunable polarity and high thermal stability. The insolubility of ionic liquids in some solvents and their ability to dissolve catalysts, particularly transition metal catalysts, has made them attractive with respect to both solvent and catalyst recycling. Herein, we report the unique favorable features as well as the limitations of proline-catalyzed direct asymmetric Mannich reactions in ionic liquids (Scheme 1).



Scheme 1 L-Proline-catalyzed direct asymmetric Mannich reactions in [bmim][BF₄]

Table 1Catalyst and Ionic Liquid Solvent Recycling in the L-Pro-line Catalyzed Direct Asymmetric Mannich Reaction of Cyclohex-anone with N-PMP Protected α -Imino Ethyl Glyoxylate

PI	MP_N II_CO ₂ Ft	roline (5 mol%)	O HN PMP	
\checkmark	0.0221	30 min		
Run	Yield (%)	dr ^a	ee (%) ^b	
1	99	>19:1	>99	
2	92	>19:1	>99	
3	87	>19:1	>99	
4	83	>19:1	>99	

¹ Determined by ¹H NMR analysis of unpurified products.

^b Determined by HPLC analysis using Chiralpk AS column.

We initially studied⁸ the Mannich reaction of *N*-PMP protected α -imino ethyl glyoxylate with cyclohexanone using a catalytic amount of L-proline (5 mol%) in [bmim]BF₄ at room temperature (Table 1). We were delighted to find that the reaction was complete within 30 minutes and

provided the Mannich product in quantitative yield with excellent ee (>99%) and diastereoselectivity (>19:1). In order to study catalyst and solvent recycling, the product was extracted with Et_2O . The recovered ionic liquid containing L-proline was then used for the next reaction run. Again, the Mannich product was obtained in excellent yield and ee's. Following four consecutive reaction cycles there was no diminution in ee and a slight decrease in yield when the 30 minutes reaction time was strictly maintained. The use of another ionic liquid, [bmim]PF₆, as reaction solvent also afforded the Mannich products with identical yields and ee's.

Encouraged by these promising results we next studied the Mannich reaction using various aldehydes and ketones as nucleophiles or donors in this reaction.^{2d,3a} In all cases, the reactions were complete within 30 minutes to furnish various functionalized amino acids with excellent yields and ee's. In most of the cases (Table 2, entries 1-3 and 5-6) the amino acid derivatives were obtained as single enantiomers with excellent diastereoselectivity (>19:1). The use of aldehyde donors, possible only through organocatalysis, afforded the corresponding α - and β -amino acid derivatives. Reducing the catalyst loading to 1 mol% using ionic liquid solvent did not compromise the enantioselectivity of the reaction but required a longer, albeit reasonable, 2 hour reaction time (Table 2, entry 6). These results demonstrate that the use of ionic liquids as solvents for these reactions leads to higher yields and markedly accelerated reactions. Our original disclosure of these reactions involving traditional organic solvents required 2-24 h reaction times with 5–20 mol% catalysts.

With this success next we investigated the three component Mannich reaction in ionic liquids (Table 3).⁹ Various

Table 2L-Proline-Catalyzed Direct Asymmetric Mannich Reactions in $[bmim][BF_4]$

, j	+ PM	PN	L-proline (5 mol	%)	O HN	PMP
R'1	R^2	H [⊥] CO₂EI	[bmim]BF ₄ 30 min	F	R ¹	CO ₂ Et
Entry	R ¹	R ²		Yield (%)	dr ^a	ee (%) ^b
1	Н	<i>n</i> -Bu		87	13:1	>99
2	Н	n-Pent		96	>19:1	>99
3	Н	×~~/	~~~~	95	>19:1	>99
4	Н	<i>i</i> -Pr		90	5:1	93
5	Me	Me		77	>19:1	>99
6 ^c	-(CH ₂) ₂ -	-(CH ₂) ₂ -		99	>19:1	>99
7	Me	Н		80	_	97

^a Determined by ¹H NMR analysis of reaction mixtures.

^b Determined by HPLC analysis using Chiralpk AS or Chiralpk AD columns.

aromatic and aliphatic aldehydes were employed in this three component Mannich reaction affording the products with good yields and ee's. Interestingly, reactions involving 5-hexene 2-one afforded a single regioisomer. The reactions involving aliphatic aldehydes were faster (1 h) (Table 3, entry 5 and 6) than those involving aromatic aldehydes (6 h). These results are comparable with respect to yield and enantioselectivity with the reactions conducted in organic solvents,^{2c,e} though again the reaction rates are significantly faster. In entry 6 the product yield and ee's are superior to those reported using traditional solvent (82% yield and 75% ee).^{2e}

 Table 3
 L-Proline-Catalyzed Asymmetric Three Component Mannich Reactions in [bmim][BF₄]

R ¹	< ⁺ H ^O R ²	+ H_2 OMe L -proline (5 [bmim]E	$rac{mol\%}{} ightarrow R^1$	
Entry	\mathbb{R}^1	R ²	Yield (%)	ee (%)
1	Н	X NO2	54	95
2	Н	×	63	82
3	allyl	X NO2	60	87
4	allyl	jet C	52	93
5	Н	×	80	43
6	Н	xo	98	93

Limitations on the Use of Ionic Liquids in the Proline-Catalyzed Mannich Reaction

The first significant limitation we noted concerned Mannich reactions involving hydroxyacetone as a nucleophile. Hydroxyacetone is a unique donor whose properties we initially described in the context of our studies of aldolase antibodies.¹⁰ Here we studied the hydroxyacetone Mannich reaction under a variety of reaction conditions presented in Table 4. While the desired amino alcohol products were obtained with excellent yield, the diastereoand enantioselectivity of the reaction was severely compromised as compared to the same reaction in organic solvents, e.g. DMSO or DMF. In these solvents we had obtained products with ee's of 99% and dr's of > 19:1. Indeed, it was hydroxyacetones' characteristic of acting as a

^c With 1 mol% of L-proline the reaction was complete in 2 h.

nucleophilic enamine to generate products with exceptional enantio- and diastereoselectivity that made this ketone an exceptional donor in our antibody studies and later in organocatalysis. To determine if the poor performance of hydroxyacetone in ionic liquids was a general phenomenon, we studied the aldol reaction shown in Scheme 2. Contrary to the results we obtained in the Mannich reaction, the Aldol reaction using hydroxyacetone afforded the desired product with excellent diastereo- and enantioselectivity. (Scheme 2) In accord with studies of simple unsubstituted ketones in proline catalyzed aldol reactions in ionic liquids,¹¹ no increase in the reaction rate was noted in the special case of hydroxyacetone.



Scheme 2 L-Proline-catalyzed aldol reaction of hydroxyacetone in $[bmim][BF_4]$

The next limitation we noted came in the context of our recently developed catalytic direct asymmetric anti-selective Mannich reaction. The (S)-2-methoxymethylpyrrolidine (SMP)-catalyzed^{3b} reaction of isovaleraldehyde with protected α -imino ethyl glyoxylate *N*-PMP in [bmim][BF₄] provided the desired anti-Mannich product albeit in only 20% yield and 33% ee (Scheme 3). With dioxane as the solvent, this reaction provides the product in 48% yield with an ee of 69% and a dr >10:1.



Scheme 3 (S)-2-Methoxymethylpyrrolidine (SMP)-catalyzed synthesis of anti-Mannich product in [bmim][BF₄]

In summary, proline-catalyzed direct asymmetric Mannich reactions in ionic liquids are substantially faster than the corresponding reactions in standard organic solvents, ca 4-50 times faster. We speculate that enhanced rates result from ionic liquid-based activation of the imine electrophiles. These results are noteworthy compared to the proline-catalyzed aldol reactions involving unsubstituted ketones in ionic liquids, where the reactivity, yields and ees are comparable or inferior as compared to the reactions performed in standard organic solvents.¹¹ Limitations include poor performance in hydroxyacetone Mannich reactions and in SMP-catalyzed anti-Mannich reactions. Together these results go a long way to creating a 'green' class of Mannich reactions wherein both solvent and catalyst are readily recycled and reaction times are minimized thereby significantly improving the overall economy of this reaction. The catalyst itself is edible. These reactions can be performed on a multi-gram scale under operationally simple and safe conditions. Further studies aimed at exploring the scope of organocatalytic reactions in ionic liquids are ongoing.

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OH +	PMP_N L H CO ₂ Et	-proline (5 mol%)				
Entry	Ionic liquid	Temperature (°C)	Time (min)	Yield (%)	dr	ee (%) (syn/anti)
1	[bmim][BF ₄]	22	30	97	68:32	3/24
2	[bmim][BF ₄]	0	180	50	67:33	0/25
3	[bmim][BF ₄]	-20	180	20	67:33	2/39
4	[bmim][PF ₆]	22	30	93	58:42	3/37

 Table 4
 L-Proline-Catalyzed Direct Asymmetric Mannich Reactions in [bmim][BF₄] with Hydroxyacetone

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- (8) General experimental procedure: To a glass vial charged with L-proline (3 mg, 0.025 mmol) was added [bmim]BF₄ (1 mL) followed by α -imino ethyl glyoxylate (104 mg, 0.5 mmol), aldehyde (1.5 equiv) or ketone (1 mL) and the reaction was stirred at r.t. for 30 min. After completion of the reaction (as monitored by TLC), the product was isolated by extraction with Et₂O (4 × 5 mL). The combined Et₂O extracts were concentrated to obtain the Mannich product. The ionic liquid containing L-proline was dried under vacuum prior to reuse.
- (9) General experimental procedure for three component Mannich reaction (Table 3): To a glass vial charged with L-proline (3 mg, 0.025 mmol) were added [bmim]BF₄ (1 mL), *p*-anisidine (68mg, 0.55 mmol), aldehyde (0.5 mmol) and ketone (1 mL) and the reaction was stirred at r.t. After completion of the reaction (as monitored by TLC), the product was isolated by extraction with Et_2O (4×5 mL). The combined ether extracts were concentrated and chromatographed to obtain the Mannich product.
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