Asian Journal of Chemistry Vol. 20, No. 7 (2008), 5203-5208

Amino Acid Catalyzed Direct Asymmetric Mannich Type Reactions Employing Unmodified Donors: Structure Based Catalyst Screening for *Anti/syn* Selectivity

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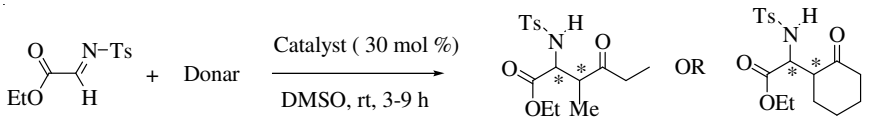
Amino acid catalyzed direct Mannich-type additions to N-Tos protected α-imino ethyl glyoxylate employing unmodified carbonyl donors is described. The reaction was performed in DMSO using a catalytic amount (30 mol %) of L-proline and its derivatives providing a facile route to functionalized β-*keto* substituted α-amino acid derivatives with excellent diastereo- and enantioselectivities. Unmodified 3-pentanone and cyclohexanone were used as donors for the one pot generation of two quaternary stereocenter. Organocatalysis using L-proline and 5,5-dimethyl thiazolidinium-4-carboxylate were typically *syn*-diastereoselective. *Anti*-diastereoselectivity was achieved using (S)-2-methoxymethyl-pyrrolidine and L-proline benzyl ester. Stereochemical outcomes are explained on the basis of previously proposed transition state and the reasons governing *syn*- and *anti*-selectivity are described. Poor selectivity of (S)-2-methoxy-methylpyrrolidine compared to L-proline benzyl ester in contrast to earlier reports are explained in terms of a fast *cis-trans* event and possible sterics.

Key Words: Amino acids, Mannich reaction, *Anti/syn* Selectivity.

INTRODUCTION

Stereoselective transformation employing asymmetric organocatalysis is a rapidly growing field[1-3]. Reactions utilizing proline as chiral enantioselective organocatalyst in catalytic amount has been the focus of great interest recently[4,5]. Organocatalytic reactions of proline and its derivatives has been well demonstrated for its versatility and potential to create both functional and structural diversity[6]. Recently, stereoselective construction of a wide variety of asymmetric carbon-carbon bond forming reactions *viz.*, aldol, Mannich, Michael, Diels-Alder, Robinson annulation and in multicomponent reactions has been successfully performed employing proline and its derivatives[7,8]. Organocatalytic Mannich reactions for the

preparation of optically active amino acids and its derivatives through asymmetric alkylation of imines are particularly attractive because of several key features although there are several complementary approaches for achieving this goal[9]. These reactions proceeds through *in situ* activation of unmodified carbonyl compounds (donor) *via* enamine generation in the presence of a organocatalyst which undergoes asymmetric additions to preformed imines. Additionally these reactions are atom economical, uses unmodified substrate, readily available and inexpensive starting materials, with appropriate reaction partners generates two quaternary stereocenter in a single step protocol, do not need rigorous exclusion of water, amenable to solid phase synthesis and high throughput screening technique (**Scheme-I**).



donor = 3-pentanone or cyclohexanone

Scheme-I: Direct asymmetric intermolecular Mannich additions of unmodified donors to tosyl imine

Direct Mannich-type additions to *p*-methoxyphenyl (PMB)-protected α-imino ethyl glyoxylate (acceptor) with carbonyl donars (*in situ* activated by way of enamine formation with the catalyst) provides a facile route to functionalized α- and β-amino acids, β-lactams and amino alcohols. These reactions are typically performed in organic solvents (*e.g.*, DMSO, DMF, or chloroform) under mild conditions. In an extention to existing protocol, amino acid catalyzed direct Mannich-type additions to N-Tos protected α-imino ethyl glyoxylate employing unmodified carbonyl donors is presented.

EXPERIMENTAL

All solutions were purified and dried in the usual way. Thin layer chromatography was performed on alumina plates coated with silica gel 60 F_{254} (E. Merck), with visualization by treatment with a solution of 1 % anisaldehyde/acetic acid and 10 % sulphuric acid and heating at 150 ºC or with iodine chamber. Flash chromatography was carried out with silica gel 60 (E. Merck, 40-63 μm). Optical rotations were determined at room temperature with a Perkin Elmer P 241 polarimeter. NMR spectra were recorded with Varian Mercury 300 instruments at 300 MHz (^{1}H) and 75 MHz (^{13}C) using TMS as an internal standard. Mass spectra (MS-FAB) were recorded on a Finnigan MAT 112 S. Elemental analyses were performed with a Perkin-Elmer 2400 CHN elemental analyzer. The diastereomeric and enantiomeric ratios were determined by Chiralcel OD chiral HPLC column and

by chiral shift reagent (+)-Pr (hfc)$_3$. The title α-imino ester was synthesized by refluxing ethyl glyoxylate and N-toluenesulfonyl isocyanate in toluene by Weinreb's procedure[10,11].

General procedure for the preparation of Mannich products: To a stirred mixture of anhydrous DMSO (4 mL) and ketone donor (0.75 mm) was added α-imino ester acceptor (100 mg, 0.40 mm) followed by the catalyst (30 mol %) and the resulting mixture was stirred at room temperature for 3-9 h. The reaction mixture was treated with saturated ammonium chloride solution, the layers were separated and aqueous layer was extracted several times with ethyl acetate, dried with anhydrous $MgSO_4$ and evaporated. The pure Mannich product were obtained by flash chromatography (silica gel, mixture of hexane/ethyl acetate.

(1R,2S)-Ethyl-2-(2'-oxocyclohexyl)-2-(tosylamino)acetate[12]: White crystalline, solid m.p. 125-127 ºC; $[\alpha]_D$ = +38.5 (c = 0.050,CH_2Cl_2); ^{1}H NMR ($CDCl_3$) (**1R, 2S**): δ 7.70 (d, 2H), 7.24 (d, 2H), 5.45 (d, 1H), 3.90 (m, 1H), 3.81 (m, 2H), 3.18 (m, 1H), 2.40 (m, 3H), 1.90-2.35 (m, 5H), 1.60-1.78 (m, 3H), 1.00 (t, 3H) ppm; (**1S, 2S**): δ 7.70 (d, 2H), 7.24 (d, 2H), 5.45 (d, 1H), 3.50 (m, 1H), 2.96 (m, 1H), 2.40 (s, 3H), 1.90-2.35 (m, 5H), 1.60-1.78 (m, 3H), 1.19 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) (**1R,2S**): δ 211.0, 170.1, 143.3, 137.3, 129.4, 127.2, 61.7, 56.5, 53.4, 41.8, 30.6, 26.9, 24.6, 21.4, 13.6 ppm; (**1S,2S**): δ 209.7, 170.3, 143.5, 136.8, 129.5, 127.2, 61.6, 56.4, 55.2, 41.5, 30.7, 26.8, 24.7, 21.4, 13.9 ppm; IR (CH_2Cl_2): 3361, 1746, 1707, 1596, 1339, 1167; Anal. Calcd. (%) for $C_{17}H_{23}NO_5$: C, 57.77; H, 6.56; N, 3.97. Found C, 57.53; H, 6.61; N, 3.92.

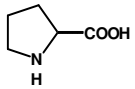
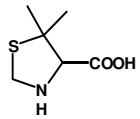
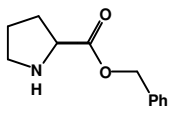
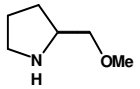
(2S,3R)-Ethyl-3-methyl-4-oxo-2-(tosylamino)hexanoate[12]: White crystalline solid m.p. 103-105 ºC; $[\alpha]_D$ = +48.3 (c = 0.035, $CDCl_3$); ^{1}H NMR ($CDCl_3$) (**2S,3R**): δ 7.68 (d,2H), 7.22 (d,2H), 5.58 (d, 1H), 3.97 (m, 1H), 3.82 (m, 2H), 3.20 (m, 1H), 2.41 (m, 2H), 2.38 (s, 3H), 1.24 (d, 3H), 0.98 (t, 6H) ppm; (**2S,3S**): δ 7.68 (d, 2H), 7.22 (d, 2H), 5.30 (d, 1H), 4.04 (m,1H), 3.90 (m, 2H), 2.92 (m, 1H), 2.42 (m, 2H), 2.39 (s, 3H), 1.20 (d, 3H), 1.03 (t, 3H), 0.98 (t, 3H), ^{13}C NMR ($CDCl_3$) (**2S,3R**): δ 212.7, 170.2, 143.3, 137.4, 129.4, 127.2, 61.7, 57.8, 48.2, 33.9, 21.4, 13.8, 13.7, 7.5 ppm; (**2S,3S**): δ 210.8, 170.3, 143.7, 136.5, 129.6, 127.3, 61.9, 57.1, 49.5, 34.2, 21.4, 13.7, 13.1, 7.4 ppm; IR (CH_2Cl_2): 3335, 2983, 1735, 1714, 1599, 1346, 1166, 1092; Anal. Calcd. (%) for $C_{16}H_{23}NO_5S$: C, 56.29; H, 6.79; N, 4.10. Found C, 56.36; H, 6.77; N, 4.12.

RESULTS AND DISCUSSION

Direct Mannich-type reactions employing N-Tos protected α-imino ethyl glyoxylate as the acceptor with unmodified carbonyl donors was perfo-rmed in DMSO using a catalytic amount (30 mol %) of L-proline and its derivatives providing a facile route to functionalized β-*keto* substituted

α-amino acid derivatives with excellent diastereo- and enantioselectivities. Since, the authros are interested in one pot generation of two quaternary stereo center therefore the selection of 3-pentanone and cyclohexanone as donors is obvious. The reaction with 3-pentanone yielded the Mannich product in high yields with excellent stereoselectivity. These reactions were typically *syn*-diastereoselective providing a practical route to quaternary product generating two new stereocenters and introducing a γ-*keto* functionality, a key fulcrum for a large variety of further chemical transformation. We have assumed the participation of stable (E)-configuration for the enamine equivalent of 3-pentanone and also for the imine (the alternate configuration in sterically unfavourable) in the transition state leading Mannich product. In contrast to 3-pentanone, the enamine formation with cyclohexanone is constrained to be E-diastereoselective due to its cyclic nature. The geometry of enamine formation however may not necessarily dictate the diastereoselectivity of the products. For both 3-pentanone and cyclohexanone, L-proline catalyzed reactions were typically *syn* diastereoselective with percent ee > 90. Compared to this catalysis by commercially available 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC, Table-1, entry 2),

TABLE-1
SCREENED CATALYST FOR THE DIRECT ASYMMETRIC INTERMOLECULAR MANNICH ADDITIONS OF SELECTED UNMODIFIED DONORS TO TOSYL IMINE: A FACILE ENTRY TO QUARTERNARY AMINO ACID DERIVATIVE

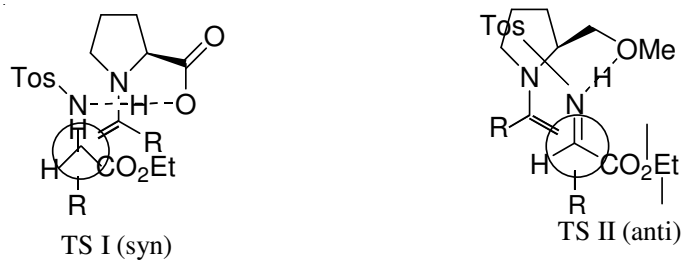
Entry	Catalyst	Donor	Time (h)	Yield (%)	De	% ee
1		Cyclohexanone	5.0	78	75:25(*syn/anti*)	91[a]
		3-pentanone	6.5	72	63:35(*syn/anti*)	93[a]
2		Cyclohexanone	4.5	83	84:16(*syn/anti*)	91[a]
		3-pentanone	3.0	84	82:18(*syn/anti*)	96[a]
3		Cyclohexanone	9.0	71	80:20(*anti/syn*)	85[b]
		3-pentanone	8.5	78	86:14(*anti/syn*)	92[b]
4		Cyclohexanone	4.5	81	68:32(*anti/syn*)	78[b]
		3-pentanone	4.5	92	73:30(*anti/syn*)	75[b]

Isolated yields after silica-gel column chromatography. De as determined by NMR analyses of crude product. [a]Determined by CHIRALCEL OD chiral-phase HPLC analyses. [b]As determined by the chiral shift reagent (+)-Pr(hfc)$_3$. NMR was in accord with the previously known report data [Ref. 8].

a promising catalyst known for enamine based Mannich reactions[13] provided the Mannich product with comparable enantioselectivity but with superior diastereoselectivity and in good yields with low reaction time. *Anti*-distereoselectivity in these reactions was achieved using (S)-2-methoxymethylpyrrolidine (SMP) and L-proline benzyl ester which are demonstrated to be *anti*-selective[14]. Reactions of SMP catalyst proceeded with a better yield with less reaction time than benzyl esters albeit with poor selectivity.

The stereochemical outcome of these reactions is readily explained on the basis of previously proposed transition state[14,15].

Attack of si-face of the imine by the enamine's si-face with a hydrogen bond from proline's carboxylate which mitigates the *cis-trans* isomerism assists in fixing the relative topicity of the attack and accounts for the formation of *syn* product (**Scheme-II**. TSI). In the SMP-catalyzed reaction a favourable coulombic interaction between ethereal oxygen and imine nitrogen results in a favourable approach between the si-face of the enamine and re-face of the imine leading to *anti*-diastereoselectivity (**Scheme-II**. TSII). Although the reaction with SMP catalyst proceeded with a better yield with less reaction time than L-proline benzyl esters the selectivity was poor. The poor selectivity was attributed to a fast *cis-trans* isomerism about the C=N bond in the imine, the poor stereodirecting coulombic interaction between ethereal oxygen and nitrogen being unable to mitigate the *cis-trans* event. L-proline benzyl ester catalyzed reaction proceeded with a compromised yield but with higher selectivity presumably due to sterics between aromatics located on both catalyst and the enamine. Higher selectivity in this reaction can be explained due to an unfavourable interaction between the closer drawn aromatic ring and the Tos group on the imine in its alternative Z-configuration which complements the stereodirecting coulombic interaction and simultaneously mitigates the *cis-trans* isomerism in the imine. In a typical experiment, a 80:20 *anti*/*syn* mixture of Mannich diastereomer was not altered when exposed to the reaction condition, indicating that the selectivity in these reactions are not the result of equilibration.



Scheme-II: Proposed transition states for syn and anti diastereoselectivity

In conclusion, a useful method for the direct enantio- and diastereoselective alkylation using unmodified donor substrates employing N-Tos protected α-imino ethyl glyoxylate as acceptor is presented. The reaction provides functionalized β-*keto* substituted quaternary α-amino acids derivatives with selected catalyst demonstrating high yields and enantioselectivity up to 92 %. The reaction simple to perform and proceeds under mild condition. Presence of a β-*keto* functionality in the quarternary Mannich product widens the scope for further modification.

ACKNOWLEDGEMENTS

Thanks are due to Head, Department of Chemistry, North Orissa University for providing necessary laboratory facilities, Indian Institute of Technology, Kharagpur and Tokushima Bunri University, Japan for obtaining spectra.

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(*Received*: 21 June 2007; *Accepted*: 15 April 2008) AJC-6522