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Enantioselective Synthesis of β-Nitroethanols Catalyzed by Pyrrolidine Based Organocatalyst *via* Henry Reaction

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Abstract: A highly enantioselective Henry reaction has been developed using a chiral pyrrolidine based organocatalyst. The catalytic loading works well with a wide range of aromatic aldehydes to afford the corresponding nitroethanols with high enantioselectivity up to 94% with excellent yields. The organocatalyst shows good enantioselectivity with 10 mol % of catalytic loading at room temperature condition.

Keywords: Henry reaction, Enantioselectivity, Organocatalysis, Nitroethanols, Asymmetric synthesis.

Introduction

The Henry reaction is an important carbon-carbon bond forming reaction,[1] which can give a new stereogenic center at the β-position of the nitro functionality. Since the resultant β-nitro alcohols are advantageous synthetic intermediate and valuable building blocks for numerous bioactive compounds,[2] therefore large effort has been focused on the improvement of the asymmetric Henry reactions. Although there were many new protocols have been documented for the asymmetric Henry reaction.[3-4] Shibasaki *et al* in 1997 reported first method for the asymmetric Henry reaction.[5] While then a range of metal based catalysts with chiral organic molecules as ligand including Cu,[6-7] Zn,[8] Mg,[9] Co,[10] Cr,[11] zeolite,[12] and organocatalyst[13] have been reported. Numerous methods for the enantioselective Henry reaction has some disadvantages, such as low temperature,[14-15] high catalyst loading[16-17]and the necessary of activation of the nitroalkane.[18] Thus, there is still need for the enhancement of an effective method for the asymmetric Henry reaction. Thus, herein we describe an efficient method for highly enantioselective Henry reaction using a chiral pyrrolidine based organocatalyst under ambient temperature *via* hydrogen-bonding interaction.

Experimental

All solvents were employed as commercial

anhydrous grade without further purification. The column chromatography was carried out over silica gel (100-120 mesh). Melting points were determined in open capillary tube and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-300 MHz spectrometer in $CDCl_3$ solvent. Mass spectra were taken on PE SCIEX, API-2000 Analyst (1.4.2). Enantiomeric purity is determined on Waters alliance 2696 separation module HPLC Systems.

General procedure for synthesis of nitroethanols *via* Henry reaction

Aromatic aldehyde (2 mmol) was added in solution of nitromethane (4 mmol) in ethyl alcohol (20 mL) with 0.10 mmol of organocatalyst (*S*)-N-(2,4-dinitrophenyl) pyrrolidine-2-carboxamide and triethylamine (0.01 mmol). The reaction mixture was stirred for appropriate time at room temperature as indicated in Table 3. The progress of reaction was monitored with thin layer chromatography. After completion of reaction as indicated by TLC, 25mL cold distilled water was added to it. This reaction mixture was then extracted with dichloromethane (15mL x 3). Solvent was removed under *vacuo,* to obtain crude product. The crude mixture was purified with silica gel column chromatography.

(*S*)-N-(2,4-Dinitrophenyl)pyrrolidine-2-carboxamide (3b): yellow solid; M. P.: 195 °c; **IR**: 835, 1517, 1629, 3108, 3336 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.21 (s, 1H), 8.19-8.29 (m, 2H), 7.70-7.73 (m, 1H), 3.55 (d, 1H), 1.91-2.13(m, 4H), 1.78 (s,1H), 1.25-1.46 (m, 2H); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 25.80, 34.83, 48.61,59.74, 118.86, 123.88, 129.88, 140.24, 142.03, 146.17, 170.5; **HPLC:** 100 % *ee*. [Determined by chiral HPLC using chiralcel OD-H, n-Hexane: Ethanol: Diethylamine (95:5:0.1), Flow rate 1.0 mL/min, ƛ = 254 nm; tR =15.31min].

2-Nitro-1-(4-nitrophenyl) ethanol (6a): IR: 860, 1521, 1556, 2852, 3444 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.04-8.31 (m, 2H), 7.39-7.51 (m, 2H), 4.85 (m, 1H),4.80 (m, 1H), 4.51 (m, 1H), 2.79 (bs, 1H, OH); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 148.22, 144.90, 127.10, 124.55, 80.61, 69.97; **MS:** *m*/*z* 211.90 (M^+) obtain; expected 212.15 (M^+); **HPLC:** 92 % *ee*. [Determined by chiral HPLC using chiral cel OD-H, n-Hexane: Ethanol: Diethylamine (95:5:0.1), Flow rate 1.0 mL/min, ƛ= 258 nm; tR (minor) = 14.7 min, tR (major) = 16.3 min].

4-(1-Hydroxy-2-nitroethyl)-2-methoxyphenol (6c): IR: 855, 1123, 1208, 1268, 1515, 3188, 3444 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 6.91-7.48 (m, 3H), 6.12 (s, 1H), 4.92 (m, 2H), 4.68 (m, 1H), 3.95 (s, 3H), 1.52 (s, 1H, OH); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 151.66, 147.14, 129.96, 127.51, 114.37, 108.79, 88.62, 73.58, 56.14; **MS:** *m*/*z* 212.92 (M^+) obtain; expected 213.06

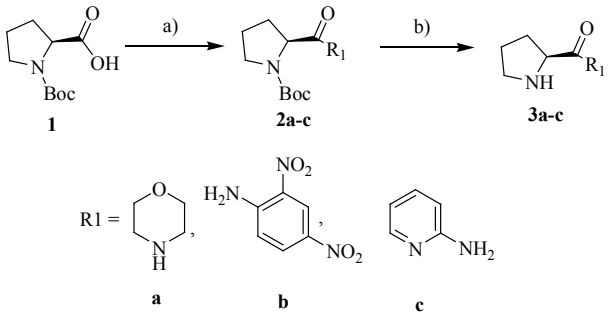
HPLC: 88 % *ee*. [Determined by chiral HPLC using chiralcel OD-H, n-Hexane:Ethanol: Diethylamine (95:5:0.1), Flow rate 1.0 mL/min, ƛ = 258 nm; tR (minor) = 14.7 min, tR (major) = 16.3 min].

Results and discussion

Catalysts (3a-3c) were prepared from the N-boc protected *L*-Proline and the corresponding amines as morpholine, 2, 4-dinitro aniline and 2-amino pyridine according to the known synthetic routes (**Scheme 1**).

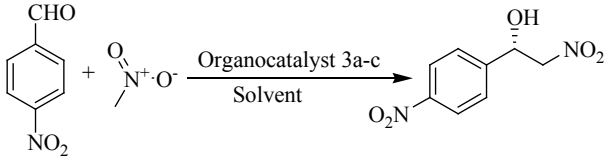
These organocatalysts were purified by column chromatography and characterized by IR, ^{1}H NMR, ^{13}C NMR, and Chiral HPLC. The procedures for preparing pyrrolidine based chiral organocatalysts 3a-c were outlined in Scheme 1. First, commercially available N-boc-*L*-Proline reacted with cyanuric chloride in ethyl acetate solvent and triethylamine as a base, at the 0 °C.

After stirring for half hour amine was added to it. The reaction mixture was left stirring for additional 60 min. The solid from the reaction mixture was then filtered and washed with small amount of ethyl acetate. The filtrate was washed with 1 x 20 ml of 1M NaOH solution and separated. Then the separated organic layer was extracted with 2 x 20 ml distilled water, organic layer separated and dried over Na_2SO_4. The obtained organic phase was evaporated on vacuo. The resulting solid was then digested in ether to get crude product. After it, the N-boc protecting group was removed to get pyrrolidine based chiral organocatalysts 3a-c.



Scheme 1. *Reagent and conditions*: (a) Cyanuric chloride, Ethyl acetate, Et_3N, R_1-NH_2, r.t.; (b) TFA, DCM, 0 °C.

Table 1: Effect of catalysts and solvents on Henry reaction[C]



Entry	Catalyst	Solvent	mol%	Time (h)	Yield[A] (%)	*ee*[B]
1	3a	DCM	10	48	42	34
2	3b	DCM	10	30	58	42
3	3c	DCM	10	36	48	40
4	3b	EtOH	10	20	70	72
5	3b	MeOH	10	24	58	48
6	3b	THF	10	36	54	52
7	3b	DCE	10	38	50	40
8	3b	EtOH	12	20	72	70
9	3b	EtOH	15	20	68	70
10	3b	EtOH	-	52	38	-

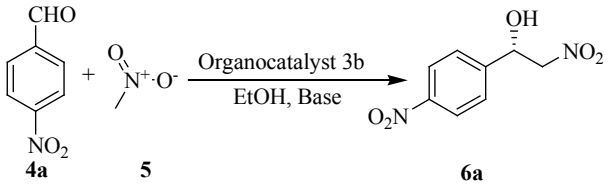
[A] Isolated yields.

[B] Determined by chiral HPLC.

[C] Progress of reaction was determined by thin layer chromatography.

The results of catalyst selection are summarized in Table 1, when compounds **3a, 3b and 3c** were used as the organocatalyst, an adequate yield for product **6a** was obtained with low enantioselectivity in solvent DCM. With the catalyst 3a, the model reaction afford 42 % yield in 48 hours with 34 % ee (Table 1, entry 1). However, organocatalyst **3b** was conspicuous in forming Henry products in good yield (58 %) in 30h with 42% ee (Table 1, entry2). Along with the organocatalyst 3c, 48% product yield was observed in 36h with 40% ee. From above observations, further optimization of solvent is done with organocatalyst 3b.The different solvents were used for optimization such as ethanol, methanol, THF and DCE. When the solvent was replaced to ethanol then enhancement in yield was observed 70% yield with72 % ee (Table 1, entry 4). However the decrease in yield and enantioselectivity was observed when reaction performed in other solvent like methanol, THF and DCE respectively (Table 1, entries 5-7 respectively). So considering ethanol as suitable solvent for the Henry reaction, the effect of catalytic amount was studied. There was no considerable effect of increase in amount of catalyst, for 12 mol% and 15 mol%, the reaction gave almost similar results as compared with 10 mol % (Table 1, entry 8-9).

Table 2: Effect of base on reaction condition [c]



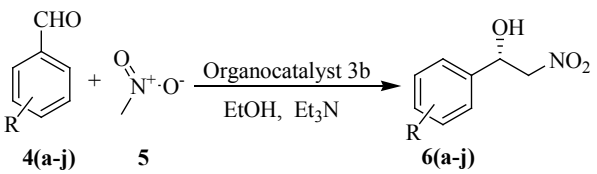
Entry	Base	mol%	Time (h)	Yield[A] (%)	*ee*[B]
1	Pyridine	5	24	56	58
2	Triethylamine	5	15	76	78
3	Piperidine	5	28	50	55
4	DMAP	5	22	60	70
5	Morpholine	5	36	55	65
6	Triethylamine	10	12	88	92
7	Triethylamine	12	12	84	90

[A] Isolated yields.

[B] Determined by chiral HPLC.

[C] Progress of reaction was determined by thin layer chromatography.

From the survey of literature it can be observed that, organic bases can affect the productivity of Henry reaction. So that assuming the above results of optimization of catalyst and solvent further study of base selection is done as show in table 2. At first Pyridine was used as base with organocatalyst 3b in ethanol, it offers 56% yield in 24h with 58% *ee* (Table 2, entry 1). While triethylamine gives affordable results that is76% yield in 15h and 78 % *ee* (Table 2, entry 2). The reaction with other bases such as piperidine, DMAP and morpholine gives lower yield as well as enantioselectivity with extended reaction time as compared to triethylamine (Table 2, entries 3-5 Vs. 2 respectively). To study the effect of base on reaction, we increased the base amount from 5 mol % to 10 mol %. The reaction shows some superior effect on the reaction. Triethyl amine with 10 mol % offered best results for the reaction. It gives 88 % product yield in reaction time 12 h with 92 % *ee* (Table 2, entry 6). Further increase in base amount up to 12 mol %, no significant change was observed in the yield and enantioselectivity (Table 2, entry 7).



4(a-j) **5** **6(a-j)**

Scheme 2

Table 3: Enantioselective Henry Reaction[c]

Entry	R	Time (h)	Product	M. P. (°c)	Yield[A] (%)	*ee*[B]
1	4- NO_2	9	6a	81-82	87	92
2	4-OH	10	6b	Yellow oil	89	87
3	3-OCH_3,4-OH	10	6c	Pale yellow oil	85	88
4	4-Cl	12	6d	Pale yellow oil	82	86
5	4-F	9	6e	Colourless oil	88	94
6	4-OCH_3	10	6f	Pale yellow oil	91	87
7	3,4-OCH_3	11	6g	Pale yellow oil	86	85
8	2-Cl	12	6h	Pale yellow oil	80	89
9	H	11	6i	Pale yellow oil	78	86
10	3-NO_2	10	6j	72-74	84	90

[A] Isolated yields.

[B] Determined by chiral HPLC.

[C] Progress of reaction was determined by thin layer chromatography.

To expand the scope of our work (Scheme 2), we studied Henry reaction using an optimized method for several aromatic aldehydes. The results are listed in Table 3, the reactions proceeded smoothly with 10 mol % of organocatalyst and afford to highly enantio-enriched adducts in good yields. The electron-deficient aromatic aldehydes showed better yield and enantioselectivity requiring less reaction time for completion. For the neutral and electron-rich aromatic aldehydes, longer reaction time was required.

Conclusion

We have developed a new facile method for asymmetric synthesis *via* the Henry reaction (nitroaldol). The reaction was studied using various organocatalysts 3a-3c. The organocatalyst (S)-N-(2,4-dinitrophenyl)

pyrrolidine-2-carboxamide (3b) proved to be the best organocatalyst in ethanol to get corresponding products with excellent yield and ee. The method was studied for a broad range of aromatic aldehydes. The yield of products for aromatic aldehydes was consistently high regardless of the type of substituent on the aromatic ring. Mild reaction conditions, eco-friendly solvent and high yields with excellent stereoselectivity with a wide range of substrates are some striking features of the reaction.

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