Research Article

Asymmetric Baylis–Hillman reaction catalyzed by pyrrolidine based organocatalyst

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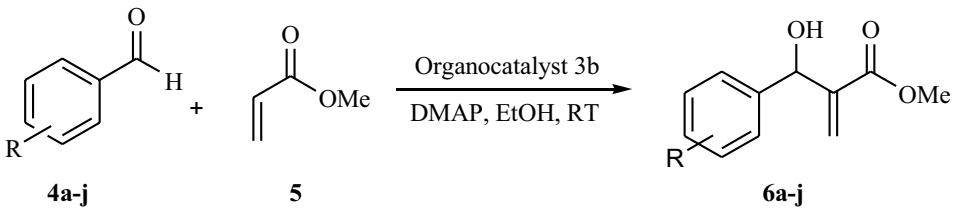
Abstract
An asymmetric Baylis–Hillman reaction protocol has been developed using a chiral pyrrolidine based organocatalyst. The catalytic loading works well with a wide range of aromatic aldehydes to afford the corresponding β-hydroxy acrylate with high enantioselectivity up to 100% with excellent yields. The organocatalyst shows excellent enantioselectivity with 10 mol% of catalytic loading at room temperature condition.

Graphic abstract



Keywords Enantioselectivity · Organocatalysis · Baylis–Hillman reaction · Asymmetric synthesis

1 Introduction

The Baylis–Hillman reaction is an important carbon–carbon bond formation process and has drawn considerable attention over the past few years [1–5]. The condensation reaction of an acrylate or otherwise activated terminal olefin with an aldehyde, provides a simple and appropriate route to a very useful class of functionalized olefins. This reaction involves three components, an activated alkene, electrophile and nucleophilic catalyst respectively. DABCO [6], DMAP [7], DBU [8], phosphines [9], chalcogen species [10] and imidazole [11] are frequently used as Lewis bases in this reaction as catalysts. Besides, Lewis acid accelerated reactions were also reported, such as $TiCl_4$ [12], Et_2AlI [13] and BF_3 [14] Not only variations of catalysts and solvent [15], but also modifications such as the use of high pressure [16], microwave [17] and ultrasound [18] have given some promising results. Conversely, the solvent also has a significant effect on the reaction rate [19] and even different salt effects [20] on the reaction rate. This prompted us to develop a new series of pyrrolidine based catalysts to replace the Lewis bases in the traditional Baylis–Hillman reaction. Thus in continuation of our work in enantioselective organocatalytic synthesis [21–23], herein we report an efficient method for highly enantioselective Baylis–Hillman reaction using a chiral pyrrolidine based organocatalyst under ambient temperature via hydrogen-bonding interaction.

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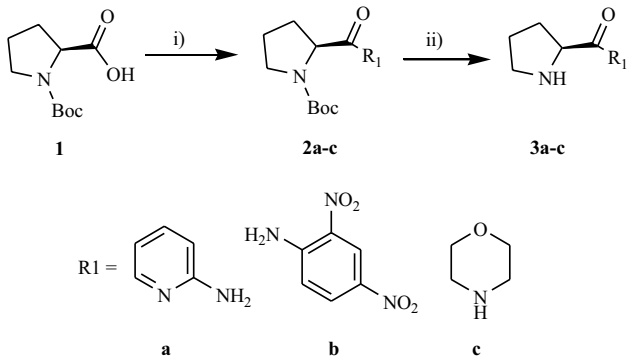
2 Results and discussion

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 ^{1}H NMR, ^{13}C NMR, mass, IR and Chiral HPLC. The procedures for preparing pyrrolidine based chiral organocatalysts **3a**–**3c** 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 × 20 ml of 1 M NaOH solution and separated. Then the separated organic layer was extracted with 2 × 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**–**3c**.



Scheme1 Reagent and conditions: (i) Cyanuric chloride, Ethyl acetate, Et_3N, R_1-NH_2, r.t.; (ii) TFA, DCM, 0 °C

In the initial studies, set of experiments were performed by the model reaction of p-nitrobenzaldehyde **4a** with methyl acrylate **5** using various solvent in the presence of organocatalysts (**3a**–**3c**) to give product methyl 2-(hydroxy(4-nitrophenyl)methyl)acrylate **6a**. The results obtained are shown in Table 1. In presence of organocatalyst **3a**, the reaction took 42 h to complete with 46% isolated yield in solvent DCM (Entry 1, Table 1). The same reaction with organocatalyst **3b** in DCM offered a yield of 62% in 30 h (Entry 2, Table 1). When the reaction was carried out in DCM in presence of organocatalyst **3c**, we obtained desired product in 36 h with 50% yield (Entry 3, Table 1). However, the affordable result was obtained when the reaction was carried out in ethanol using organocatalyst 3b; good yield of 72% was obtained with 74% ee in 16 h (Entry 4, Table 1). So further we studied with organocatalyst **3b** in different solvent such as toluene, DMF and water respectively (Entry 5–7 respectively, Table 1). From this study, we have decided to perform next optimization in solvent ethanol with organocatalyst **3b**.

Next, we studied optimization of reaction using ethanol as solvent and varying the organocatalyst amount. When the catalyst loading was raised from 12 mol% and 15 mol%, there was no significant enhancement in the results (Entry 8–9, Table 1). In absence of catalyst, the

Table 1 Effect of catalyst and solvent on Baylis–Hillman reaction

Entry	Catalyst	Solvent	mol%	Time (h)	Yield[a] (%)	*ee*[b]
1	3a	DCM	10	42	46	44
2	3b	DCM	10	30	62	59
3	3c	DCM	10	36	50	52
4	**3b**	**EtOH**	**10**	**16**	**72**	**74**
5	3b	Toluene	10	28	54	46
6	3b	DMF	10	30	48	52
7	3b	Water	10	48	42	38
8	3b	EtOH	12	18	72	64
9	3b	EtOH	15	17	68	64
10	3b	EtOH	–	48	40	–

Conditions: p-Nitrobenzaldehyde (1.0 mmol), methyl acrylate (1.2 mmol), solvent (10 ml) and organocatalyst (mol%) at RT

Bold indicates selected reaction conditions

[a]Isolated yields

[b]Determined by chiral HPLC

Table 2 The optimization of base on Baylis–Hillman reaction

Entry	Base	mol%	Time (h)	Yield[a] (%)	ee[b]
1	Pyridine	5	24	66	56
2	Triethylamine	5	22	70	78
3	Piperidine	5	26	48	52
4	DMAP	5	18	75	80
5	Morpholine	5	36	42	54
6	**DMAP**	**10**	**14**	**89**	**98**
7	DMAP	12	14	85	88

Conditions: p-Nitrobenzaldehyde (1.0 mmol), methyl acrylate (1.2 mmol), ethanol (10 ml), organocatalyst 3b (10 mol%) and base (mol%) at RT

Bold indicates selected reaction conditions

[a]Isolated yields

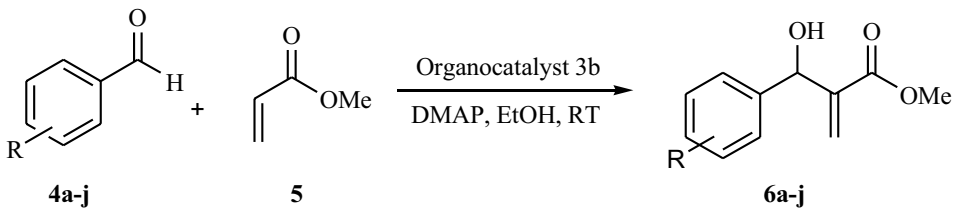
[b]Determined by chiral HPLC

reaction affording low product yield with extended reaction time (Entry 10, Table 1).

Further we studied the effect of organic bases on the reaction as shown in Table 2. The use of base, such as pyridine (5 mol%) as an additive gave the corresponding product **6a** in 66% yield in 24 h with 56% ee (Entry 1, Table 2). With base triethylamine, the reaction affords 70% yield in a 22 h and 78% ee (Entry 2, Table 2). The piperidine as the base offers 48% product yield in 26 h with 52% ee (Entry 3, Table 2). DMAP appears to be suitable base for the Baylis–Hillman reaction as the best results were obtained with this (75% yield and 80% ee), (Entry 4, Table 2). Using morpholine as a base, the reaction offered low yield with low enantioselectivity (Entry 5, Table 2). Thus, DMAP has chosen the best base for Baylis–Hillman reaction. In order to study the effect of base amount for the better productivity, we carried out there action at different mol% of DMAP. At 10 mol% of DMAP, the superior result was observed in order to yield and enantioselectivity. The reaction completed in 14 h with higher 89% yield and 98% enantioselectivity (Entry 6, Table 2). Further increase in base amount up to 12 mol%, no improvement was observed with correspond to yield and enantioselectivity (Entry 7, Table 2).

On exploring present method, the other aromatic aldehydes reacted with methyl acrylate smoothly in the presence of DMAP under the optimized conditions to give the corresponding Baylis–Hillman adducts in good to moderate yields (Scheme 2). The results are summarized in Table 3. The nature of the substituent on the phenyl ring has a profound effect. When substituent with fluoro, nitro functional group were used as the substrate, the Baylis–Hillman reaction was finished within 14–15 h, which

Scheme 2 Baylis-Hillman Reaction Catalyzed by Organocatalyst



4a-j **5** **6a-j**

Table 3 Synthesis of Baylis–Hillman adducts

Entry	R	Time (h)	Product	Yield[a] (%)	*ee*[b]	(a)$^{c}_{D}$
1	4- NO_2	14	6a	89	98	−15.8
2	4-OH	15	6b	80	100	−11.3
3	1-Naphthaldehyde	16	6c	76	88	−51.5
4	4-Cl	14.5	6d	82	86	−10.1
5	4-F	14	6e	90	96	−56.7
6	4-OCH_3	17	6f	84	87	−13.7
7	3,4-OCH_3	19	6 g	84	85	−26.2
8	3-OH	15	6 h	80	97	−49.2
9	H	18	6i	75	86	−50.4
10	3-NO_2	15	6j	87	90	−61.3

Conditions: Aromatic aldehyde (1.0 mmol), methyl acrylate (1.2 mmol), ethanol (10 ml), organocatalyst 3b (10 mol%) and DMAP (10 mol%) at RT

[a]Isolated yields

[b]Determined by chiral HPLC

should be attributed to the strong electron-withdrawing ability of functional group on phenyl ring, whereas an electron-donating substituent lowered the yield and increased the reaction time.

3 Experimental

All solvents were employed as commercial anhydrous grade without further purification. Optical rotations were measured on a Polax-2L digital polarimeter. ^{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 2996 separation module HPLC Systems.

4 General procedure for the Baylis–Hillman reaction

To the stirred mixture of aromatic aldehyde (1.0 mmol) and methyl acrylate (1.2 mmol) were added DMAP (10 mol%) and organocatalyst (10 mol%) in ethanol solvent. Initially the homogeneous reaction mixture was stirred in ice bath for 1 h. Then the reaction mixture was stirred at room temperature for appropriate time (Table 3). The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction as directed by TLC, the solvent was evaporated and dichloromethane was added. Washed with dil HCl and dried over anhydrous sodium bisulphate, filtrated, and then concentrated to vacuo. The resulting crude product was further purified by column chromatography using silica gel (mesh 80–100), and ethyl acetate and Hexane as eluent to give the pure product as Baylis–Hillman adduct.

4.1 Methyl 2-(hydroxy(4-hydroxyphenyl) methyl) acrylate (6b)

Optical rotation [α]D: − 11.3 (c 0.5, ethyl acetate); IR: 858, 1112, 1598, 1667, 2924, 3168 cm^{-1}; ^{1}H NMR (300 MHz, CDCl3): δ 7.81–7.95 (m, 2H), 6.92–7.10(m, 2H), 6.35(m, 1H), 5.90(d, 1H), 5.58 (s, 1H), 4.80 (s, 1H), 3.70 (s, 3H), 2.18 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 58.42, 77.33, 115.91, 124.34, 132.35, 138.26, 144.82, 161.13, 190.06; MS: m/z 208 expected and m/z 211.20 obtained (M–); HPLC: 100% ee. [Determined by chiral-pack OD–H (250 × 4.6 mm) 5 µm, mobile phase: n-Hexane: Ethanol: Diethylamine (95:5:0.1), Flow rate 1.0 mL/min, ƛ = 280 nm; tR (major) = 10.48 min, run time = 30 min, column temperature = Ambient].

4.2 Methyl 2-(hydroxy(3-hydroxyphenyl) methyl) acrylate (6 h)

Optical rotation [α]D: − 49.2 (c 0.5, ethyl acetate); IR: 783, 1152, 1580, 1668, 2956, 3211 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20–7.75 (m, 4H), 6.43(m, 1H), 5.79(m, 1H), 5.35 (s, 1H), 4.92 (s, 1H), 3.89 (s, 3H, OCH_3), 2.32(s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 56.21, 76.70, 110.24, 114.76, 121.89, 123.39, 130.39, 137.95, 145.28, 156.31, 192.66; MS: m/z 208.16 expected and m/z 209.90 obtained (M–); HPLC: 100% ee. [Determined by chiral-pack OD–H (250 × 4.6 mm) 5 µm, mobile phase: n-Hexane: Ethanol: Diethylamine (95:5:0.1), Flow rate 1.0 mL/min, ƛ = 280 nm; tR (major) = 10.48 min, run time = 30 min, column temperature = Ambient].

5 Conclusion

We have developed a new facile method for asymmetric synthesis via the Baylis–Hillman reaction. 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 with excellent ee. The method was studied for a broad range of aromatic aldehydes. The yields of products for aromatic aldehydes were consistently high regardless of the type of substituent on the aromatic ring. Mild reaction conditions and high yields with excellent stereoselectivity with a wide range of substrates are some striking features of the reaction.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Basavaiah D, Reddy BS, Badsara SS (2010) Recent contributions from the Baylis–Hillman reaction to organic chemistry. Chem Rev 29:5447
2. Pellissier H (2017) Recent developments in the asymmetric organocatalytic Morita–Baylis–Hillman reaction. Tetrahedron 73:2831
3. Ma GN, Jiang J-J, Shi M, Wei Y (2009) Recent extensions of the Morita–Baylis–Hillman reaction. Chem. Commun. 37:5496

4. Basavaiah D, Veeraraghavaiah G (2012) The Baylis–Hillman reaction: a novel concept for creativity in chemistry. Chem Soc Rev 41:68
5. Singh V, Batra S (2008) Advances in the Baylis-Hillman reaction-assisted synthesis of cyclic frameworks. Tetrahedron 64:4511
6. Yu C, Hu L (2002) Successful Baylis–Hillman reaction of acrylamide with aromatic aldehydes. J Org Chem 67:219
7. Sohtome Y, Tanatani A, Hashimoto Y, Nagasawa K (2004) Development of bis-thiourea-type organocatalyst for asymmetric Baylis–Hillman reaction. Tetrahedron Lett 45:5589
8. Ballini R, Barboni L, Bosica G, Fiorini D, Mignini E, Palmieri A (2004) Fast diastereoselective Baylis–Hillman reaction by nitroalkenes: synthesis of di-and triene derivatives. Tetrahedron 60:4995
9. Hayase T, Shibata T, Soai K, Wakasuki Y (1998) Catalytic Asymmetric Baylis–Hillman Reactions and Surroundings. Chem Commun 2533–2534
10. Yu C, Liu B, Hu L (2001) Efficient Baylis–Hillman reaction using stoichiometric base catalyst and an aqueous medium. J Org Chem 66:5413
11. Luo S, Zhang B, He J, Janczuk A, Wang PG, Cheng J (2002) Aqueous Baylis-Hillman reactions of cyclopent-2-enone using imidazole as catalyst. Tetrahedron Lett 43:7369
12. Patra A, Batra S, Joshi BS, Roy R, Kundu B, Bhaduri AP (2002) TiCl4-Promoted Baylis–Hillman Reactions of Substituted 5-Isoxazolecarboxaldehydes with Cycloalkenones1. J Org Chem 67:5783
13. Pei W, Wei H, Li G (2002) The Baylis–Hillman condensation of α, β-conjugate cycloketones with aldehydes using diethylaluminum iodide alone as the promoter. Chem Commun 20:2412
14. Kinoshita H, Osamura T, Kinoshita S, Iwamura T, Watanabe S, Kataoka T, Tanabe G, Muraoka O (2003) Chalcogeno–Morita–Baylis–Hillman reaction of enones with acetals: simple α-alkoxyalkylation of enones. J Org Chem 68:7532
15. Luo S, Mi X, Wang PG, Cheng JP (2004) The azoles: effective catalysts for Baylis-Hillman reaction in basic water solution. Tetrahedron Lett 45:5171
16. Hayashi Y, Okado K, Ashimine I, Shoji M (2002) The Baylis–Hillman reaction under high pressure induced by water-freezing. Tetrahedron Lett 43:8683
17. Kundu MK, Mukherjee SB, Balu N, Padmakumar R, Bhat SV (1994) Synlett 444
18. Coelho F, Almeida WP, Veronese D, Mateus CR, Silva Lopes EC, Rossi RC, Silveira GPC, Pavam CH (2002) Ultrasound in Baylis–Hillman reactions with aliphatic and aromatic aldehydes: scope and limitations. Tetrahedron 58:7437
19. Luo S, Wang PG, Cheng J (2004) Remarkable rate acceleration of imidazole-promoted Baylis–Hillman reaction involving cyclic enones in basic water solution. J Org Chem 69:555
20. Kumar A, Pawar SS (2003) Salt effects on the Baylis–Hillman reaction. Tetrahedron 59:5019
21. Thorat PB, Goswami SV, Khade BC, Bhusare SR (2012) Organocatalyzed Baylis–Hillman reaction: an enantioselective approach. Tetrahedron Asymmetry 23:1320
22. Thorat PB, Goswami SV, Khade BC, Bhusare SR (2012) Synthesis and application of proline based organocatalyst for highly enantioselective aldol reaction by hydrogen bonding. Tetrahedron Lett. 53:6083
23. Pendalwar SS, Chakrawar AV, Bhusare SR (2018) Enantioselective organocatalytic synthesis of the chiral chromenes by domino oxa-Michael-aldol reaction. Chin Chem Lett 29:942