The Chiral Diamine Mediated Asymmetric Baylis–Hillman Reaction

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Abstract: A chiral diamine, easily prepared from proline, is an effective, asymmetric organic catalyst for the Baylis–Hillman reaction of aldehydes and methyl vinyl ketone, affording adducts with enantioselectivities up to 75%.

Keywords: asymmetric synthesis; Baylis–Hillman reaction; diamines; enones; Lewis base catalysts; organic catalysis

The Baylis–Hillman reaction is a synthetically useful method for the preparation of β-hydroxy-α-methylene carbonyl compounds in one-step from electrophilic alkenes and carbonyl compounds by using a tertiary amine or tertiary phosphine as an organic catalyst.[1] As chiral β-hydroxy-α-methylene carbonyl compounds are useful intermediates in natural product synthesis, several enantioselective versions of this reaction involving chiral catalysts have been developed. For the Baylis–Hillman reaction of acrylate esters as electrophilic alkenes,[2,3] excellent enantioselectivities of up to 99% ee have been attained using β-isocupreidine (β-ICD) by Hatakeyama.[2] For the asymmetric Baylis–Hillman reaction of α,β-unsaturated ketones as electrophilic alkenes, however, although there were several precedents until recently, the enantioselectivity achieved has been moderate: Hirama[4] and Marko[5] developed chiral DABCO-type and quinidine- or cinchonine-based catalysts, respectively, which afforded modest enantioselectivities (47% ee, 45% ee) under high pressure conditions. The combination of a chiral calcium catalyst and tributylphosphine developed by Ikegami gave moderate enantioselectivity (56% ee) in the reaction of cyclopentenone.[6] Good enantioselectivity (72% ee) has been attained using a chiral pyrrolizidine catalyst developed by Barrett.[7] The combination of a chiral sulfide with $TiCl_4$ promoted the Baylis–Hillman reaction of 3-phenylpropanal, affording the product in 74% ee, though an equimolar amount of the chiral sulfide had to be employed.[8] Just recently, Miller et al. have reported a dual catalyst composed of a nucleophile-loaded peptide and proline, which affords the product in up to 81% ee,[9] while Schaus reported that the combined use of chiral BINOL derivatives with PEt_3 realized enantioselectivities of up to 96% in the reaction of aldehydes and cyclohexenone.[10]

The generally accepted concept used in designing effective catalysts for the Baylis–Hillman reaction is that they should possess both a nucleophilic moiety and an acidic part,[2,5,7] or that two molecules, one acting as a nucleophile and the other as an acid, should be employed.[3b,6,8–10] Marko[5] reported that a hydroxy group suitably positioned on an amine catalyst exerts a marked effect on rate acceleration as well as improving asymmetric induction by stabilizing the oxyanion intermediate through hydrogen bonding.

Chiral diamines have been developed by Mukaiyama et al. as effective ligands with various uses as asymmetric catalysts;[11] such compounds are also excellent organic catalysts for the kinetic optical resolution of alcohols as developed by Oriyama et al.[12] In our continuing investigation of asymmetric reactions using organic catalysts,[13] we have discovered that a chiral diamine can promote the Baylis–Hillman reaction enantioselectively, even though the catalyst does not possess an acidic moiety, as disclosed in this communication.

The reaction of *p*-nitrobenzaldehyde and methyl vinyl ketone (MVK) was selected as a model. The reaction was carried out in the presence of (*S*)-1-methyl-2-(1-pyrrolidinylmethyl)-pyrrolidine (**1**)[14] as organic catalyst and using *i*-PrOH as solvent at room temperature, affording the Baylis–Hillman adduct in 28% yield with 54% ee. As moderate enantioselectivity was attained in spite of the low yield, the reaction conditions were investigated further. First, the diamine was examined. Because of their ready preparation, we focused on pyrrolidine-based diamines, the effects of which on the yield and the enantioselectivity are summarized in Table 1. It was found that the diamine's structure affects both reactivity and enantioselectivity a great deal, and the following features were observed: 1) The substituent on the nitrogen of the pyrrolidine derived from proline is very important. Moderate enantioselectivity with low yield (28%, 54% ee) was obtained with *N*-methyldiamine **1**, while moderate yield and low enantioselectiv-

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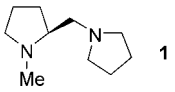
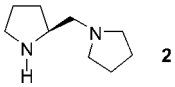
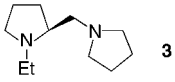
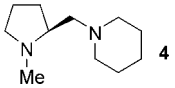
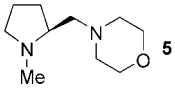
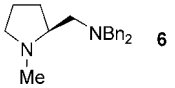
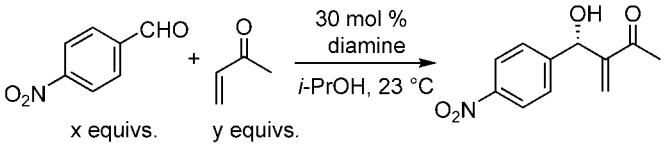
Table 1. Effect of diamine on the enantioselectivity of the Baylis–Hillman reaction.[a]

Entry	Diamine	Yield [%][b]	Optical Yield [% ee][c]
1	 **1**	28	54 (*S*)
2	 **2**	61	4 (*S*)
3	 **3**	6	43 (*S*)
4	 **4**	30	7 (*S*)
5	 **5**	5	3 (*R*)
6	 **6**	5	5 (*R*)

[a] The reaction conditions; *p*-nitrobenzaldehyde:MVK: diamine = 1.2 : 1.0 : 0.3, solvent: *i*-PrOH, temperature: 23 °C.
[b] Yield of isolated product.
[c] Determined by HPLC using a Chiralcel OD-H column.



Scheme 1. The chiral diamine-mediated asymmetric Baylis–Hillman reaction.

ity were observed with *N*-H diamine **2**, and the reaction scarcely proceeded with the corresponding *N*-ethyldiamine **3**. 2) The amine moiety not derived from proline is also very important. Minor changes in this amine moiety also affect the reactivity and enantioselectivity a great deal. The enantioselectivity with piperidine catalyst **4** is lower than that with pyrrolidine catalyst **1** in spite of their having the same reactivity, while the catalysts containing a morpholine **5** or dibenzylamine group **6** hardly promote the reaction at all. As the diamine **1** was found to be the best catalyst examined, further investigations were performed using it as the organic catalyst.

Next, the solvent was examined with the results summarized in Table 2. While the reaction is slow in DMF, DMSO, toluene and CH_2Cl_2, affording the product in low yield, the reaction is fast in hexane, CH_3CN and

Table 2. Solvent effects for the Baylis–Hillman reaction between *p*-nitrobenzaldehyde and methyl vinyl ketone.[a]

Entry	Solvent	Yield [%][b]	Optical Yield [% ee][c]
1	DMF	6	5
2	DMSO	10	2
3	toluene	7	7
4	CH_2Cl_2	8	5
5	hexane	44	33
6	CH_3CN	46	40
7	MeOH	12	29
8	EtOH	51	62
9	*i*-PrOH	28	54
10	*n*-PrOH	46	61
11	*t*-BuOH	14	21
12	CF_3CH_2OH	17	8

[a] The reaction conditions; *p*-nitrobenzaldehyde:MVK:diamine **1** = 1.2 : 1.0 : 0.3, 23 °C.
[b] Yield of isolated product.
[c] Determined by HPLC using a Chiralcel OD-H column.

Table 3. Effects of molar ratio of the reagents and temperature for the Baylis–Hillman reaction between *p*-nitrobenzaldehyde and methyl vinyl ketone.[a]

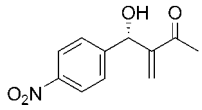
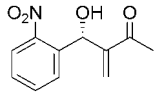
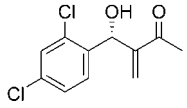
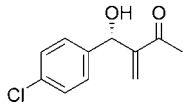
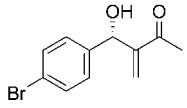
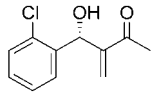
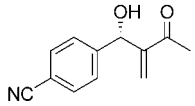
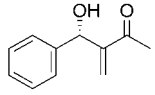
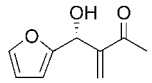
Entry	X [equivs.][b]	Y [equivs.][c]	Temp. [°C]	Yield [%][d]	Optical Yield [% ee][e]
1	5	1	23	82	57
2	3	1	23	72	59
3	1	1.2	23	51	62
4	1	1.2	0	31	64
5	1	1.2	−20	12	65
6	1	1.2	−40	2	68
7	1	3	23	62	58
8	1	5	23	71	63
9	1	5	0	70	65

[a] The reaction was performed in EtOH for 48 h in the presence of 30 mol % of the diamine **1**.
[b] Equivalents of *p*-nitrobenzaldehyde.
[c] Equivalents of methyl vinyl ketone.
[d] Yield of isolated product.
[e] Determined by HPLC using a Chiralcel OD-H column.

protic solvents. As protic solvents gave promising results, alcoholic solvents have been investigated in detail: The yield in MeOH was low, because 4-hydroxy-3-methoxymethyl-4-(*p*-nitrophenyl)-2-butanone, the Michael adduct of MeOH with the desired Baylis–Hillman product, was obtained in substantial amounts. *t*-BuOH and acidic alcohols such as CF_3CH_2OH gave low yields of the product. EtOH, however, gave good results, affording the Baylis–Hillman product in moderate yield and enantioselectivity (51%, 62% ee).

In order to increase the yield and enantioselectivity, further optimization of the reaction conditions such as

Table 4. The asymmetric Baylis–Hillman reaction of various aldehydes.[a]

Entry	Aldehyde	Product	Time [d]	Yield [%][b]	Optical Yield [% ee]
1	*p*-nitrobenzaldehyde		2	70	65[f]
2	*o*-nitrobenzaldehyde		4	40	68[f]
3	2,4-dichlorobenzaldehyde		3	72	75[f]
4[c]	*p*-chlorobenzaldehyde		4	78	70[f]
5			4	72	64[f]
6[d]			6	67	46[f]
7	*p*-bromobenzaldehyde		4	67	69[f]
8	*o*-chlorobenzaldehyde		4	96	45[g]
9	*p*-cyanobenzaldehyde		4	71	61[h]
10[e]	benzaldehyde		6	70	49[g]
11	furylaldehyde		5	64	44[f]

[a] Unless otherwise shown, reactions were conducted with 30 mol % of the diamine **1**, 1.0 equiv. of aldehyde, and 5.0 equivs. of methyl vinyl ketone in EtOH at 0 °C.
[b] Yield of isolated product.
[c] The diamine **1** was used in 60 mol %.
[d] The diamine **1** was used in 10 mol %.
[e] The reaction was performed at 23 °C.
[f] Determined by HPLC using a Chiralcel OD-H column.
[g] Determined by HPLC using a Chiralpak AD-H column.
[h] Determined by HPLC using a Chiralpak AD-H column after conversion of the vinylidene species to the corresponding epoxide.

molar ratio of aldehyde, methyl vinyl ketone and diamine **1**, and reaction temperature has been performed with the results summarized in Table 3. A good yield was obtained when excess aldehyde or methyl vinyl ketone was employed (entries 1–3, 7, 8). When the reaction was performed at lower temperature, the optical purity was increased with a decrease in the yield (entries 3–6). Because of the low cost and the easy removal under reduced pressure of methyl vinyl ketone, the generality of the reaction was investigated using 5 equivalents of methyl vinyl ketone at lower temperature (0 °C) in EtOH (entry 9) with the results summarized in Table 4.

Not only *p*-nitrobenzaldehyde, but also the reactive *o*-nitrobenzaldehyde and 2,4-dichlorobenzaldehyde reacted at 0 °C, affording the Baylis-Hillman adducts in 40% and 72% yield with 68% ee and 75% ee, respectively (entries 2 and 3). *p*-Chlorobenzaldehyde and *p*-bromobenzaldehyde gave the Baylis–Hillman products in good yield with good enantioselectivity (entries 4–7), while lower enantioselectivity and good yield was ob-

tained in the reaction of *o*-chlorobenzaldehyde (entry 8). Not only electron-deficient aldehydes, but also benzaldehyde and a heteroaromatic aldehyde, such as furylaldehyde, gave the Baylis–Hillman product in reasonable yield with moderate enantioselectivity (entries 10 and 11). Good enantioselectivity (70% ee) was attained when 60 mol % of diamine was employed, while a decrease in enantioselectivity (46% ee) was observed in the presence of only 10 mol % of the catalyst (entries 4 and 6). The reaction scarcely proceeded, affording the Baylis–Hillman adducts in less than 5% yield under the same reaction conditions when electron-rich aromatic aldehydes such as *p*-anisaldehyde and aliphatic aldehydes such as cyclohexanecarbaldehyde were employed.

The absolute configuration of the Baylis–Hillman adducts derived from *p*-nitrobenzaldehyde,[4] *o*-nitrobenzaldehyde,[9] and furylaldehyde[9] was determined by comparison of the optical rotations with those reported in the literature.

In summary, we have found that the diamine **1** can promote the Baylis–Hillman reaction of methyl vinyl ketone and various aldehydes, affording adducts in good yield with moderate to good enantioselectivity (up to 75% ee). As described above, most of the amine catalysts for the asymmetric Baylis–Hillman reaction possess two functionalities, a basic amine part such as a nucleophilic amine, and an acidic part such as a hydroxy or phenoxy group. The present reaction is the first demonstration that a chiral diamine possessing two basic amine moieties without an acidic part can promote the Baylis–Hillman reaction enantioselectively. Although more experimentation is needed to clarify the reaction mechanism, including the role of the two amine moieties, and there is room for improvement in the enantioselectivity, the finding that not only amino alcohols but also diamines can promote the Baylis–Hillman reaction opens the way for the design of new asymmetric organic catalysts for this reaction.

Experimental Section

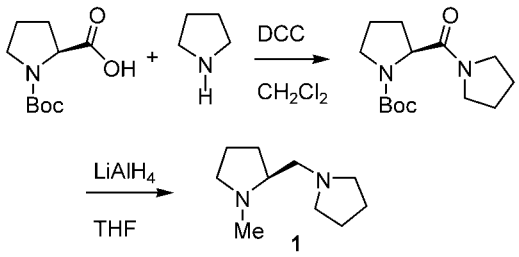
Typical Experimental Procedure (Table 4, entry 1)

To an ethanol solution (0.45 mL) of *p*-nitrobenzaldehyde (75.6 mg, 0.5 mmol) and methyl vinyl ketone (204 μL, 2.5 mmol) was added (*S*)-1-methyl-2-(1-pyrrolidinylmethyl)-pyrrolidine (**1**; 25.2 mg, 0.15 mmol) at 0 °C, and the reaction mixture was stirred for 2 days at this temperature. After removal of the volatile materials under reduced pressure, the residue was purified by thin-layer chromatography to afford the Baylis–Hillman adduct in a yield of 77.6 mg (70%) with 65% ee, as determined by HPLC analysis on a chiral stationary phase;[15] $[\alpha]_D^{26}$: +4.8 (*c* 1.7, $CHCl_3$), 65% ee.[4,9]

Synthesis of (*S*)-1-Methyl-2-(1-pyrrolidinylmethyl)-pyrrolidine (1)[14]

To a CH_2Cl_2 suspension (30 mL) of (*S*)-Boc-proline (21.5 g, 100 mmol) was added a CH_2Cl_2 solution (60 mL) of DCC (20.6 g, 100 mmol) at 0 °C under an argon atmosphere and the reaction mixture was stirred for 30 minutes at that temperature. To this reaction mixture was added a CH_2Cl_2 solution (40 mL) of pyrrolidine (8.35 mL, 100 mmol) slowly at 0 °C, and the reaction temperature was increased to room temperature after 15 minutes. After 12 h, volatile materials were removed under reduced pressure, and ethyl acetate (100 mL) was added to the residue. After insoluble materials had been removed by filtration, the filtrate was washed with 1 N HCl (20 mL), saturated $NaHCO_3$ solution (20 mL) and brine successively, before drying over anhydrous Na_2SO_4. After removal of the volatile materials under reduced pressure, the residue was purified by silica gel column chromatography ($CHCl_3$:AcOEt = 10:0 to 5:1) to afford the amide; yield: 21.7 g (81%).

To a THF suspension (73 mL) of $LiAlH_4$ (7.0 g, 183 mmol) was added a THF solution (73 mL) of the amide (19.7 g, 73 mmol) at 0 °C and the temperature of the reaction mixture was raised to room temperature gradually. After refluxing the reaction mixture for 4 h, saturated Na_2SO_4 solution was added to the reaction mixture at 0 °C until the evolution of H_2 ceased. After filtration of the inorganic materials, volatile materials were removed under reduced pressure and the residue was purified by column chromatography using Al_2O_3 (hexane:AcOEt = 6:1) followed by distillation to afford the diamine **1**; yield: 15.0 g (80%); bp 74 °C/6 mmHg.



Scheme 2. Synthesis of the diamine **1**.

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[15] HPLC conditions: Chiralcel OD-H column, hexane:*i*-PrOH 20:1, 1.0 mL min^{-1}, retention times: 21.6 min (minor) and 23.7 min (major).

