An enantioselective Baylis–Hillman reaction catalyzed by chiral phosphines under atmospheric pressure

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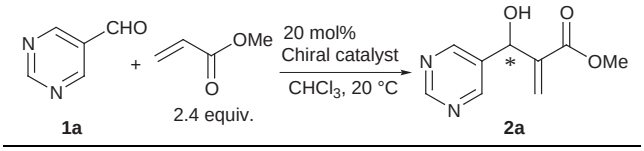
2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) catalyzes the enantioselective Baylis–Hillman reaction between pyrimidine- 5-carbaldehydes and acrylates to provide chiral α-methylene β-hydroxy esters in up to 44% ee under atmospheric pressure.

The condensation of an aldehyde and acrylate is known as the Baylis–Hillman reaction, and increasing interest has been focused on this reaction.[1] It affords α-methylene β-hydroxy esters, which are furnished with functional groups for further transformations.[2] Therefore the development of an enantioselective Baylis–Hillman reaction would provide a useful synthetic tool for the preparation of chiral polyfunctionalized compounds. However, only very limited examples have been reported, such as an enantioselective Baylis–Hillman reaction between nitrobenzaldehyde[3] or aliphatic aldehydes[4] and methyl vinyl ketone catalyzed by chiral tertiary amines. Moreover, very high pressure is required to afford adducts with low to moderate enantiomeric excess (ee). Thus, exploration of enantioselective Baylis–Hillman reactions is a challenging problem.[5]

Here we report the first example, to the best of our knowledge, of a chiral phosphine-catalyzed intermolecular enantioselective Baylis–Hillman reaction under atmospheric pressure.[6,7]

In the presence of a catalytic amount (20 mol%) of various chiral phosphines, the enantioselective Baylis–Hillman reaction of pyrimidine-5-carbaldehyde **1a** with methyl acrylate was examined at 20 °C in $CHCl_3$ (Table 1, entries 1–6). By the use of bidentate chiral phosphines (DIOP, NORPHOS), a chiral phosphine possessing a hydroxy group (BPPFOH) or an axially chiral monodentate phosphine (MOP), Baylis–Hillman adduct **2a** was obtained; however, almost no or only slight asymmetric induction was observed (entries 1–4). On the other hand, we found that (*S*)-BINAP,[8] an axially chiral bidentate phosphine, catalyzes the enantioselective reaction to give chiral (−)-α-methylene β-hydroxy ester **2a** in 44% ee (entry 5). Adduct (+)-**2a** with 43% ee was obtained by the use of (*R*)-BINAP. These enantioselectivities are comparable with those of the reported enantioselective methods using chiral tertiary amines under high pressures.[3,4] (*S*)-Tol-BINAP is also an effective asymmetric catalyst and **2a** was provided in improved yield along with slightly decreased ee (entry 6).

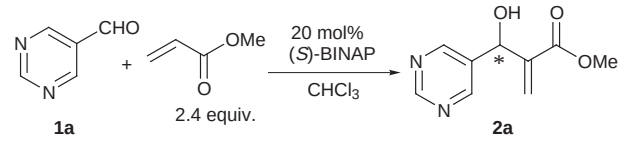
Table 1 Chiral phosphine-catalyzed Baylis–Hillman reaction



Entry	Chiral catalyst	*t*/h	Yield (%)	Ee (%)[a]
1	(2*R*,3*R*)-DIOP[b]	19	28	< 1
2	(2*R*,3*R*)-NORPHOS[c]	21	32	3
3	(*R*,*S*)-BPPFOH[d]	20	46	2
4	(*S*)-MOP[e]	66	53	< 1
5	(*S*)-BINAP	85	24	44
6	(*S*)-Tol-BINAP[f]	89	41	31

[a] Determined by HPLC analyses using a chiral column. [b] DIOP = 2,3-*O*-isopropylidine-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane. [c] NORPHOS = 2,3-bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene. [d] BPPFOH = (*R*)-1-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethanol. [e] MOP = 2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl. [f] Tol-BINAP = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl.

Table 2 Effect of reaction temperature



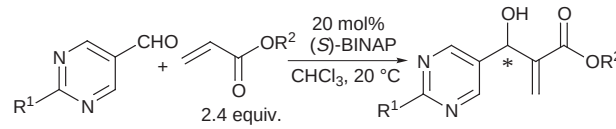
Entry	*T*/°C	*t*/h	Yield (%)	Ee (%)[a]
1	0	127	18	43
2	20	85	24	44
3	50	38	49	42
4	70	19	38	41

[a] Determined by HPLC analyses using a chiral column.

Next, the BINAP-catalyzed Baylis–Hillman reaction was performed at various temperatures (Table 2). In this reaction, the temperature did not significantly affect the enantioselectivities, however, **2a** was obtained in the highest yield (49%) at 50 °C (entry 3).‡

Various acrylates were submitted to this enantioselective Baylis–Hillman reaction (Table 3, entries 1–3). The yield and ee were dependent on the bulk of the acrylate: the less bulky acrylate gave the higher yield and ee. 2-Methylpyrimidine-5-carbaldehyde **1b** also reacts with methyl acrylate in the presence of BINAP. The reaction proceeded slowly but adduct

Table 3 Reaction of aldehydes **1a,b** with various active olefins



Entry	R^1	R^2	*t*/h	Yield (%)	Ee (%)[a]
1	H	Pr^i	95	8	9
2	H	Et	62	12	25
3	H	Me	85	24	44
4	Me	Me	329	18	37
5[b]	Me	Me	62	26	30

[a] Determined by HPLC analyses using a chiral column. [b] Tol-BINAP was used as a chiral catalyst.

2b was obtained in moderate ee (entry 4). Acceleration of the reaction was observed by the use of Tol-BINAP, and **2b** was provided in higher yield but with lower ee (entry 5).

As described, the present chiral phosphine-catalyzed reaction would provide a new method for enantioselective Baylis–Hillman reaction under atmospheric pressure.

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Notes and References

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‡ *General experimental procedure* (Table 2, entry 3): To a $CHCl_3$ solution (1.0 ml) of (*S*)-BINAP (62.3 mg) and pyrimidine-5-carbaldehyde **1a** (54.4 mg) was added methyl acrylate (0.11 ml) at ambient temperature. The reaction mixture was stirred for 38 h at 50 °C, then it was evaporated to dryness under reduced pressure. Purification of the crude product by TLC gave pure Baylis–Hillman adduct (–)-**2a** (47.8 mg, 49%). The ee was determined to be 42% by HPLC analysis (chiral column: Daicel Chiralcel OD-H, eluent: 3% Pr^iOH in hexane, flow rate: 1.0 ml min^{-1}, wavelength for UV detector: 254 nm, retention time: 36 min for the major isomer and 41 min for the minor isomer).

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