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Efficient Baylis–Hillman reactions promoted by mild cooperative catalysts and their application to catalytic asymmetric synthesis

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Abstract

Baylis–Hillman reactions were promoted by mild cooperative catalysts of tributylphosphine with phenols such as (±)-1,1′-bi-2-naphthol (BINOL) in THF to give α-methylene-β-hydroxyalkanones in high yield. The reactions proceeded much faster in the presence of 1,1′-bi-2-naphthol than in its absence. The ^{1}H NMR studies suggested that 1,1′-bi-2-naphthol functions as a Brønsted acid to activate the carbonyl group of an aldehyde and a polarized alkene. Application of the reactions to catalytic asymmetric synthesis was examined by using cooperative catalysts of tributylphosphine with the calcium chiral catalyst to give the desired product with fairly good % ee in fairly good yield.

The Baylis–Hillman reaction, the coupling of a polarized alkene with an aldehyde catalyzed by a rather strong base, 1,4-diazabicyclo[2,2,2]octane (DABCO), is an important carbon–carbon bond-forming reaction, which serves as the key step for the synthesis of several biologically active substances.[1] However, since long-sustained reaction time, at least 1 week (sometimes 1 month), for completing the Baylis–Hillman reaction is common due to the low reaction rate,[1] the development of an efficient Baylis–Hillman reaction is among the most challenging themes in organic synthesis.

A mechanism of this reaction is as follows (Scheme 1): A conjugated addition of a Lewis base (**I**) to a polarized alkene (**III**) affords an enolate (**IV**), which reacts with an aldehyde (**V**) to give an aldol-type intermediate (**VI**) followed by β-elimination with a Lewis base (**I**) to yield an α-methylene-β-hydroxyalkanone (**VII**). It is well-known that the rate-determining step is the addition stage of **IV** to **V**.[2] Therefore, we envisioned that a *mild* Brønsted acid as a co-catalyst (**II**) would activate the carbonyl groups of an enolate (**IV**) and an aldehyde (**V**) to accelerate the reaction rate, affording a Baylis–Hillman product in high yield as shown in Scheme 1.[3] Recently, Hatakeyama et al. reported excellent asymmetric Baylis–Hillman reactions catalyzed by a amine possessing a phenolic hydroxy group derived from a *cinchona* alkaloid which stabilized **VI** and facilitated the enantioselective reactions.[4] Unfortunately, the phenolic proton of the catalyst did not accelerate the reactions in this system. Herein, we would like

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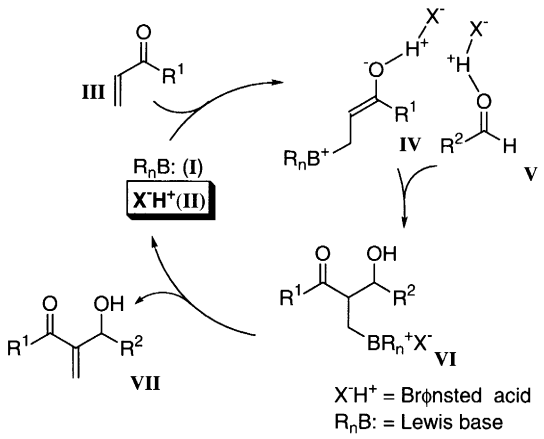
to report remarkable acceleration of Baylis–Hillman reactions catalyzed by *mild* cooperative catalysts consisting of tributylphosphine as a mild Lewis base and *phenols* or *naphthols* as a mild Brønsted acid.



Scheme 1. Mechanism of the Baylis–Hillman reaction

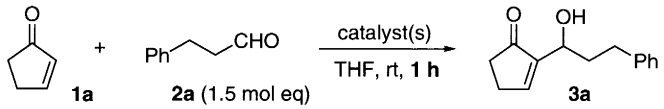
Predictably, when the reaction of 2-cyclopenten-1-one (**1a**) with 3-phenyl-1-propanal (**2a**) was carried out in the presence of 20 mol% of DABCO in THF for 1 h, no products were obtained (Table 1, entry 1). The reaction catalyzed by 20 mol% of tributylphosphine (**4**)[3a,5] proceeded to give the corresponding Baylis–Hillman product, albeit in only 23% yield (entry 2). However, we were pleased to find that the reaction catalyzed by 20 mol% of **4** in the presence of 10 mol% of a *mild* Brønsted acid, 1,1′-bi-2-naphthol (BINOL) (**5**), as a co-catalyst in THF for 1 h proceeded smoothly to give the desired product **3a** in quantitative yield (entry 6), while the reaction catalyzed by methanol, benzoic acid or *p*-toluenesulfonic acid as the Brønsted acid did not proceed efficiently (entries 3–5). The reaction catalyzed by 20 mol% of 2-naphthol, 10 mol% of 2-hydroxy-2′-methoxy-1,1′-binaphthyl (**6**) and 10 mol% of 2,2′-dimethoxy-1,1′-binaphthyl (**7**) gave **3a** in quantitative yield, 80% and 24%, respectively (entries 7–9), indicating that both of the two protons of **5** work as Brønsted acids to accelerate the Baylis–Hillman reaction. The use of DABCO,[6] triphenylphosphine or dibutyl sulfide as Lewis bases was not effective and afforded no products (entries 10–12). Phenol and *p*-toluenesulfonamide, which has the same Brønsted acidity as phenol, were effective (entries 13 and 14).[7]

Following on from these results, we turned our attention to broadening the range of substrates (Table 2). The reaction of **1a** with octanal (**2b**) in THF gave the desired product **3b** in quantitative yield (entry 1). An aromatic aldehyde (benzaldehyde (**2c**)) also reacted with **1a** and **1b** to give **3c** and **3g** in 92% and 57% yields, respectively (entries 2 and 6).[7] Moreover, the (2-methoxyethoxy)methyl (MEM) group, which is often deprotected by Lewis acids such as $ZnBr_2$ and $TiCl_4$,[8] was intact under these mild conditions, so that the reaction of **2d** with **1a** afforded **3d** in 98% yield (entry 3). The reaction of methyl and ethyl acrylate proceeded smoothly (entries 8–10).

The typical procedure is as follows: Under an argon atmosphere, to a stirred solution of (±)-**5** (0.05 mmol; 14.3 mg) in THF (0.5 ml) was added **1a** (0.5 mmol; 41.9 μl), **2a** (0.75 mmol; 98.8 μl) and **4** (0.10 mmol; 24.9 μl) successively, which was stirred for 1 h at room temperature. The mixture was diluted with 0.5 ml of hexane, and was purified by flash column chromatography (SiO_2, Et_2O/hexane=1/1) to give **3a** in quantitative yield. After completion of the reaction, the mixture was subjected to chromatographic purification without the usual work-up procedure.

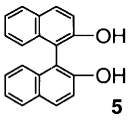
To determine the possibility of coordination between an aldehyde and an acidic proton of **5** and/or between a polarized alkene and an acidic proton of **5**, we examined ^1H NMR studies on **1a**, **2a** and **5**

Table 1
The Baylis–Hillman reaction of **1a** with **2a** catalyzed by a Lewis base and a Brønsted acid as a co-catalyst



1a **2a** (1.5 mol eq) **3a**

Entry	Catalyst	Co-catalyst	Yield (%)
1	DABCO (20 mol %)	–	no reaction
2	Bu_3P (**4**) (20 mol %)	–	23
3	**4** (20 mol %)	methanol (20 mol %)	23
4	**4** (20 mol %)	BzOH (20 mol %)	32
5	**4** (20 mol %)	TsOH•H_2O (20 mol %)	no reaction
6	**4** (20 mol %)	(±)-1,1'-bi-2-naphthol (**5**) (10 mol %)	**quant**
7	**4** (20 mol %)	2-naphthol (20 mol %)	**quant**
8	**4** (20 mol %)	(±)-**6** (10 mol %)	80
9	**4** (20 mol %)	(±)-**7** (10 mol %)	24
10	DABCO (20 mol %)	(±)-**5** (10 mol %)	no reaction
11	Ph_3P (20 mol %)	(±)-**5** (10 mol %)	no reaction
12	Bu_2S (20 mol %)	(±)-**5** (10 mol %)	no reaction
13	**4** (20 mol %)	phenol (20 mol %)	**quant**
14	**4** (20 mol %)	*p*-toluenesulfonamide (20 mol %)	70



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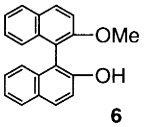

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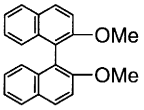

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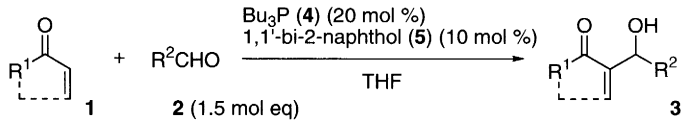
in THF-d_8. When **5** was added to the THF-d_8 solution of **1a** or **2a**, the upfield shifts (~0.1 ppm) of the hydrogen signals of **1a** and **2a** were observed in a concentration-dependent manner of **5**. By contrast, when **1a** or **2a** was added to the THF-d_8 solution of **5**, the downfield shifts (~0.1 ppm) of the signals of the hydroxy protons of **5** were observed in a concentration-dependent manner of **1a** or **2a**. These results might indicate that **5** functions as a Brønsted acid to coordinate with the carbonyl groups of an enone and an aldehyde.

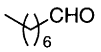
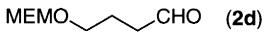
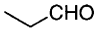
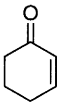
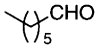
On the basis of the reaction system mentioned above, we focused on developing a catalytic asymmetric Baylis–Hillman reaction. Recently, several examples of catalytic asymmetric Baylis–Hillman reactions have been reported.[4,5d,9] However, moderate % ees and yields were achieved when substituted-aryl aldehydes were used as substrates with a chiral Lewis base.[4] Therefore, the development of this reaction constitutes a formidable challenge for organic chemists. We report herein a preliminary example of a catalytic asymmetric Baylis–Hillman reaction of an aliphatic aldehyde and an α,β-unsaturated ketone promoted by cooperative catalysts[10] of the first optically active calcium catalyst (*R*)-**6** as a chiral Lewis acid with tributylphosphine (**4**) as an achiral Lewis base.

Unfortunately, the reaction of **1a** with **2a** catalyzed by **4** and (*R*)-1,1′-bi-2-naphthol ((*R*)-**5**) gave **3a** with low ee (<10% ee). After screening, we were surprised to find that an optically active *calcium* catalyst (*R*)-**6** which was prepared from a strong base Ca(O-*i*-Pr)$_2$ and (*R*)-**5** in THF was an effective *chiral Lewis acid* for a catalytic asymmetric Baylis–Hillman reaction (Scheme 2).[11] To our knowledge, this is the first example of an optically active calcium catalyst. The reaction of **1a** and 1.5 mol equiv. of **2a** in the presence of 16 mol% of the chiral calcium catalyst (*R*)-**6** and 10 mol% of **4** afforded (*S*)-**3a**[12] with 56% ee in 62% yield.[13]

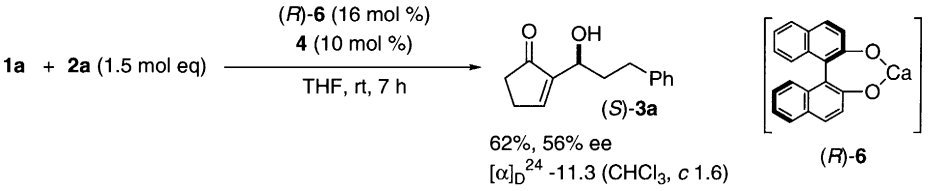
In conclusion, we have found that the cooperative catalysts of tributylphosphine with (±)-1,1′-bi-2-naphthol are effective for the Baylis–Hillman reactions to give the desired products in high yield. Moreover, it was found that the cooperative catalysts of the first calcium chiral catalyst with tributylphos-

Table 2
The Baylis–Hillman reaction of a polarized alkene with an aldehyde catalyzed by tributylphosphine (**4**) with 1,1′-bi-2-naphthol (**5**)



Entry		R^2CHO	Time (h)	Temp (°C)	Product	Yield (%)
1	**1a**	 (**2b**)	3	rt	**3b**	quant
2	**1a**	PhCHO (**2c**)	2	rt	**3c**	92
3	**1a**	 (**2d**)	4	rt	**3d**	98
4	**1a**	 (**2e**)[a]	24	rt	**3e**	91
5	 (**1b**)	**2a**	19	rt	**3f**	88
6	**1b**	**2c**	48	rt	**3g**	57
7	**1b**	**2e**[a]	13	rt	**3h**	90
8[b]	 (**1c**)	 (**2f**)	5	50	**3i**	52
9[b]	 (**1d**)	**2b**	16	50	**3j**	56
10[b]	**1d**	**2f**	5	50	**3k**	60

[a] **2e** (3.0 mol eq); [b] **1** (2.0 mol eq), **2** (1.0 mol eq), Yields were based on **2**.



Scheme 2. A catalytic asymmetric Baylis–Hillman reaction promoted by the first chiral calcium catalyst with tributylphosphine (**4**)

phine were effective for a catalytic asymmetric Baylis–Hillman reaction. Since there is a great potential for the combination catalysts of the chiral calcium catalyst and tributylphosphine, further investigations for the improvement of the catalysts are currently in progress.

Acknowledgements

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Monguchi for their technical assistance. We thank Dainippon Ink and Chemicals, Inc. for the 1998 Award in Synthetic Organic Chemistry, Japan to Y.M.A.Y.

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11. Preparation of the calcium catalyst: Under an argon atmosphere, to a solution of $Ca(O\text{-}i\text{-}Pr)_2$ (120.6 mg; 0.762 mmol) (purchased from High Purity Chemicals Lab. Co., Ltd) in THF (7.65 ml) was added a solution of (*R*)-1,1′-bi-2-naphthol (327.3 mg; 1.14 mmol) in THF (11.4 ml) at room temperature, and the mixture was stirred overnight at the same temperature. THF was evaporated under reduced pressure, the residue was dried in vacuo for 4 h, THF (19.5 ml) was again added under an argon atmosphere, and the suspension was allowed to stand for several hours to give a solution of the catalyst.
12. The enantiomeric excess of **3a** was determined by HPLC analysis (Daicel Chiralpak AS; detection at 254 nm; eluent: 2-propanol/hexane (1/9)), and the absolute configuration was determined by Mosher's method after conversion to (2*R**)-2-((1*S**)-1-hydroxy-3-phenylpropyl)cyclopentanone. For Mosher's method, see: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
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