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Enantioselective Morita–Baylis–Hillman (MBH) reaction promoted by a heterobimetallic complex with a Lewis base

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Abstract—A new double-activation catalysis is presented for the Morita–Baylis–Hillman (MBH) reaction of an α,β-unsaturated ketone and an aldehyde by the combined use of a heterobimetallic asymmetric complex and tributylphosphine ((*n*-Bu)$_3$P) to afford the α-methylene-β-hydroxy ketone with up to 99% ee.

The Morita–Baylis–Hillman (MBH) reaction is one of the most important carbon–carbon bond-forming reactions of electron-deficient alkenes such as α,β-unsaturated ketones with aldehydes catalyzed by nucleophilic amines or phosphines.[1] The products of the MBH reaction are highly functionalized allylic alcohols,[2] which prove to be valuable building blocks for biologically important compounds and natural products. A number of attractive systems utilizing chiral Lewis or Brønsted acid catalysts,[3a–d] chiral amino- or phosphino-type catalysts,[3e–i] chiral amino acid derivatives,[3j,k] a chiral thiourea-type catalyst,[3l] and chiral ionic liquids[3m] have been reported for this asymmetric catalytic process. However, in general, the applicability of the known catalysts for the MBH reaction has been limited to particular substrates. Thus, the development of easy, practical and efficient enantioselective MBH catalysis has been a challenge for organic chemists.

The mechanism of the MBH reaction catalyzed by a Lewis base such as phosphine or amine is understood to proceed through the Michael addition and β-elimination sequence (Fig. 1). The first step in the catalytic cycle involves Michael-type addition of a Lewis base to an electron-deficient alkene to form a key intermediate (I), which adds to an aldehyde in an aldol fashion to generate a second intermediate (II). Subsequent proton migration and release of the Lewis base yields the adduct.

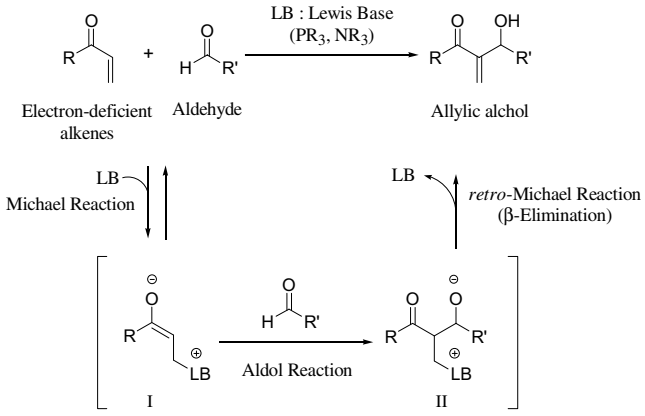

Figure 1. Mechanism of the MBH reaction.

It was assumed that chiral Lewis acid catalysts would activate electron-deficient alkenes to facilitate the Michael addition of the Lewis base. The generated chiral intermediate could then furnish the MBH adduct with high enantioselectivity. To establish this catalytic system, referred to as double activation,[4] heterobimetallic asymmetric catalysts such as aluminum-lithium-bis(binaphthoxide) (ALB) and lanthanum-lithium-tris-(binaphthoxide) (LLB) (Fig. 2) were initially examined.[5]

In this communication, the combination of tributylphosphine ((*n*-Bu)$_3$P) and heterobimetallic asymmetric complexes is shown to be effective for promoting the

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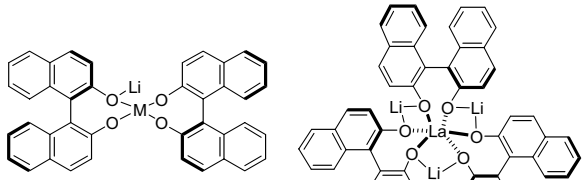


(*R*)-Al-Li-bis(binaphthoxide)
(*R*)-ALB (M = Al)

(*R*)-B-Li-bis(binaphthoxide)
(*R*)-type A BLB (M = B)

(*R*)-La-Li$_3$-tris(binaphthoxide)
(*R*)-LLB

Figure 2. (*R*)-ALB, (*R*)-type A BLB, and (*R*)-LLB.

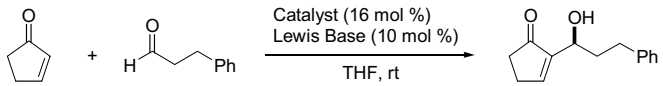
enantioselective MBH reaction of α,β-unsaturated ketone **1** and aldehyde **2** via double activation. In particular, a boron-lithium-mono(binaphthoxide) (type B BLB) complex prepared from LiB(*s*-Bu)$_3$H and BINOL promotes the reaction efficiently with up to 99% ee.

The reaction of 2-cyclopenten-1-one (**1a**) and hydrocinnamaldehyde (**2a**) as prototypical substrates was initially attempted using ALB or LLB in combination with catalytic amounts of amines or phosphines. Among the Lewis bases examined, including BINAP, PPh_3, DABCO, DBU, SMe_2, and 1,4-dithiane,[3,6] the combination of (*n*-Bu)$_3$P and heterobimetallic complexes was found to promote the reaction. LLB with (*n*-Bu)$_3$P promoted the reaction to give **3a** in 75% yield with 33% ee, accompanied by the self-condensation of aldehyde and the formation of an unidentified byproduct (entry 1, Table 1). The combination of ALB with (*n*-Bu)$_3$P afforded **3a** in quantitative yield with 33% ee after 24 h (entry 2). In the absence of a base, neither ALB nor LLB promoted this reaction (entries 4 and 5). An alkali-metal-free complex prepared from Me_3 Al (16 mol%) and BINOL (16 mol%)[7] was also found to be ineffective, even in the presence of (*n*-Bu)$_3$P. In the absence of an Al source, the mixture derived from *n*-BuLi (16 mol%), BINOL (16 mol%),[8] and (*n*-Bu)$_3$P (10 mol%), or (*n*-Bu)$_3$P (10 mol%) and BINOL (16 mol%)[3c] promoted the MBH reaction to afford **3a** with 9% ee and 4% ee, respectively. Although further mechanistic investigations are necessary to clarify the role of the Li-phenoxide unit in ALB, these results suggest that double activation using a heterobimetallic asymmetric complex and (*n*-Bu)$_3$P may play an important role in promoting the MBH reaction efficiently.

Among the heterobimetallic catalysis investigated, boron-lithium-bis(binaphthoxide) (type A BLB) (Fig. 2), which was prepared from $BH_3 \cdot THF$ (16 mol%), *n*-BuLi (16 mol%) and BINOL (32 mol%), fruitfully promoted the reaction to afford **3a** in excellent yield with 46% ee (entry 3, Table 1).[9,10] Furthermore boron-lithium-mono(binaphthoxide) (type B BLB) prepared from LiB(*s*-Bu)$_3$H (16 mol%) and BINOL (16 mol%) exhibited high catalytic activity even at −40 °C (entry 1, Table 2), whereas the reactions catalyzed by ALB, LLB, or type A BLB did not proceed under similar reaction conditions. The results of type B BLB mediated MBH reaction of α,β-unsaturated cyclic ketone **1** and aldehyde **2** were summarized in Table 2. The MBH reactions performed using the combination of (*n*-Bu)$_3$P and type B BLB were smoothly accelerated, although low enantioselectivities were obtained in the case of aromatic aldehydes such as benzaledhyde (entries 6 and 7). In contrast, moderate asymmetric induction was observed in the reaction of aliphatic aldehydes (entries 1–3, 8 and 10). In particular, the reactions of aliphatic branched aldehydes afforded the adducts with excellent enantioselectivities (entries 4, 5 and 9). In all cases utilizing the combination of (*n*-Bu)$_3$P and type B BLB, the corresponding aldol product was not obtained under the optimized reaction conditions.[11]

Encouraged by the success with the use of type B BLB, the structure of the complex was characterized by ^{13}C NMR and ESI-TOF mass spectroscopy.[12] ^{13}C NMR studies of the complex in THF-d_8 revealed downfield shifts of the carbon signals for C1, C1′, C2, C2′ in BINOL from δ 114.01 to 118.57 (C1, C1′) and from δ 153.91 to 159.97 (C2, C2′), but the parent peak of BINOL was not observed. The ESI-TOF MS spectrum of the catalyst in THF revealed the LiB(*s*-Bu)$_2$-BINOL complex to be the major constituent in solution with (*n*-Bu)$_3$P coordinated to boron. The proposed

Table 1. Enantioselective MBH reaction promoted by heterobimetallic catalysis[a]



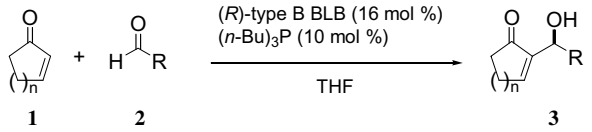
1a **2a** **3a**

Entry	Catalyst	Lewis base	Time (h)	Yield (%)	Ee (%)[b]
1	LLB	(*n*-Bu)$_3$P	2	75	33
2	ALB	(*n*-Bu)$_3$P	24	Quant	33
3	type A BLB	(*n*-Bu)$_3$P	2	Quant	46
4	ALB	None	48	No reaction	–
5	LLB	None	48	No reaction	–

[a] Reactions were carried out using the heterobimetallic complex (0.08 mmol), **1a** (41.9 μL, 0.5 mmol), **2a** (98.8 μL, 0.75 mmol) and (*n*-Bu)$_3$P (12.5 μL, 0.05 mmol).

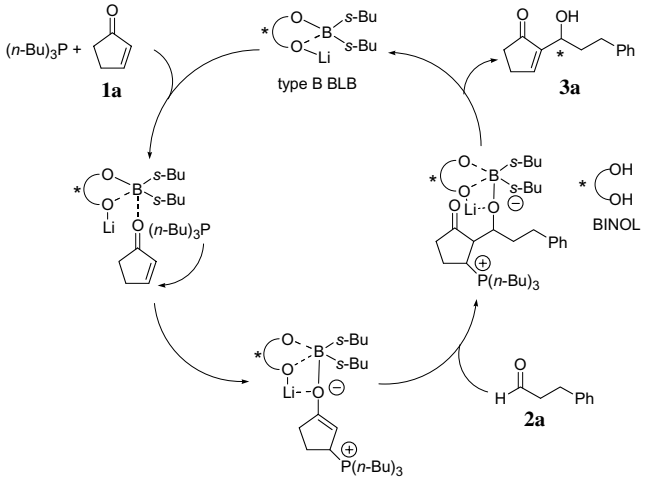
[b] The enantiomeric excess of the adduct was determined by chiral stationary phase HPLC analysis using a Daicel Chiralpak AS column (detection: 254 nm, eluent: hexane/2-PrOH = 9). The (*S*)-configuration was determined by optical rotation of purified products.

Table 2. Enantioselective MBH reaction of **1** with **2** promoted by boron-lithium-mono(binaphthoxide) (type B BLB) in the presence of $(n\text{-Bu})_3$P[a]



Entry	n = 1 or 2	R	Temp (°C)	Time (h)	Product	Yield (%)	Ee (%)[b]
1	**1a** (n = 1)	$PhCH_2CH_2$ (**2a**)	−40	120	**3a**	70	64
2	**1b** (n = 2)	**2a**	0	240	**3b**	49	58
3	**1b**	Et (**2b**)	0	288	**3c**	23	85
4[c]	**1b**	i-Pr (**2c**)	0	288	**3d**	94	99
5[c]	**1a**	t-Bu (**2d**)	−40	288	**3e**	42	97
6	**1a**	Ph (**2e**)	rt	3.5	**3f**	93	19
7	**1b**	**2e**	0	120	**3g**	32	15
8	**1b**	C_5H_9 (**2f**)	rt	240	**3h**	60	52
9[c]	**1a**	C_6H_{11} (**2g**)	−40	168	**3i**	88	93
10	**1b**	**2g**	rt	48	**3j**	71	63

[a] Reactions were carried out using type B BLB (0.08 mmol), **1** (41.9 μL, 0.5 mmol), **2** (98.8 μL, 0.75 mmol) and $(n\text{-Bu})_3$P (12.5 μL, 0.05 mmol).
[b] The enantiomeric excess of the adduct was determined by chiral stationary phase HPLC analysis (**3a**,**f**,**g**: Daicel Chiralpak AS column, **3b**: Daicel Chiralcel OD column, **3c**–**e**,**h**,**j**: Daicel Chiralpak AS-H column, **3i**: Daicel Chiralcel OD-H column; detection: **3a**,**b**,**f**,**g**: 254 nm, **3c**–**e**,**h**–**j**: 226 nm; eluent: hexane/2-PrOH = 9). The (*S*)-configuration was determined by optical rotation of purified products.
[c] 2.5 mmol of **2** was used.



Scheme 1. Proposed mechanism of MBH reaction promoted by heterobimetallic catalyst with $(n\text{-Bu})_3$P.

mechanism of this MBH reaction promoted by heterobimetallic catalyst with $(n\text{-Bu})_3$P is shown in Scheme 1.

In conclusion, asymmetric catalysis using a combination of a heterobimetallic complex and $(n\text{-Bu})_3$P was found to accelerate the enantioselective MBH reaction to afford the adduct in good chemical yield with moderate to high enantioselectivity. Further studies aimed at elucidating the structure of the catalysts and the mechanism of double activation are currently in progress.

Acknowledgements

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10. While the type A BLB-mediated reaction proceeded in various solvents with high chemical yield, the selectivity varied dramatically (Et_2O 9% ee, toluene 12% ee, CH_2Cl_2 20% ee, MeCN 37% ee). THF was the most effective solvent with respect to chemical yield and enantioselectivity.
11. General procedure for catalytic enantioselective MBH reaction promoted by boron-lithium-mono(binaphthoxide) (type B BLB) complex with (n-Bu)$_3$P: To a solution of BINOL (22.9 mg, 0.08 mmol) in THF (0.5 mL) was added LiB(s-Bu)$_3$H (80 μL (1 M in TMF)) at 0 °C. After sttiring for 0.5 h, α,β-unsaturated ketones (**1**, 0.5 mmol), aldehydes (**2**, 0.75 mmol) and tributylphosphine (12.5 μL, 0.05 mmol) were added to a solution of the boron-lithium-BINOL complex. The mixture was stirred until the reaction had reached completion as determined by TLC analysis. The mixture was then diluted with 0.5 mL of hexane and purified by flash column chromatography (SiO_2, hexane/ether=1–2) to give the adducts **3** as a colourless oil.
12. Due to the small needle-like crystals of type B BLB, X-ray crystallographic analysis has yet to be performed successfully.