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Direct Catalytic Asymmetric Aldol Reactions Promoted by a Novel Barium Complex

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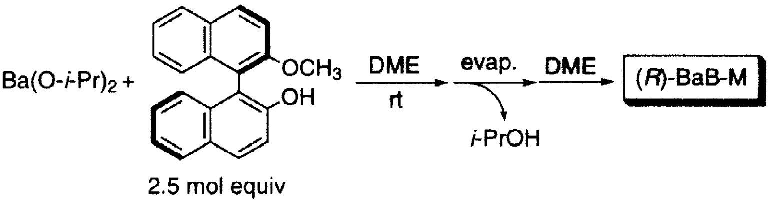
Abstract

A direct catalytic asymmetric aldol reaction of an aldehyde and an unmodified ketone promoted by an asymmetric barium complex has been achieved. The possible structure of the barium catalyst, BaB-M, which possesses the function of a Lewis acid and a Brϕnsted base, was characterized by LDI-TOFMS, ^{13}C-NMR spectroscopy and extensive studies of reaction conditions.

Keywords: *Aldol reactions; Asymmetric catalysis; Barium and compounds; Unmodified ketones*

The catalytic asymmetric aldol reaction is one of the most powerful carbon-carbon bond-forming reactions which allows to construct a multitude of optically active aldols from a catalytic amount of chiral information [1]. In particular, the development of direct catalytic asymmetric aldol reactions, starting from aldehydes and *unmodified* ketones constitutes a formidable challenge for organic chemistry in terms of scientific interest, synthetic utility and atom economy. Recently we have achieved success in carrying out the first direct catalytic asymmetric aldol reactions of aldehydes with unmodified ketones utilizing LaLi$_3$tris(binaphthoxide) (LLB) [2], which displays both Lewis acidity and Brϕnsted basicity [3]. However, the requirement of excess amounts of ketone, 20 mol % of LLB and a reaction time of more than three days has been a problem awaiting solution. A new potential catalyst would be expected to function not only as a stronger Brϕnsted base [4] compared to LLB, but should also contain a Lewis acidic center to control the orientation of the aldehyde and to activate the aldehyde [5]. We imagined that barium phenoxides, which have been well characterized [6], could be very interesting for such



Scheme 1. Preparation of (*R*)-BaB-M.

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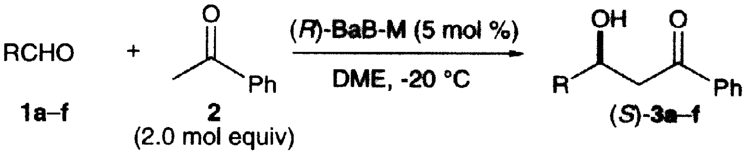
application. Moreover, we envisioned that some optically active barium complexes would control π-facial selectivity of both an aldehyde and an enolate to provide favorable levels of enantioselection, because the coordination number of Ba^{2+} complexes with oxygen ligands can range over 7-12 [7]. In this communication, we would like to report the first example of a direct catalytic asymmetric aldol reaction of an aldehyde and an unmodified ketone promoted by a novel barium complex.

Table 1. Direct Catalytic Asymmetric Aldol Reactions Promoted by (*R*)-BaB-M.



entry	R (aldehyde, adduct)	time (h)	yield (%)	ee (%)
1	*t*-C_4H_9 (**1a**, **3a**)	48	77	67
2	$PhCH_2C(CH_3)_2$ (**1b**, **3b**)	39	77	56
3	*c*-C_6H_{11} (**1c**, **3c**)	18	87	54
4	*i*-C_3H_7 (**1d**, **3d**)	24	91	50
5	$BnOCH_2C(CH_3)_2$ (**1e**, **3e**)	40	83	69
6[a]	$BnOCH_2C(CH_3)_2$ (**1e**, **3e**)	48	86	70
7	$BnOC(CH_3)_2$ (**1f**, **3f**)	20	99	70

[a] BaB-M (10 mol %), –25 °C

After screening a variety of ligands, solvents and metal sources, it was found that the most effective barium catalyst (BaB-M) could be prepared from Ba(O-*i*-Pr)$_2$ and 2.5 mol equiv of (*R*)-2-hydroxy-2'-methoxy-1,1'-binaphthyl (BINOL-Me) [8] in DME (Scheme 1). To our knowledge, this is the first example of an asymmetric barium catalyst. We were pleased to find that in the presence of 5 mol % of BaB-M the reaction of **1a** and 2 mol equiv of **2** proceeded much faster than in the presence of 20 mol % of LLB and 5 mol equiv of **2** to afford **3a** in 77% yield and 67% ee (Table 1, entry 1)[1]. BaB-M can be stored as a golden yellow solution for several months under an argon atmosphere. The catalyst not only can be applied to the reaction of other tertiary aldehydes (**3b**: 77%, 56% ee, entry 2) but also to secondary aldehydes with an acidic α-hydrogen, affording the aldol adducts **3c** and **3d** in excellent yields with 54% and 50% ee, respectively, after less than 24 h and without the formation of self-aldol adducts (entries 3, 4)[2,3]. The reaction of **1e** with **2** gave **3e**, which could be useful for the synthesis of some optically active natural products [9], in 86% yield and 70% ee (entries 5, 6) [10]. In addition, the reaction of

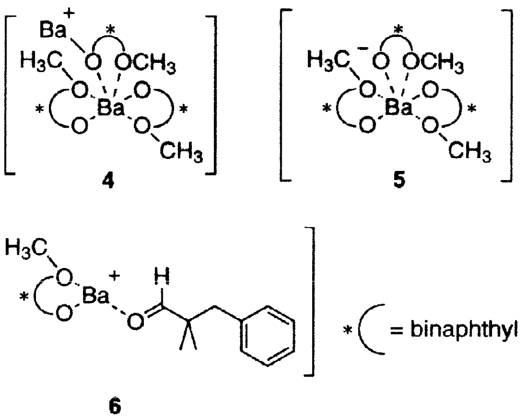


Figure 1. Structures of 4–6.

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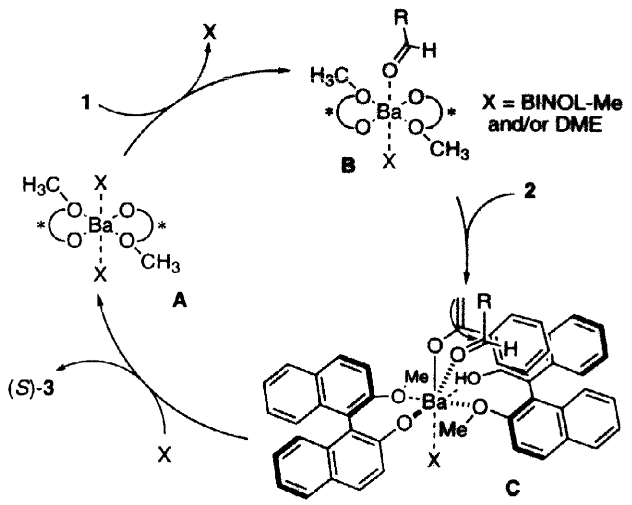
[1] Preparation of (*R*)-BaB-M: Under an argon atmosphere was added a 1.0*M* solution of Ba(O-*i*-Pr)$_2$ (aldrich, powder, 99.9%; stored in dry box) in DME to a 1.0*M* solution of (*R*)-BINOL-Me (2.5 mol equiv) in DME at room temperature and the mixture was stirred overnight at the same temperature. The solution was evaporated under reduced pressure, the residue was dried for 3 h, and under an argon atmosphere DME was again added to give a 0.05*M* (*R*)-BaB-M solution.

Direct aldol reaction: To a golden yellow solution of 0.05*M* (*R*)-BaB-M (0.0125 mmol; 0.25 mL) in DME was added **2** (0.5 mmol) and **1a** (0.25 mmol) at -20 °C, and the mixture was stirred for 48 h at -20 °C. The reaction was quenched by adding 2 mL of 1*N* H_2SO_4 and worked up as usual to give (*S*)-**3a** in 77% with 67% ee.

1f afforded **3f** after 20 h in 99% yield and 70% ee (entry 7).



Scheme 2. Proposed Mechanism of Direct Catalytic Asymmetric Aldol Reactions Promoted by BaB-M.

To obtain information about the structure of the catalyst and about the reaction mechanism, we analyzed the asymmetric barium complex by Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (LDI-TOF MS) [11,12]. The LDI-TOF(+)MS spectrum of BaB-M showed a strong peak at m/z = 1172 (**4**) and weak peaks at 1592 and 858, and the LDI-TOF(-)MS of BaB-M showed the base peak of **5** at m/z = 1034 and weak peaks at m/z = 1454 and 721. The stoichiometry of at least 2.5 mol equiv of BINOL-Me per Ba^{2+} in BaB-M was found to be essential for the effective reaction, giving products in excellent yields and modest to good ees, in spite of the fact that Ba^{2+} is a two-valent metal. Under these conditions, no free BINOL-Me peaks were detected in the ^{13}C-NMR spectrum of BaB-M, strongly indicating that the excess of half a BINOL-Me equivalent interacts with the barium complex. In addition, as expected, nonlinear effects (asymmetric amplification) [13] were observed. Taking together the above mentioned facts, it appears that **A** (Scheme 2) is a likely structure of BaB-M.

To investigate possible catalyst substrate interactions, a LDI-TOF(+)MS spectrum of 10 mol equiv of **1b** in the presence of BaB-M was recorded, and we found two new peaks, which were neither detected in the spectrum of BaB-M itself, one at m/z = 736 and one at m/z = 598, probably *a fragment of a complex of the catalyst and the aldehyde* (**6**). This important result appears to suggest that a monomeric barium complex **B** in which an aldehyde is coordinated to barium was generated (Scheme 2). That is, BaB-M should function not only as a Brϕnsted base but also as a Lewis acid. Interestingly, the reaction of Ba(O-*i*-Pr)$_2$, which is a stronger Brϕnsted base than BaB-M, afforded the adduct **3c** in less satisfactory yield (40%) because of the formation of the dehydrated product (28% yield). This result confirms how the tuning of the Lewis acidity and Brϕnsted basicity of metals by optically active ligands strongly influences the desired reaction.

A proposal for the reaction mechanism is as follows (Scheme 2): The dissociation of **A** takes place in the presence of an aldehyde to form **B** in which the barium metal as a Lewis acid activates the aldehyde. The orientation of the aldehyde is controlled by a chiral environment. After that a Brϕnsted base unit of **B** deprotonates an α-proton of **2** to form the intermediate **C**. Then the reaction partners aldehyde and barium enolate react in a

[2] The reaction of benzaldehyde with **2** gave the desired aldol adduct in quantitative yield, albeit with 8% ee.

[3] The reaction of **1c** with **2** in other solvents (DME in the presence of 18-crown-6, toluene, CH_2Cl_2, Et_2O, THF, diglyme, THF-HMPA (1:1) or THF-dioxane(1:1) gave **3c** with lower ee (in THF: 32% ee, others: <10% ee).

chelation-controlled manner around the asymmetric environment of the barium complex to afford the optically active aldol adduct (*S*)-**3a–f** while regenerating the catalyst.

In conclusion, we have developed a direct catalytic asymmetric aldol reaction of an aldehyde and an unmodified ketone promoted by a novel asymmetric barium complex, possibly a monometallic bifunctional catalyst. To develop a new group of catalysts for perfect direct asymmetric aldol reactions, we introduced BaB-M which shows good reactivities and fairly good enantioselectivities. At the moment, BaB-M is superior to LLB as a catalyst for the direct asymmetric aldol reaction of an aldehyde and an unmodified ketone, suggesting that there is a great possibility for BaB-M to be improved further for direct catalytic asymmetric aldol reactions. Investigations along these lines are currently in progress.

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References and Notes

[1] For reviews, see a) Nelson SG, Tetrahedron: Asymmetry 1998;9:357-389; b) Gröger H, Vogl EM, Shibasaki M, Chem. Eur. J. 1998;4:1135-1139.

[2] Yamada YMA, Yoshikawa N, Sasai H, Shibasaki M, Angew. Chem. Int. Ed. Engl. 1997;36:1871-1873.

[3] For reviews on heterobimetallic catalysts, see a) Shibasaki M, Sasai H, Arai T, Angew. Chem. Int. Ed. Engl. 1997;36:1236-1256; b) Steinhagen H, Helmchen G, Angew. Chem. Int. Ed. Engl. 1996;35:2339-2342; c) Shibasaki M, Iida T, Yamada YMA, J. Synth. Org. Chem. Jpn. 1998;56:344-356.

[4] For examples of BaO or $Ba(OH)_2$ catalyzed reactions, see a) Parshall GW, Ittel SD, Homogeneous Catalysis, 2nd Ed., Wiley, New York, 1992; b) Ai M, Bull. Chem. Soc. Jpn. 1991; 64:1342-1345; c) Zhang G, Hattori H, Tanabe K, Appl. Catal. 1988;36:189-197; d) Gercia-Raso A, Sinisterra JV, Marinas J, Pol. J. Chem. 1982;56:1435-1445; e) Gong Y-D, Kurth MJ, Tetrahedron Lett. 1998;39:3379-3382.

[5] Yamamoto et al. suggested a coordination of an aldehyde to an allylic barium reagent; see a) Yanagisawa A, Yamada Y, Yamamoto H, Synlett 1997;1090-1092; b) Yanagisawa A, Habaue S, Yasue K, Yamamoto H, J. Am. Chem. Soc. 1994;116:6130-6141, and references cited therein.

[6] Caulton KG, Chisholm MH, Drake SR, Folting K, Huffman JC, Streib WE, Inorg. Chem. 1993;32:1970-1976, and references cited therein.

[7] Huang L, Turnipseed SB, Haltiwanger RC, Barkley RM, Sievers RE, Inorg. Chem. 1994: 33:798-803, and references cited therein.

[8] For other applications of BINOL-Me, see a) Ishihara K, Nakamura S, Kaneeda M, Yamamoto H, J. Am. Chem. Soc. 1996;118:12854-12855; b) Taniguchi T, Ogasawara K, Tetrahedron Lett. 1997;38:6429-6432, and references cited therein.

[9] Blanchette MA, Malamas MS, Nantz MH, Roberts JC, Somfai P, Whritenour DC, Masamune S, J. Org. Chem. 1989;54:2817-2825, and references cited therein.

[10] The absolute configurations of **3e** and **3f** were determined by Mosher's method to be (*S*)-form; see Dale JA, Mosher HS, J. Am. Chem. Soc. 1973;95:512-519; The enantiomeric excess of **3e** and **3f** was determined by HPLC analysis using DAICEL CHIRALPAK AS. For other adducts, see ref [2].

[11] a) Sasai H, Suzuki T, Itoh N, Tanaka K, Date T, Okamura K, Shibasaki M, J. Am. Chem. Soc. 1993;115:10372-10373; b) Gröger H, Saida Y, Sasai H, Yamaguchi K, Martens J, Shibasaki M, J. Am. Chem. Soc. 1998;120:3089-3103.

[12] Arai T, Yamada YMA, Yamamoto N, Sasai H, Shibasaki M, Chem. Eur. J. 1996;2:1368-1372.

[13] For review, see Avalos M, Babiano R, Cintas P, Jiménez JL, Palacios JC, Tetrahedron: Asymmetry 1997;8:2997-3017.