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Mild and Highly Enantioselective Vinylogous Aldol Reaction of Brassard's Diene with Aromatic Aldehydes by Combined Lewis Acid Catalyst

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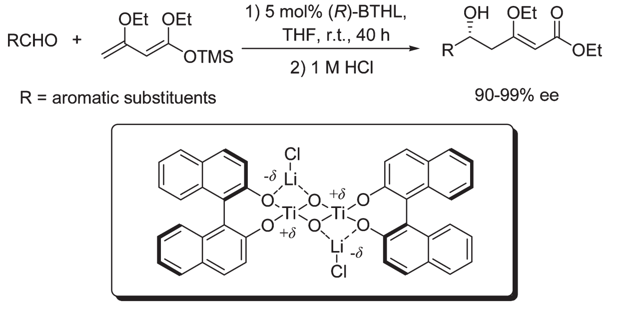

(*R*)-BTHL: weak Lewis acid (LiCl) assisted BINOL-Ti species

The combined Lewis acid catalytic system, generated from (*R*)-1,1′-bi-2-naphthol [(*R*)-BINOL], Ti(O-*i*-Pr)$_4$, H_2O, and lithium chloride, effectively catalyzed the enantioselective vinylogous aldol reaction of Brassard's diene with aromatic aldehydes affording the (*Z*)-δ-hydroxyl-α,*β*-unsaturated esters exclusively in good yields with excellent enantioselectivities (90−99% ee) under mild conditions. A Lewis acid−Lewis acid bifunctional working model was proposed for the catalytic process based on some control experiments.

The development of novel chiral metal complexes for the catalytic production of optically active compounds is among the most important tasks in current organic chemistry. In this context, the strategy of combined Lewis acid has attracted much attention in the design of asymmetric catalyst. Combination of Lewis acids, also referred as Lewis acid assisted Lewis acid, could enhance the inherent acid reactivity by associative interaction, while reorganized structure provides a more efficient chiral induction.[1] Recently, some successful applications of this concept in the asymmetric catalyst design have been reported.[2] For instance, Maruoka and co-workers designed a novel mono-oxygen bridged bis-Ti oxide with strong activation of aldehydes promoting a catalytic enantioselective allylation of aldehydes with allyltributyltin.[2e] The authors proposed that the high reactivity might be ascribed to the intramolecular coordination of one isopropoxy oxygen atom to the other titanium center, thereby allowing a stronger carbonyl activation caused by enhanced Lewis acidity of the original Ti center.

The design and use of chiral homo- or heterobimetallic complexes, especially those in which the two metal centers work synergistically in a catalytic process, constitute another promising approach in asymmetric catalyst design.[3,4] For example, the rare earth−alkali heterobimetallic complexes developed by Shibasaki's group have been successfully used as Lewis acid−Brønsted base bifunctional catalysts in a variety of transformations with high selectivities.[5] This catalyst functions as not only a Lewis acid to activate the electrophiles but also a Brønsted base to deprotonate the nucleophiles to form active metal species. In this paper, we wish to report a combination of the two concepts mentioned above to develop a novel BINOL−Ti catalyst assisted by weak Lewis acid LiCl which may work as a Lewis acid−Lewis acid bifunctional reagent to promote the enantioselective vinylogous aldol reaction of Brassard's diene with aromatic aldehydes.

The asymmetric vinylogous aldol (AVA) reaction has been one of the versatile C−C bond-forming reactions with extensive application in the synthesis of natural polyketides producuts.[6] In the last two decades, several asymmetric catalysts have been successfully developed for the AVA reactions between aldehydes and preformed silyl dienol ether donors.[7] However, among most of these successful examples, low-temperature or stoichiometric additives was usually required

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(1) For review of combined acid, see: Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924.

(2) For selected examples of combined Lewis acid in asymmetric catalysis, see: (a) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071. (b) Oishi, M.; Aratake, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 8271. (c) Ishihara, K.; Kobayashi, J.; Inanaga, K.; Yamamoto, H. *Synlett* **2001**, 393. (d) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3186. (e) Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708. (f) Li, P.; Yamamoto, H. *J. Am. Chem. Soc.* **2009**, *131*, 16628.

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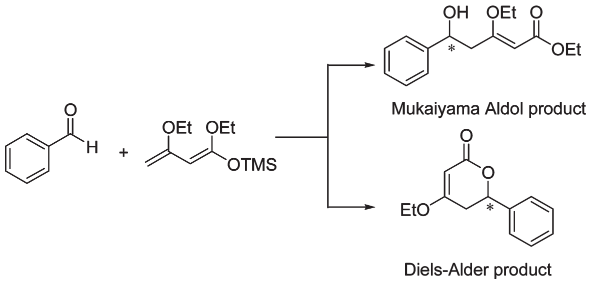
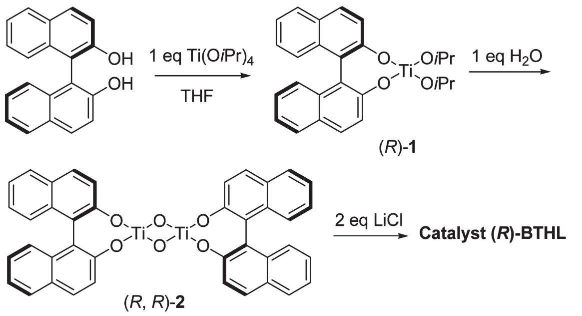
SCHEME 1. Two Competitive Reactions between Benzaldehyde and Brassard's Diene



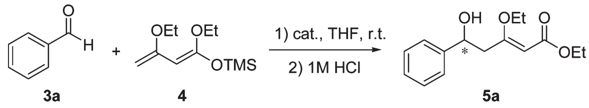
SCHEME 2. Preparation of the Novel Catalyst (*R*)-BTHL



to obtain high enantioselectivity. In addition, effective catalytic system for AVA reaction of Brassard's diene with aldehydes is still undeveloped. The main challenge lies in the competition between the aldol pathway and the HDA pathway (Scheme 1), and most concerned reports to date proceeded through the HDA-concerted pathway to give the cycloadducts directly.[8,9] Consequently, considering the potential utility of the δ-hydroxyl-α,β-unsaturated esters in natural product synthesis, it would be an interesting task to investigate the AVA reaction of Brassard's diene with aldehydes via an efficient and practical catalyst under mild conditions.

This novel combined-acid catalyst is easily available. As shown in Scheme 2, the in situ prepared (*R*)-BINOL−Ti(O-*i*-Pr)$_2$ (*R*)-**1** was hydrolyzed with 1 equiv of water to give the precatalyst μ-oxo bititanium species (*R*,*R*)-**2**,[10] and then 2 equiv of lithium chloride was added to afford the catalyst BTHL. Using 10 mol % of BTHL as catalyst, we initially tested the reaction between benzaldehyde and Brassard's diene **4** (1.5 equiv) in THF at room temperature. To our delight, the reaction proceeded through an aldol pathway to give the linear product exclusively instead of the cycloproduct after workup with 1 M HCl.[11] The (*Z*)-δ-hydroxyl-α,β-unsaturated ester **5a** was obtained in 60% yield with 96% ee. To the best of our knowledge, this is the first example of highly enantioselective catalytic AVA reaction of Brassard's diene with benzaldehyde.

TABLE 1. AVA Reaction of Brassard's Diene 4 with Benzaldehyde by (*R*)-BTHL[a]



entry	BINOL/Ti/ H_2O/LiCl	diene **4** (mmol)	cat.[d] (mol %)	yield[e] (%)	ee[f] (%)
1	1:1:0.5:1	1.5	10	48	88
2	1:1:1:1	1.5	10	60	96
3	1:1:1.5:1	1.5	10	50	95
4	1:1:1:1	2.5	10	72	96
5[b]	1:1:1:1	2.5	10	78	97
6[b,c]	1:1:1:1	2.5	10	80	97
7[b]	1:1:1:1	2.5	5	55	96
8[b,c]	1:1:1:1	2.5	5	74	96
9[b]	1:1:1:1	2.5	2.5	41	92

[a] Unless specially noted, all reactions were performed with 1 mmol of benzaldehyde and Brassard's diene **4** in 4 mL of THF at 25 °C over 16 h. [b] Concentration of substrate was 0.125 M. [c] Time extended to 40 h. [d] Based on bis-Ti complex. [e] Isolated yield. [f] The enantiomeric excess was determined by HPLC analysis with the *E* isomer of **5a**.

As is well known, water has a dramatic and sensitive effect on the structure and catalytic performance of BINOL−Ti species.[10,12] Thus, we investigated what effect the amount of water exerted on the performance of the catalytic system. It turned out that increase or decrease of the amount of water would cause decreased results (Table 1, entries 1 and 3). Utilizing the BTHL (1:1:1:1) as catalyst, the reaction conditions were then optimized, and the results are summarized in Table 1 (entries 4−9). Solvent effect was not investigated as a result of the bad solubility of BTHL in other solvents except THF. Chemical yield was increased to 72% with 2.5 equiv of Brassard's diene **4**, while the enantioselectivity was still maintained (entry 4). When the concentration of the substrate was reduced to 0.125 M, both the yield and enantioselectivity were increased (78% yield and 97% ee, entry 5), and we speculated that reduced aggregate of the active titanium species at lower concentration was responsible for the improved chemical yield.[13] Over a prolonged time of 40 h, the result did not made a substantial difference (80% yield and 97% ee, entry 6). Next, we reduced the catalyst loading

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(7) For selected examples, see: (a) Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360. (b) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837. (c) Evans, D. A.; Kozlowski, J. A.; Christopher, S. B.; Campos, K. R.; Connell, B. T.; Staples, R. *J. Am. Chem. Soc.* **1999**, *121*, 669. (d) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800. (e) Denmark, S. E.; Heemstra, J. R., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 1038. (f) Rosa, M. D.; Acocella, M. R.; Rega, M. F.; Scettri, A. *Tetrahedron: Asymmetry* **2004**, *15*, 3029. (g) Gondi, V. B.; Gravel, M.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 5757.

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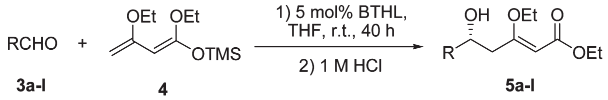
TABLE 2. AVA Reaction of Brassard's Diene 4 with Various Aromatic Aldehydes by (*R*)-BTHL[a]



entry	R	product	yield[b] (%)	ee[c] (%)
1	C_6H_5 (**3a**)	**5a**	74	96
2	*p*-$CH_3C_6H_4$ (**3b**)	**5b**	69	94
3	*o*-$CH_3OC_6H_4$ (**3c**)	**5c**	61	93
4	*p*-$CH_3OC_6H_4$ (**3d**)	**5d**	58	99
5	3,4,5-$(CH_3O)_3C_6H_2$ (**3e**)	**5e**	64	92
6	*o*-ClC_6H_4 (**3f**)	**5f**	73	90
7	*p*-ClC_6H_4 (**3g**)	**5g**	73	91
8	*p*-BrC_6H_4 (**3h**)	**5h**	75	91 (*R*)[d]
9	*p*-FC_6H_4 (**3i**)	**5i**	77	96
10	*m*-$NO_2C_6H_4$ (**3j**)	**5j**	49	91
11	2-furyl (**3k**)	**5k**	75	95
12	$C_6H_5CH{=}CH$ (**3l**)	**5l**	71	90
13	$(CH_3)_2CH$ (**3m**)	**5m**	16	96[e]

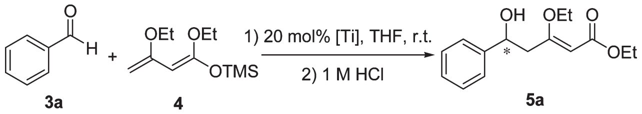
[a] All reactions were performed with 1 mmol of aldehyde and 2.5 mmol of diene **4** in 8 mL of THF at 25 °C over 40 h. [b] Isolated yield. [c] The enantiomeric excess was determined by HPLC analysis with the (*E*) isomer of **5a**−**l**. [d] The absolute configuration was determined by X-ray crystal structure analysis (see the Supporting Information for details). [e] Determined with **5m** by HPLC analysis.

from 10 to 5 mol %, the yield sharply dropped to 55% while the enantiomeric excess only dropped slightly (96% ee, enry 7). However, over extended time to 40 h, the reaction gave 74% yield with 5 mol % of catalyst (entry 8). Further reduced catalyst loading to 2.5 mol % caused an obvious decrease in both the chemical yield and enantioselectivity (41% yield, 92% ee, entry 9). From the viewpoint of catalyst efficiency, we took entry 8 as the optimal conditions for further substrate generality investigation.

With the optimized conditions in hand, the aldol reaction of Brassard's diene with various substituted aromatic aldehydes was investigated. As shown in Table 2, a wide substrate generality was tolerated, and various substituted aromatic aldehydes underwent the vinylogous aldol reaction to afford the target products in high enantiomeric excess (90−99% ee) with moderate to good yields (49−77%). A significant electronic effect was observed that electron-withdrawing groups caused enhanced reactivity and slightly reduced enantioselectivity. An extension to aliphatic aldehyde was also investigated with isobutylaldehyde (entry 13), and 96% ee was obtained with obviously decreased reactivity (yield 16%).

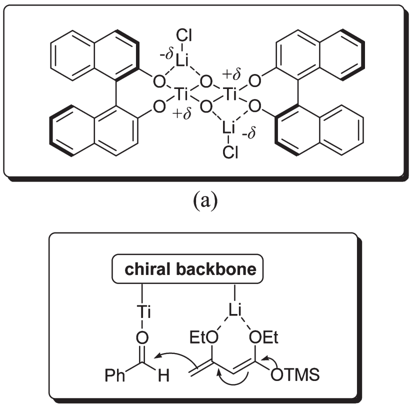
Several control experiments were performed to gain preliminary mechanistic insight into the catalytic system. As shown in Table 3, the simple combinations of (*R*)-BINOL and Ti(O-*i*-Pr)$_4$ with a molar ratio of 1:1 and 2:1 both gave unsatisfactory results (entries 1 and 3). When LiCl was added as additive, both the yields and enantioselectivities were improved, which implied that LiCl was a potentially powerful additive (entries 2 and 4). When the precatalyst (*R*,*R*)-**2** was used in our model reaction, poor results were obtained (entry 5). However, when LiCl was added to this hydrolyzed (*R*)-BINOL−Ti species, the best result was obtained in terms of chemical yield and enantioselectivity (entry 6). An increase of the amount of LiCl gave exactly the same result (entry 7). Other chloride represented by NaCl was also examined in place of LiCl. However, the added NaCl was totally insoluble in the solution, and this catalyst gave identically poor results as (*R*,*R*)-**2** (entry 8 vs entry 5). The anionic effect of lithium salts was also investigated with LiBr and LiOTf, and both the results (entries 9 and 10) were inferior to LiCl. The results manifest that the Lewis acids Ti and Li work cooperatively in the catalytic process while H_2O and chlorine anion facilitated the formation of high-performance catalyst.

TABLE 3. Control Experiments of AVA Reaction of Benzaldehyde with Brassard's Diene 4 by Various (*R*)-BINOL−Ti Species[a]



entry	BINOL/Ti/H_2O/LiCl	yield[b] (%)	ee[c] (%)
1	1:1:0:0	48	67
2	1:1:0:1	51	91
3	2:1:0:0	40	84
4	2:1:0:1	50	91
5	1:1:1:0	16	16
6	1:1:1:1	60	96
7	1:1:1:2	58	96
8	1:1:1:1 (NaCl)	14	20
9	1:1:1:1 (LiBr)	27	70
10	1:1:1:1 (LiOTf)	38	95

[a] All reactions were performed with 1 mmol of benzaldehyde and 1.5 mmol of diene **4** in 4 mL of THF at 25 °C over 16 h, and catalyst loading was based on mono-Ti complex. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis with the (*E*) isomer of **5a**.



(a)

(b)

FIGURE 1. (a) Proposed structure of the active catalyst. (b) Possible bifunctional working model for the catalytic process.

Though the structure of the active catalyst species and the details of the catalytic mechanism are still ambiguous, we proposed a Lewis acid assisted Lewis acid model for this catalytic system based on the control experiments (Figure 1a). When LiCl was added to the precatalyst μ-oxo bititanium complex, the lithium should coordinate to oxygen owing to its strong oxygen affinity,[14] thereby enhancing the acidity of the Ti center through associative interaction (Table 3, entry 5 vs entry 6). For the catalytic process, a possible Lewis acid−Lewis acid bifunctional working model is depicted based on Shibasaki's outstanding work[15] (Figure 1b). The strong

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(14) Olsher, U. *Chem. Rev.* **1991**, *91*, 137.

(15) A Lewis acid−Lewis acid bifunctional catalytic manner was described: (a) Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 16178. (b) Yamagiwa, N.; Qin, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13419.

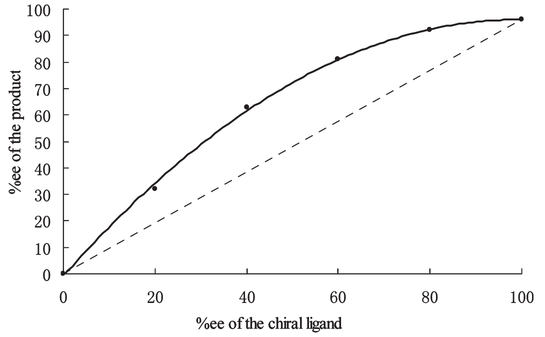


FIGURE 2. Nonlinear effect (NLE) in the AVA reaction of benzaldehyde with Brassard's diene 4.

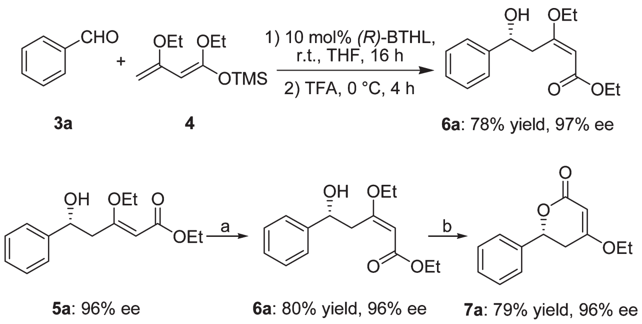
Lewis acid Ti activates the carbonyl group and discriminates the prochiral face. Meanwhile, the diene would coordinate to the weak Lewis acid Li center in a chelating manner and be positioned close to the aldehyde. The two metal centers function differently and both are essential for high selectivity.

We also carried out the nonlinear effect (NLE) experiment for this catalytic system using partially racemic BINOL while keeping the other conditions unchanged. As shown in Figure 2, a strong positive NLE implied that an oligomeric titanium structure may work as the active species to promote the reaction,[16] which also provides an evidence for the proposed bis-Ti structure.

We also found that after the indicated time if the reaction solution was treated with TFA and stirred for several hours, the (*E*) isomer **6a** would be obtained with sustained chemical yield and enantioselectivity (Scheme 3). Alternatively, the isolated (*Z*) product could be readily converted to the (*E*) isomer when treated with TFA in THF. It seemed that (*Z*)-δ-hydroxy-α,β-unsaturated esters **5a** would isomerize to a more thermodynamically stable (*E*) isomer under acid conditions. Further treatment of the (*E*) isomer **6a** with NaOH would afford δ-lactone **7a**, which shares the same cyclic subunit with many biologically active products.[17] These transformations broaden the utility of this developed methodology.

In summary, we have demonstrated that a combination of the weak Lewis acid LiCl with hydrolyzed (*R*)-BINOL−Ti complex would generate a novel bimetallic catalytic system. Employing this catalyst, highly enantioselective vinylogous aldol reaction between Brassard's diene and aromatic aldehydes was first realized with high enantioselectivities and good yields at room temperature. We believe that this strategy of combined Lewis acid would provide a convenient and effective approach for screening of high-performance asymmetric catalysts. Further research will be devoted to elucidation of the structural details of the catalyst and application to other transformations.

SCHEME 3. Transformation of the Aldol Product[a]



[a]Reagents and conditions: (a) TFA, THF, 0 °C, 4 h; (b) 1 M NaOH, MeOH, 0 °C, 15 min.

Experimental Section

General Procedure for the Vinylogous Aldol Reaction of Brassard'S Diene 4 and Benzaldehyde. Under N_2 atmosphere in a dry Schlenk tube, a mixture of Ti(O-*i*-Pr)$_4$ (0.2 mmol) and (*R*)-BINOL (0.2 mmol) was stirred in THF (16 mL) at room temperature for 20 min. Then to this mixture was added H_2O (7.2 μL, 0.2 mmol) with a syringe. After another 20 min, anhydrous LiCl (8.6 mg, 0.2 mmol) kept in a Schlenk tube was quickly added bottle to bottle under N_2 atmosphere. After the mixture was stirred over 30 min, 8 mL of the catalyst solution was transferred to another Schlenk tube and the benzaldehyde (1 mmol) and Brassard's diene **4** (2.5 mmol) were added successively by a syringe. After being stirred for 40 h at 25 °C, the reaction solution was cooled to 0 °C and quenched with five drops of 1 M HCl. After an additional 15 min, the mixture was neutralized with saturated $NaHCO_3$. After usual workup, the residue was purified by chromatography on silica gel (acetone/petroleum ether = 1/12) to afford **5a** as a colorless oil in 74% yield: $[\alpha]^{25}_D$ 39.5 (*c* 0.08, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.37 (m, 5H), 5.08 (s, 1H), 4.93−4.97 (m, 1H), 4.14−4.22 (m, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 2.59 (s, 1H), 2.57 (s, 1H), 2.49 (d, *J* = 3.2 Hz, 1H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 165.4, 143.5, 128.7, 127.9, 125.8, 99.0, 72.3, 67.8, 59.7, 45.2, 15.5, 14.4; ESI-HRMS $(M + Na)^+$ calcd for $C_{15}H_{20}O_4Na$ 287.1259, found 287.1263. Enantiomeric excess was determined to be 96% with the (*E*) isomer of **5a** (determined by HPLC using chiralcel OD-H column, hexane/2-propanol = 9/1, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 7.6 min, t_{minor} = 8.3 min).

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Supporting Information Available: Experimental details and characterization and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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