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Asymmetric alkylation of aldehydes catalyzed by novel dinuclear bis-BINOLate titanium(IV) complexes

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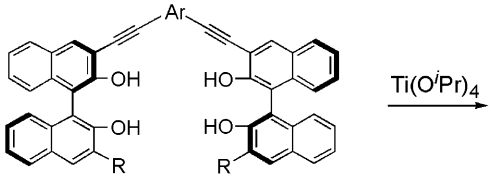
Abstract—Bis-BINOLs **1a**,**b** in which two BINOL units are tethered by *o*- and *m*-phenylenebis(ethynyl) groups form stable dinuclear bis-BINOLate titanium(IV) complexes **2a**,**b** by treatment with titanium tetraisopropoxide. In the presence of excess titanium tetraisopropoxide, **2a** and **2b** (2–20 mol%) catalyze diethylzinc addition to aromatic and aliphatic aldehydes in an efficient manner to give the ethylation products with high enantioselectivities. While more than 1 equiv of titanium tetraisopropoxide (with respect to a substrate aldehyde) is generally employed for obtaining high turnover frequency and selectivity in reactions catalyzed by a parent (BINOLate)Ti(O^{i}Pr)$_2$, the amount can be reduced as low as 0.2 equiv in the reactions catalyzed by **2a**,**b**.

1. Introduction

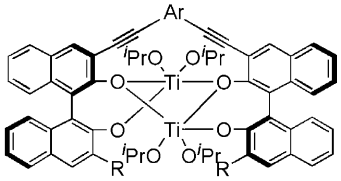
Titanium complexes of 1,1′-bi-2-naphthol (BINOL) and its derivatives stand for one of the most important and versatile classes of chiral Lewis acid catalysts.[1] In spite of their synthetic importance, there is little information regarding the structures of these titanium complexes.[2,3] Of these, (BINOLate)Ti(O^{i}Pr)$_2$ and its derivatives are relatively well-characterized. The solid-state structure of trimeric aggregate [(BINOLate)Ti(O^{i}Pr)$_2$]$_3$, with one six-coordinate and two five-coordinate titanium centers, has been established by X-ray crystallography.[4] However, its structure in solution remains elusive owing to the kinetic lability of titanium alkoxide ligands. Moreover, the aggregation phenomenon hampered the identification of active catalyst structures in enantioselective reactions.

We have recently reported the preparation and characterization of intramolecular dimeric titanium(IV) aggregates (*R*,*R*)-**2a**–**c**.[5] These dinuclear complexes are prepared by treatment of phenylenebis(ethynyl)-tethered bis-BINOLs (*R*,*R*)-**1a**–**c** with titanium tetraisopropoxide (Eq. 1). Their structures in solution have been established unambiguously by NMR spectroscopy. By the advantageous use of **2a**–**c** as catalysts, information on the enantioselectivity of the dimeric aggregate of a parent BINOLate titanium(IV) complex is anticipated to be obtained not obscured by the kinetic lability. Such study will provide a basis for the development of dimeric aggregate-based chiral Lewis acid catalysts.[6]



1a; Ar = *o*-C$_6$H$_4$, R = H
1b; Ar = *m*-C$_6$H$_4$, R = H
1c; Ar = *o*-C$_6$H$_4$, R = Me

(1)



2a; Ar = *o*-C$_6$H$_4$, R = H
2b; Ar = *m*-C$_6$H$_4$, R = H
2c; Ar = *o*-C$_6$H$_4$, R = Me

Asymmetric addition of diethylzinc to aldehydes catalyzed by a titanium complex prepared from BINOL and titanium tetraisopropoxide was first reported by the groups of Nakai[7] and Chan.[8,9] Subsequently,

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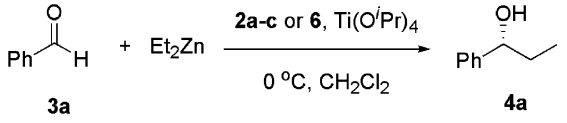
titanium tetraisopropoxide/dialkylzinc system has been examined with a variety of BINOL-based ligands. The reaction is now recognized to be the primary testing ground for new ligands to evaluate their utility in asymmetric catalysis.[10] Herein, we report the use of intramolecular dimeric titanium(IV) aggregates **2a**–**c** as catalysts for the prototypical diethylzinc addition to aldehydes.

2. Results and discussion

We first focused our effort on the asymmetric ethylation of benzaldehyde catalyzed by **2a**–**c** (Eq. 2, Table 1). According to the reaction conditions reported by Chan et al., reactions were carried out by using 3 equiv of diethylzinc in CH_2Cl_2 at 0 °C for 19 h in the presence of excess titanium tetraisopropoxide. With a 20 and 10 mol% catalyst load, *o*-phenylenebis(ethynyl)-tethered complex **2a** exhibited high enantioselectivity comparable to that reported for (BINOLate)Ti(O^iPr)$_2$ (entries 1 and 2).[7,8] Even at a 2 mol% catalyst loading, the reaction proceeded smoothly with slightly diminished selectivity (entry 3). *m*-Phenylenebis(ethynyl)-tethered complex **2b** also showed similar enantioselectivities at 2–20 mol% catalyst load (entries 4–6). In contrast to the high catalytic activity of **2a** and **2b**, the reaction using sterically hindered dimethyl derivative **2c** was sluggish and nonselective (entries 7 and 8). For comparison, we examined reactions catalyzed by (3-phenylethynyl-BINOLate)-Ti(O^iPr)$_2$ **6** prepared from the corresponding ligand **5** (entries 9 and 10). This catalyst also exhibited enantioselectivities comparable to that reported for (BINOLate)Ti(O^iPr)$_2$.



(2)

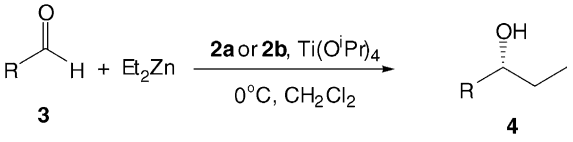
The addition of diethylzinc to other aromatic and aliphatic aldehydes **3b**–**e** was examined by using **2a** and **2b** at a 10 and 2 mol% catalyst load (Table 2). 1-Naphthaldehyde **3b** gave the corresponding ethylation product with higher selectivities (90–91% ee) than benzaldehyde irrespective of the catalysts (entries 1–4). It is noteworthy that relatively high ee was obtained even at a 2 mol% catalyst load of **2b**. In the reactions of substituted benzaldehydes **3c**,**d**, enantioselectivities were not attenuated even when 2 mol% of the catalysts was employed (entries 5–12). In comparison with aromatic aldehydes, 3-phenylpropanal **3e** was less reactive and the reaction did not attain full conversion after 19 h (entries 13–16). When **2b** (10 mol%) was used, enantioselectivity comparable to that observed for benzaldehyde was obtained for **3e**.

Table 1. Asymmetric ethylation of benzaldehyde catalyzed by **2a**–**c** and **6**[a]

Entry	Catalyst	mol%	Ti(O^iPr)$_4$[b]	Conversion[c](%)	Ee[d] (%)
1	**2a**	20	0.8	>98	85
2		10	0.9	>98	88
3		2	1.0	>98	81
4	**2b**	20	0.8	>98	87
5		10	0.9	>98	85
6		2	1.0	>98	82
7[e]	**2c**	20	0.8	15	19
8[e]		10	0.9	17	19
9	**6**	20	0.9	>98	87
10		4	1.0	>98	86

[a] Unless otherwise noted, reactions were carried out with 3 equiv of diethylzinc at 0 °C for 19 h in CH_2Cl_2.
[b] Equivalents of titanium tetraisopropoxide used in excess with respect to aldehyde **3a**.
[c] Determined by GC.
[d] Determined by HPLC using a Chiralcel OD column.
[e] Reaction was carried out for 27 h.

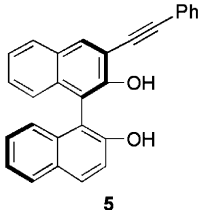
Table 2. Asymmetric ethylation of aldehydes **3b**–**e** catalyzed by **2a** and **2b**[a]



(3)

Entry	Aldehyde	Catalyst	mol%	Yield[b] (%)	Ee[c] (%)
1	**3b**; R = 1-naphthyl	**2a**	10	88	90
2		**2a**	2	98	86
3		**2b**	10	89	91
4		**2b**	2	93	91
5	**3c**; R = *p*-$CH_3C_6H_4$	**2a**	10	89	80
6		**2a**	2	95	80
7		**2b**	10	88	83
8		**2b**	2	97	82
9	**3d**; R = *p*-$CF_3C_6H_4$	**2a**	10	86	67[d]
10		**2a**	2	80	66[d]
11		**2b**	10	85	76[d]
12		**2b**	2	79	68[d]
13	**3e**; R = $PhCH_2CH_2$	**2a**	10	73	81
14		**2a**	2	73	76
15		**2b**	10	69	86
16		**2b**	2	69	75

[a] Reactions were carried out at 0 °C for 19 h in CH_2Cl_2 in the presence of titanium tetraisopropoxide (0.9 and 1.0 equiv for 10 and 2 mol% catalyst loading, respectively).
[b] Isolated yield.
[c] Unless otherwise noted, ee values were determined by HPLC using a Chiralcel OD column.
[d] Determined by NMR analysis of the MTPA ester derivative.



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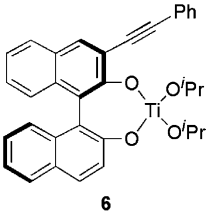


6

In the previously reported asymmetric alkylation reactions, more than 1 equiv of titanium tetraisopropoxide was usually employed for obtaining high turnover frequency and high enantioselectivity.[7,8,10] The use of a reduced amount of titanium tetraisopropoxide, as low as 0.2 equiv with respect to the aldehyde, turned out to give a similar level of selectivity in the reaction of benzaldehyde using catalysts **2a** and **2b** (20 mol%)

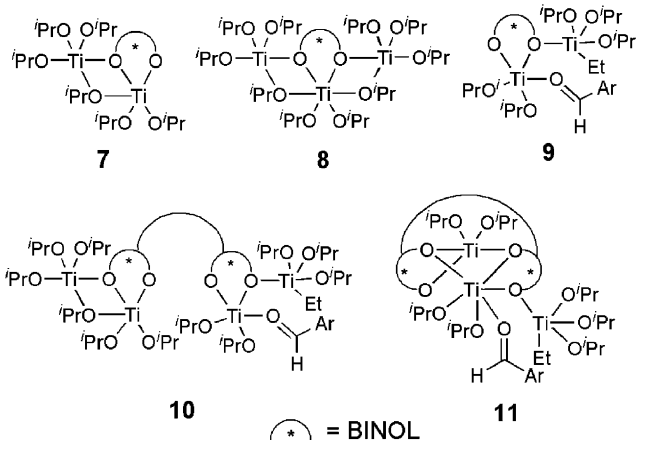
Table 3. Effect of the amount of titanium tetraisopropoxide[a]

Entry	Catalyst	$Ti(O^iPr)_4$[b]	Time (h)	Conversion[c] (%)	Ee[d] (%)
1	**2a**	0.8	19	>98	85
2		0.4	19	>98	84
3		0.2	19	>98	87
4		0.1	19	52	77
5	**2b**	0.8	19	>98	87
6		0.4	19	>98	84
7		0.2	15	>98	84
8		0.1	23	>98	77
9	**6**	0.8	19	>98	87
10		0.4	19	>98	82
11		0.2	19	93	76
12		0.1	24	88	73

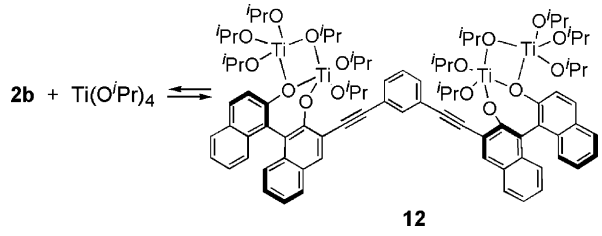
[a] Reactions of **3a** and diethylzinc (3 equiv) were carried out by using 20 mol% of catalysts at 0 °C in CH_2Cl_2.
[b] Equivalents of titanium tetraisopropoxide used in excess with respect to **3a**.
[c] Determined by GC.
[d] Determined by HPLC using a Chiralcel OD column.

(Table 3). Thus, in the presence of 0.2 equiv excess of titanium tetraisopropoxide, the reaction catalyzed by **2a** and **2b** gave the ethylation product of 87% ee and 84% ee, respectively (entries 3 and 7). Further reduction of titanium tetraisopropoxide amount resulted in reduced selectivity (entries 4 and 8). Catalyst **6** with a single BINOLate unit, on the other hand, exhibited a gradual deterioration of the ee by the decrease of titanium tetraisopropoxide amount (entries 9–12).

Recently, the mechanism of (BINOLate)$Ti(O^iPr)_2$ catalyzed asymmetric alkylation has been extensively investigated by Walsh et al.[4] Their study revealed that the role of the dialkylzinc is not to add the alkyl group to the carbonyl but rather to transfer the alkyl group to titanium, which subsequently transfers it to the aldehyde. The possibility of BINOLate titanium oligomers $[(BINOLate)Ti(O^iPr)_2]_n$ ($n = 2, 3$) as active catalysts was excluded because they undergo hetero-aggregation with excess titanium tetraisopropoxide to form dinuclear and trinuclear aggregates **7** and **8** under the reaction conditions. The possible transition-state assembly shown in **9** was proposed for the reaction.



Intramolecular dimeric titanium(IV) aggregates **2a** and **2b** show contrasting aggregation behaviors in the presence of excess titanium tetraisopropoxide.[5] ^1H NMR titration experiments demonstrated that **2a** with *o*-phenylenebis(ethynyl) tether is stable in the presence of up to 24 equiv of titanium tetraisopropoxide (with respect to **2a**) keeping the intramolecular dimeric structure.[11] On the other hand, *m*-phenylenebis(ethynyl)-tethered **2b** is relatively more labile in the presence of excess titanium tetraisopropoxide, undergoing a reversible intramolecular deaggregation to form intermolecular aggregate **12** (Eq. 4). In the presence of 2 equiv of titanium tetraisopropoxide (with respect to **2a**), a ca. 1:1 mixture of **2b** and **12** was observed in the ^1H NMR analysis while complex **12** was a main component in the presence of 10 equiv of titanium tetraisopropoxide.



(4)

The structural lability of the intramolecular aggregate **2b** and the fact that its enantioselectivity was comparable to that of **6** suggest that the reaction proceeded through open structure **10** in the presence of titanium tetraisopropoxide in excess (0.8–1.0 equiv of with respect to aldehyde **3**). It has been reported that the introduction of substituents both at the 3 and 3′ position of BINOL significantly reduces the enantioselectivity of the resulting titanium complexes.[2b] The results of **2b** and **6** suggest that, in accord with the proposed transition assembly **9**, the mono substitution at the 3 position is not influential to the enantioselectivity of the BINOLate titanium catalyst.

o-Phenylenebis(ethynyl)-tethered catalyst **2a** also exhibited a similar level of enantioselectivity in spite of the stability of the intramolecular aggregate structure in the presence of excess titanium tetraisopropoxide. The concentration of an intermolecular aggregate, analogous to **7**, if formed in equilibrium, is very low. Provided that the catalysis by **2a** also proceeded through open structure **10**, the activity of the catalyst with respect to a turnover frequency would be lowered in comparison with **2b** and **6**. However the activity of **2a** was not different from that of **2b** and **6**. It is more likely that the catalysis by **2a** proceeded through transition assembly **11** maintaining a closed structure. Comparable enantioselectivity observed for **2a** and **2b** can be rationalized by similar ligand environment around the coordinating aldehyde in **10** and **11**.

When a limited amount of titanium tetraisopropoxide (0.4–0.1 equiv with respect to an aldehyde) was used in excess, the reaction of **2b** might proceed also through closed assembly **11**. The enantioselectivity of **2a** and **2b** was less sensitive to the reduction of the titanium tetraisopropoxide amount while that of **6** was lowered gradually by the decrease of the amount (Table 3). Although the origin of the difference is not yet clear,

the intramolecular aggregate structure of **2a**,**b** might be responsible to their insensitivity of enantioselectivity.

3. Conclusion

In summary, it was demonstrated that dinuclear bis-BINOLate titanium(IV) complexes **2a** and **2b** (2–20 mol%) catalyze diethylzinc addition to aromatic and aliphatic aldehydes in an efficient manner to give the ethylation products enantioselectively. In spite of the general use of titanium tetraisopropoxide in excess to obtain sufficient turnover frequencies and high enantioselectivities, the amount of excess titanium tetraisopropoxide could be reduced to 0.2 equiv in the reactions catalyzed by **2a** and **2b**. It was proposed that *o*-phenylenebis(ethynyl)-tethered **2a** catalyzed the reaction through transition-state assembly **11** keeping its closed structure.

4. Experimental

4.1. General

GC analyses were performed with a capillary column: (OV-1, 30 m). Flash column chromatography was performed using silica gel (Wakogel C-300) as absorbent. Toluene was dried and distilled over Na–benzophenone ketyl. Dichloromethane and triethylamine were dried and distilled over CaH_2.

4.2. (*R*)-3-Phenylethynyl-1,1′-bi-2-naphthol 5

A mixture of phenylacetylene (0.204 g, 2.0 mmol), (*R*)-2,2′-bis(methoxy(methoxy))-3-iodo-1,1′-binaphthyl (1.10 g, 2.2 mmol), $Pd(PPh_3)_4$ (0.119 g, 0.10 mmol), and CuI (38 mg, 0.20 mmol) in Et_3N (10 mL) and toluene (9 mL) was stirred at 60 °C for 8 h under argon atmosphere. The reaction mixture was filtered and the filtrate was poured into aq 1 N HCl and extracted twice with ethyl acetate. The organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, toluene) to give 0.884 g (93% yield) of 3-phenylethynyl-2,2′-bis(methoxy(methoxy))-1,1′-binaphthyl as an amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.66 (3H, s, C*H*$_3$O–), 3.16 (3H, s, C*H*$_3$O–), 4.94 (1H, d, J = 5.9 Hz, O–C*H*$_2$–O), 5.01 (1H, d, J = 6.9 Hz, O–C*H*$_2$–O), 5.05 (1H, d, J = 5.9 Hz, O–C*H*$_2$–O), 5.17 (1H, d, J = 6.9 Hz, O–C*H*$_2$–O), 7.17–7.29 (5H, m), 7.31–7.44 (4H, m), 7.55–7.61 (3H, m), 7.87 (2H, d, J = 8.2 Hz), 7.97 (1H, d, J = 9.0 Hz), 8.22 (1H, s); IR (KBr disk) 3055, 2365, 1015, 810, 750 cm^{-1}.

To a mixture of the bis-MOM derivative (1.28 g, 2.7 mmol) and molecular sieves 4 Å (2.5 g) in CH_2Cl_2 (80 mL) at 0 °C was added bromotrimethylsilane (3.6 mL, 27 mmol).[12] After being stirred for 6 h at 0 °C, the reaction mixture was filtered. The filtrate was poured into aqueous 5% $NaHCO_3$ and extracted twice with Et_2O. The organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 3% ethyl acetate in toluene) to give 0.830 g (80% yield) of **5** as an amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.95 (1H, br, O*H*), 5.84 (1H, s, O*H*), 7.17 (2H, t, J = 8.0 Hz), 7.25–7.42 (8H, m), 7.58 (2H, m), 7.88 (2H, m), 7.96 (1H, d, J = 8.9 Hz), 8.24 (1H, s); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 83.8, 96.2, 111.8, 112.3, 112.5, 117.7, 122.4, 123.7, 124.4, 124.6, 124.7, 127.1, 128.2, 128.29, 128.33, 128.5, 128.88, 128.94, 129.3, 130.9, 131.7, 133.3, 133.8, 134.0, 151.6, 152.0; IR (KBr disk) 3490, 2360, 1010, 815, 750 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 386 (M^+, 1), 177 (38), 133 (67), 89 (100); HRMS calcd for $C_{28}H_{18}O_2$: 386.1307, found: 386.1317.

4.3. Asymmetric ethylation of aldehydes 3 catalyzed by bis-(BINOLate)-Ti$_2$ complexes 2a–c (a representative procedure; Table 1, entry 2)

To a solution of bis-BINOL (*R*,*R*)-**1a**[5] (34.7 mg, 0.05 mmol) in CH_2Cl_2 (4 mL) at room temperature under argon atmosphere was added titanium tetraisopropoxide (0.16 mL, 0.55 mmol). The resulting solution of catalyst **2a** was stirred for 1 h at room temperature. To this at 0 °C was added diethylzinc (1 M in hexane, 1.5 mL,[3] 1.5 mmol) and stirring was continued for 20 min. To the resulting mixture was added benzaldehyde (53 mg, 0.5 mmol) at 0 °C. After being stirred for 19 h, the reaction mixture was quenched by the addition of aqueous 1 M HCl and extracted twice with ethyl acetate. The organic layers were washed with aqueous 5% $NaHCO_3$, dried ($MgSO_4$), analyzed by capillary GC (OV-1) to determine the conversion, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 15% ethyl acetate in hexane) to give (*R*)-1-phenylpropanol of 88% ee. The enantioselectivity was determined by HPLC analysis using a chiral stationary phase column (Chiralcel OD; 1 mL/min, 3% *i*-PrOH in hexane, major *R* enantiomer; t_1 = 13.6 min, minor *S* enantiomer; t_2 = 15.5 min). The absolute structure of the product was determined by comparing the retention time with that of an authentic sample.

Reactions using 20 or 10 mol% of the catalysts were carried out at 0.125 M of a substrate in CH_2Cl_2. Reactions at 2 mol% catalyst load were performed at 0.25 M.

4.4. Determination of alcohol enantiomeric excesses

Unless otherwise mentioned, ee values of ethylation products **4** were determined by HPLC analysis using a chiral stationary phase column (Chiralcel OD). For 1-naphthyl-1-propanol [0.8 mL/min, 10% *i*-PrOH in hexane, minor (*S*)-enantiomer; t_1 = 11.8 min, major (*R*)-enantiomer; t_2 = 22.5 min]; 1-(*p*-methylphenyl)-1-propanol [1 mL/min, 0.1% *i*-PrOH in hexane, major (*R*)-enantiomer; t_1 = 77.0 min, minor (*S*)-enantiomer; t_2 = 90.0 min]; 1-phenyl-3-pentanol [1 mL/min, 3% *i*-PrOH in hexane, major (*R*)-enantiomer; t_1 = 15.0 min, minor (*S*)-enantiomer; t_2 = 25.0 min]. The ee value of 1-(*p*-trifluoromethylphenyl)-1-propanol was determined by converting the alcohol to (*S*)-MTPA ester derivative;

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (3H, t, J = 6.4 Hz, CH_3CH_2), 1.83–2.02 (2H, m, CH_3CH_2), 3.48 (3H, br s, CH_3O), 5.87 (1H, t, J = 6.9 Hz, Ar(CH_3CH_2)C*H*–O), 7.29–7.45 (7H, m), 7.56 (2H, d, J = 8.1 Hz) [minor diastereomer resonated at 3.47 (3H, br s, CH_3O), and 5.96 (1H, t, J = 6.9 Hz, Ar(CH_3CH_2)C*H*–O)].

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