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Room Temperature and Highly Enantioselective Additions of Alkyltitanium Reagents to Aldehydes Catalyzed by a Titanium Catalyst of (*R*)-H_8-BINOL

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ABSTRACT Three alkyltitanium reagents of RTi(O-*i*-Pr)$_3$ (R = Cy (**1a**), *i*-Bu (**1b**), and *n*-Bu (**1c**)) were prepared in good yields. The high-resolution mass spectroscopy showed that **1b** and 1**c** in the gas phase are monomeric species. However, the solid state of **1a** revealed a dimeric structure. Asymmetric additions of **1a–1c** to aldehydes catalyzed by a titanium catalyst of (*R*)-H_8-BINOL were studied at room temperature. The reactions produced desired secondary alcohols in good yields with good to excellent enantioselectivities of up to 94% ee. Reactivity and enantioselectivity differences, in terms of steric bulkiness of the R nucleophiles, are herein described. The addition reactions of secondary *c*-hexyl to aldehydes were slower than the reactions of primary *i*-butyl or *n*-butyl nucleophiles. For the primary alkyls, lower enantioselectivities were obtained for products from addition reactions of the linear *n*-butyl as compared with the enantioselectivities of products from the addition reactions of the branched *i*-butyl group. The same stereochemistry of RTi(O-*i*-Pr)$_3$ addition reactions as the addition reactions of organozinc, organoaluminum, Grignard, or organolithium reagents directly supports the argument of that titanium-catalyzed addition reactions of aldehydes involve an addition of an organotitanium nucleophile. *Chirality 23:929–939, 2011.*

KEY WORDS: asymmetric catalysis; alkyltitanium triisopropoxide; alkyl addition; titanium catalyst; H_8-(*R*)-BINOL; BINOL derivative

INTRODUCTION

The titanium-catalyzed asymmetric addition reaction of alkylzinc compounds to aldehydes has been one of the most important synthetic protocols for synthesis of bioactive chiral secondary alcohols.[1–4] Over the past two decades, a variety of chiral ligands have been developed to deliver desired alcohols in high enantioselectivities.[5–16] Recent studies have shown that organoaluminum compounds are effective reagents,[17–29] and addition reactions can even be completed in 10 min.[24] Grignard[30–33] and lithium[34] reagents have also been established recently as efficient nucleophiles for addition reactions despite their high reactivity. In these studies, a presence of diamine additive and/or excessive amounts of Ti(O-*i*-Pr)$_4$ were used to deactivate the high reactivity of the Grignard and lithium reagents. The presence of excess Ti(O-*i*-Pr)$_4$ is a general feature of titanium-catalyzed addition reactions for products achieving high enantioselectivities. Mechanistic studies have suggested that the reactions involve an addition of organotitanium compounds, and one of the roles of excess Ti(O-*i*-Pr)$_4$ is an in situ generation of the organotitanium reagent via transmetallation of organic nucleophile from organozinc compounds to Ti(O-*i*-Pr)$_4$.[35–39] However, only a few reports have demonstrated direct asymmetric additions of organotitanium compounds. The first catalytic asymmetric RTi(O-*i*-Pr)$_3$ addition reaction was reported by Seebach and coworkers using Ti-TADDOLate catalysts. The use of salt-free RTi(O-*i*-Pr)$_3$ and the reactions conducting at an initial low temperature of −78°C were found to be essential for producing chiral secondary alochols in excellent enantioselectivities.[35,40,41] Later, titanium-acetylenide addition reactions of aromatic ketones had been investigated at temperatures at or below −15°C.[42] Recently, we had successfully synthesized [(3-furyl)Ti(O-*i*-Pr)$_3$]$_2$ for 3-furyl addition reactions of aromatic ketones; the reactions could be conducted at a mild temperature of 0°C.[43]

To further explore organoaluminum or organotitanium compounds as efficient nucleophiles for catalytic reactions,[44–52] we report herein the synthesis of three alkyltitanium compounds of RTi(O-*i*-Pr)$_3$ (R = Cy (**1a**), *i*-Bu (**1b**), and *n*-Bu (**1c**)). Asymmetric additions of **1a–1c** to aromatic, heteroaromatic, or α,β-unsaturated aldehydes catalyzed by a titanium catalyst of (*R*)-H_8-BINOL have been studied at room temperature, affording desired secondary alcohols in good to excellent enantioselectivities of up to 94% ee.

MATERIALS AND METHODS

General Procedures for the Synthesis of RTi(O-i-Pr)$_3$

To a two-necked round bottom flask containing magnesium turning (2.40 g, 0.100 mol) in 100 mL of diethyl ether and equipped with an addition funnel and a condenser, alkyl bromide (0.102 mol) in 50 mL diethyl ether was slowly added over a period of 1 h under a dry nitrogen atmosphere. The reaction mixture was stirred for another 2 h to give an alkyl Grignard solution. The above solution was transferred via a cannula to a

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solution of Ti(O-*i*-Pr)$_4$ (22.1 mL, 0.0750 mol) and $TiCl_4$ (2.74 mL, 0.0250 mol) in 50 mL THF cooling at 0°C. The resulted solution was reacted for 3 h at 0°C to give a brownish or black solution. The solvent was removed under reduced pressures to give an oily solid. The residue was extracted with hexane (3× 100 mL), and the combined extract was concentrated to furnish RTi(O-*i*-Pr)$_3$. **1a** was prepared in THF.

(Cy)Ti(O-i-Pr)$_3$ (1a). Pale yellow crystals (25.0 g, 83.0%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.52 (sept, *J* = 6.0 Hz, 3H), 2.10–2.06 (m, 2H), 1.74–1.00 (m, 9H), 1.27 (d, *J* = 6.4 Hz, 18H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 76.1, 34.6, 29.3, 27.2, 26.8, 25.6 ppm. Elemental analysis, calcd. for $C_{15}H_{32}O_3Ti$: C 58.44, H 10.46%, found: C 58.22, H 10.22%.

(*i*-Bu)Ti(O-i-Pr)$_3$ (1b). Brownish liquid (22.3 g, 78.0%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.45 (sept, *J* = 6.0 Hz, 3H), 2.10–1.75 (m, 1H), 1.25–1.18 (m, 2H), 1.19 (d, *J* = 6.0 Hz, 18H), 0.84 (d, *J* = 6.8 Hz, 6H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 76.2, 31.8, 30.7, 26.5, 19.0 ppm. HR-MS *m/z* calcd. for $C_{13}H_{30}O_3Ti$ $[M]^+$ 282.1674, found: 282.1679.

(*n*-Bu)Ti(O-i-Pr)$_3$ (1c). Gray liquid (21.5 g, 80.0%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.46 (sept, *J* = 6.0 Hz, 3H), 1.63 (q, *J* = 7.6 Hz, 2H), 1.25–1.06 (m, 4H), 1.20 (d, *J* = 6.4 Hz, 18 H), 0.75 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 76.2, 33.2, 27.3, 26.7, 26.0, 13.7 ppm. HR-MS *m/z* calcd. for $C_{13}H_{30}O_3Ti$ $[M]^+$ 282.1674, found: 282.1683.

General Procedures for Alkyl Additions to Aldehydes

Under a dry nitrogen atmosphere, {(*R*)-H$_8$-BINOLate}Ti(O-*i*-Pr)$_2$ (0.023 g, 0.050 mmol), Ti(O-*i*-Pr)$_4$ (0.30 mL, 1.0 mmol), and (Cy)Ti(O-*i*-Pr)$_3$ (0.247 g, 0.800 mmol) were mixed in hexane (2 mL) at room temperature. After stirring the mixture for 1 h, an aldehyde (0.50 mmol) was added. The resulted solution was allowed to react for 36 h at room temperature and quenched with 2*M* NaOH (2 mL). The solution was extracted with ethyl acetate (3× 10 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography to give the secondary alcohol. Enantiomeric excesses of products were determined by HPLC using suitable chiral columns from Daicel. The addition reactions of (*i*-Bu)Ti(O-*i*-Pr)$_3$ or (*n*-Bu)Ti(O-*i*-Pr)$_3$ (0.50 mmol) did not require the addition of Ti(O-*i*-Pr)$_4$ and were carried out in THF (4 mL).

(*R*)-Cyclohexylphenylmethanol ((*R*)-5a). $[\alpha]_D^{25}$ = +28.0 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.24 (m, 5H), 4.37 (d, *J* = 7.2 Hz, 1H), 2.04–1.96 (m, 1H), 1.84–1.72 (m, 1H), 1.70–1.52 (m, 5H), 1.42–1.32 (m, 1H), 1.30–0.86 (m, 4H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 143.6, 128.1, 127.4, 126.6, 79.3, 44.9, 29.3, 28.8, 26.4, 26.04, 25.96 ppm.[31]

Cyclohexyl-*o*-tolylmethanol (5b). $[\alpha]_D^{25}$ = +29.6 (*c* 0.6, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.38 (m, 1H), 7.25–7.10 (m, 3H), 4.65 (d, *J* = 7.2 Hz, 1H), 2.34 (s, 3H), 2.06–1.98 (m, 1H), 1.82–1.74 (m, 1H), 1.72–1.58 (m, 4H), 1.42–1.36 (m, 1H), 1.28–0.98 (m, 5H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 142.2, 135.4, 130.6, 127.3, 126.5, 126.3, 75.4, 44.8, 29.8, 28.8, 26.7, 26.6, 26.3, 19.7 ppm.[53]

Cyclohexyl-*m*-tolylmethanol (5c). $[\alpha]_D^{25}$ = +22.0 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19–7.12 (m, 1H), 7.06–6.98 (m, 3H), 4.24 (dd, *J* = 2.8, 7.2 Hz, 1H), 2.28 (s, 3H), 1.96–1.88 (m, 1H), 1.82–1.78 (m, 1H), 1.74–1.65 (m, 1H), 1.64–1.48 (m, 3H), 1.34–1.26 (m, 1H), 1.22–0.78 (m, 5H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 143.6, 137.7, 128.1, 128.0, 127.2, 123.7, 79.4, 44.8, 29.3, 28.8, 26.4, 26.1, 26.0, 21.4 ppm.[54]

Cyclohexyl-*p*-tolylmethanol (5d). $[\alpha]_D^{25}$ = +28.0 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20–7.11 (m, 4H), 4.31 (d, *J* = 7.2 Hz, 1H), 2.34 (s, 3H), 2.04–1.94 (m, 1H), 1.82–1.70 (m, 2H), 1.69–1.54 (m, 3H), 1.40–1.32 (m, 1H), 1.28–0.82 (m, 5H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.0, 137.3, 129.2, 126.9, 79.6, 45.2, 29.6, 29.2, 26.8, 26.4, 26.3, 21.4 ppm.[55]

(*R*)-Cyclohexyl-(4-methoxyphenyl)-methanol ((*R*)-5e). $[\alpha]_D^{25}$ = +24.1 (*c* 1.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.30 (d, *J* = 7.2 Hz, 1H), 3.81 (s, 3H), 2.08–1.52 (m, 6H), 1.42–0.82 (m, 6H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 159.0, 135.8, 127.7, 113.6, 79.0, 55.2, 45.0, 29.3, 29.1, 26.4, 26.1, 26.0 ppm.[56]

Cyclohexyl-(naphthalen-1-yl)-methanol (5f). $[\alpha]_D^{25}$ = +52.4 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18–8.10 (m, 1H), 7.90–7.84 (m, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.56–7.44 (m, 3H), 5.19 (d, *J* = 6.4 Hz, 1H), 2.00–1.56 (m, 6H), 1.44–1.34 (m, 1H), 1.22–1.06 (m, 5H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 139.5, 133.8. 130.9, 128.8, 127.8, 125.7, 125.4, 125.2, 124.1, 123.6, 76.1, 44.3, 30.3, 28.2, 26.4, 26.3, 26.0 ppm.[57]

Cyclohexyl-(naphthalen-2-yl)-methanol (5g). $[\alpha]_D^{25}$ = +29.0 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.76 (m, 3H), 7.67 (s, 1H), 7.50–7.38 (m, 3H), 4.47 (d, *J* = 6.4 Hz, 1H), 2.15 (d, *J* = 1.6 Hz, 1H), 2.04–1.94 (m, 1H), 1.80–1.56 (m, 4H), 1.40–1.32 (m, 1H), 1.28–0.88 (m, 5H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 141.3, 133.4, 133.2, 128.2, 127.9, 126.3, 126.0, 125.7, 125.0, 79.7, 45.1, 29.6, 29.1, 26.7, 26.33, 26.27 ppm.[58]

Cyclohexyl-(2-fluorophenyl)-methanol (5h). $[\alpha]_D^{25}$ = +16.0 (*c* 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (dt, *J* = 1.6, 7.2 Hz, 1H), 7.20–7.12 (m, 1H), 7.10–7.02 (dt, *J* = 1.6, 7.2 Hz, 1H), 6.97–6.90 (m, 1H), 4.63 (d, *J* = 7.2, 1H), 1.94–1.84 (m, 2H), 1.74–1.65 (m, 1H), 1.64–1.52 (m, 3H), 1.37–1.28 (m, 1H), 1.12–0.88 (m, 5H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 160.0 (*J* = 243 Hz), 130.6 (*J* = 12.7 Hz), 128.6 (*J* = 8.2 Hz), 128.2 (*J* = 4.6 Hz), 124.0 (*J* = 3.6 Hz), 115.1 (*J* = 22.8 Hz), 72.9, 44.4, 29.0, 28.6, 26.3, 26.0, 25.9 ppm.[59]

(3-Chlorophenyl)-cyclohexylmethanol (5i). $[\alpha]_D^{25}$ = +18.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.27 (m, 1H), 7.27–7.20 (m, 2H), 7.18–7.12 (m, 1H), 4.35–4.34 (d, *J* = 6.8 Hz, 1H), 2.00–1.86 (m, 2H), 1.80–1.52 (m, 4H), 1.42–1.34 (m, 1H), 1.28–0.84 (m, 5H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 145.6, 134.1, 129.3, 127.4, 126.7, 124.7, 78.6, 44.9, 29.2, 28.4, 26.3, 26.0, 25.9 ppm.[54]

(3-Bromophenyl)-cyclohexylmethanol (5j). $[\alpha]_D^{25}$ = +18.1 (*c* 0.55, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (s, 1H), 7.33–7.27 (m, 1H), 7.14–7.07 (m, 2H), 4.22 (d, *J* = 6.8 Hz, 1H), 2.10 (br, 1H), 1.86–1.76 (m, 1H), 1.72–1.40 (m, 4H), 1.34–1.24 (m, 1H), 1.18–0.76 (m, 5H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 146.2, 130.6, 130.0, 129.9, 125.5, 122.6, 78.9, 45.2, 29.5, 28.8, 26.6, 26.3, 26.2 ppm. HR-MS: *m/z* calcd. for $C_{13}H_{17}OBr$: 268.0463 $[M^+]$, found: 268.0460.

(4-Bromophenyl)-cyclohexylmethanol (5k). $[\alpha]_D^{25}$ = +20.6 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.35 (m, 2H), 7.12–7.06 (m, 2H), 4.25 (d, *J* = 6.8 Hz, 1H), 1.93 (br, 1H), 1.88–1.80 (m, 1H), 1.74–1.65 (m, 1H), 1.64–1.52 (m, 2H), 1.52–1.42 (m, 1H), 1.34–1.26 (m, 1H), 1.20–0.86 (m, 5H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 142.5, 131.2, 128.3, 121.0, 78.6, 44.9, 29.1, 28.5, 26.3, 26.0, 25.9 ppm.[54]

Cyclohexyl-(4-trifluoromethylphenyl)-methanol (5l). $[\alpha]_D^{25}$ = +21.2 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 4.46 (d, *J* = 6.8 Hz, 1H), 1.98–1.84 (m, 1H), 1.82–1.72 (m, 1H), 1.72–1.52 (m, 4H), 1.44–1.34 (m, 1H), 1.28–0.90 (m, 5H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 147.5, 129.5 (*J* = 32.8 Hz), 126.9, 125.1 (q, *J* = 3.7), 124.2 (*J* = 270 Hz), 78.6, 45.0, 29.2, 28.3, 26.3, 26.0, 25.9 ppm.[55]

Cyclohexyl-(furan-2-yl)-methanol (5m). $[\alpha]_D^{25}$ = +15.5 (*c* 1.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.36 (m, 1H), 6.34–6.32 (m, 1H), 6.24–6.20 (m, 1H), 4.37 (d, *J* = 7.6 Hz, 1H), 2.04–1.96 (m, 1H), 1.91 (br, 1H), 1.84–1.62 (m, 4H), 1.48–1.38 (m, 1H), 1.32–0.90 (m, 5H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 156.0, 141.7, 110.0, 106.5, 72.7, 42.9, 29.0, 28.8, 26.3, 25.9, 25.8 ppm.[60]

(*E*)-1-Cyclohexyl-3-phenylprop-2-en-1-ol (5n). $[\alpha]_D^{25}$ = −22.8 (*c* 0.6, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.36 (m, 2H), 7.35–7.28 (m, 2H), 7.26–7.20 (m, 1H), 6.56–6.54 (d, *J* = 15.6 Hz, 1H), 6.23 (dd, *J* = 7.2, 15.6 Hz, 1H), 4.01 (dd, *J* = 6.8, 7.2 Hz, 1H), 1.96–1.86 (m, 1H), 1.82–1.70 (m, 3H), 1.70–1.62 (m, 2H), 1.56–1.44 (m, 1H), 1.32–0.98

(m, 5H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 136.8, 131.2, 131.0, 128.5, 127.5, 126.4, 77.5, 43.9, 28.9, 28.6, 26.5, 26.1, 26.0 ppm.[59,61]

(*R*)-3-Methyl-1-phenylbutan-1-ol ((*R*)-6a). $[\alpha]_D^{25}$ = +45.0 (*c* 1.0, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.31 (m, 4H), 7.30–7.23 (m, 1H), 4.76–4.70 (m, 1H), 1.84 (s, 1H), 1.78–1.64 (m, 2H), 1.56–1.44 (m, 1H), 0.97–0.94 (m, 3H), 0.94–0.91 (m, 3H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 145.2, 128.4, 127.5, 125.8, 72.7, 48.3, 24.8, 23.1, 22.2 ppm.[32]

(*R*)-3-Methyl-1-p-tolylbutan-1-ol ((*R*)-6b). $[\alpha]_D^{25}$ = +44.1 (*c* 1.0, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.25–7.20 (m, 2H), 7.18–7.12 (m, 2H), 4.72–4.66 (m, 1H), 2.34 (s, 3H), 1.79 (s, 1H), 1.76–1.60 (m, 2H), 1.54–1.44 (m, 1H), 0.98–0.94 (m, 3H), 0.94–0.90 (m, 3H) ppm. $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz): δ 142.2, 137.1, 129.1, 125.8, 72.6, 48.2, 24.8, 23.0, 22.3, 21.0 ppm.[32]

(*R*)-3-Methyl-1-(naphthalen-6-yl)-butan-1-ol ((*R*)-6c). $[\alpha]_D^{25}$ = +71.6 (*c* 1.1, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.88–7.84 (m, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 6.8 Hz, 1H), 7.53–7.42 (m, 3H), 5.55–5.50 (m, 1H), 2.00–1.88 (m, 1H), 1.97 (s, 1H), 1.86–1.77 (m, 1H), 1.74–1.64 (m, 1H), 1.07 (d, *J* = 6.4 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H) ppm. $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz): δ 140.7, 133.5, 129.9, 128.6, 127.4, 125.6, 125.13, 125.11, 122.7, 122.3, 69.0, 47.3, 24.9, 23.2, 21.5 ppm.[32]

(*R*)-1-(3-Chlorophenyl)-3-methylbutan-1-ol ((*R*)-6d). $[\alpha]_D^{25}$ = +31.5 (*c* 1.1, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.34 (m, 1H), 7.30–7.20 (m, 3H), 4.75–4.70 (m, 1H), 1.81 (br, 1H), 1.78–1.66 (m, 2H), 1.52–1.42 (m, 1H), 0.95 (d, *J* = 6.0 Hz, 6H) ppm. $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz): δ 147.3, 134.3, 129.7, 127.5, 126.0, 123.9, 72.2, 48.4, 24.7, 23.1, 22.1 ppm.[32]

(*R*)-(*E*)-5-Methyl-1-phenylhex-1-en-3-ol ((*R*)-6e). $[\alpha]_D^{25}$ = −8.7 (*c* 1.1, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.42–7.36 (m, 2H), 7.36–7.30 (m, 2H), 7.26–7.22 (m, 1H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.22 (dd, *J* = 6.8, 16.0 Hz, 1H), 4.36 (m, 1H), 1.80–1.78 (sept, *J* = 6.8 Hz, 1H), 1.63–1.54 (m, 1H), 1.56 (s, 1H), 1.48–1.40 (m, 1H), 0.96 (d, *J* = 6.4 Hz, 3H) 0.95 (d, *J* = 6.4 Hz, 3H) ppm. $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz): δ 136.7, 132.9, 130.1, 128.5, 127.6, 126.4, 71.3, 46.5, 24.6, 23.0, 22.5 ppm.[32]

(*R*)-1-Phenylpentan-1-ol ((*R*)-7a). $[\alpha]_D^{25}$ = +28.3 (*c* 1.2, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.32 (m, 4H), 7.31–7.24 (m, 1H), 4.66 (t, *J* = 6.8 Hz, 1H), 1.88–1.76 (m, 2H), 1.76–1.66 (m, 1H), 1.46–1.18 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 144.9, 128.4, 127.4, 125.9, 74.7, 38.8, 27.9, 22.6, 14.0 ppm.[30]

(*R*)-1-(Naphthalen-1-yl)-pentan-1-ol ((*R*)-7b). $[\alpha]_D^{25}$ = +48.0 (*c* 1.0, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.14–8.08 (m, 1H), 7.90–7.84 (m, 1H), 7.80–7.74 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 6.8 Hz, 1H), 7.54–7.44 (m, 3H), 5.48–5.44 (m, 1H), 2.02–1.86 (m, 2H), 1.82 (br, 1H), 1.60–1.48 (m, 1H), 1.46–1.30 (m, 3H), 0.90 (t, *J* = 7.2 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 140.6, 133.8, 130.4, 128.9, 127.8, 125.9, 125.44, 125.40, 123.2, 122.8, 71.3, 38.1, 28.4, 22.6, 14.0 ppm.[32]

1-(3-Chlorophenyl)pentan-1-ol (7c). $[\alpha]_D^{25}$ = +20.0 (*c* 1.0, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.34 (m, 1H), 7.30–7.24 (m, 2H), 7.24–7.19 (m, 1H), 4.66–4.65 (m, 1H), 1.82–1.64 (m, 3H), 1.44–1.20 (m, 3H), 0.88 (t, *J* = 6.4 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 147.0, 134.3, 129.7, 127.5, 126.1, 124.0, 74.0, 38.8, 27.8, 22.5, 13.9 ppm.[62]

(*E*)-1-Phenylhept-1-en-3-ol (7d). $[\alpha]_D^{25}$ = −9.5 (*c* 1.0, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz), δ 7.40–7.36 (m, 2H), 7.34–7.28 (m, 2H), 7.26–7.20 (m, 1H), 6.56 (d, *J* = 16.0 Hz, 1H), 6.22 (dd, *J* = 6.8, 16.0 Hz, 1H), 4.28–4.26 (m, 1H), 1.69 (br, 1H), 1.68–1.54 (m, 2H), 1.46–1.30 (m, 4H), 0.91 (t, *J* = 6.4 Hz, 3H) ppm. $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz): δ 136.7, 132.6, 130.2, 128.5, 127.6, 126.4, 73.1, 37.0, 27.6, 22.6, 14.0 ppm.[30]

X-Ray Crystallography

Yellow crystals of **1a** were grown in hexane. A suitable crystal was covered with FOMBLIN® Y and mounted on a cryoloop. Diffractions were performed on an Oxford Gemini S diffractometer using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å); temperature 100(2) K; ϕ and ω scan technique; multiscan absorptions were applied in the data corrections. The structure was solved by direct methods, completed by subsequent difference Fourier syntheses, and refined by full-matrix least squares calculations based on F^2 (SHELXTL-97).[63] Crystallographic data for $[(c\text{-hexyl})Ti(O\text{-}i\text{-}Pr)_2(\mu_2\text{-}O\text{-}i\text{-}Pr)]_2$ (**1a**): $C_{30}H_{64}O_6Ti_2$, MM = 616.62, monoclinic, space group *P*2(1)/*n*, *T* = 100(2) K, *a* =11.8924(2) Å, *b* = 9.4982(2) Å, *c* = 16.1349(3) Å, β = 94.382(2)°, *V* = 1817.21(6) Å^3, *Z* = 2, absorption coefficient = 0.473 mm^{-1}, total reflections collected 17,832, unique 3570 (R_{int} = 0.0274), Goodness of fit indicator = 1.309, R_1 = 0.0540, wR_2 = 0.1767. A cif file of **1a** (CCDC 812103) has been deposited to the Cambridge Crystallographic Data Centre and can be obtained via www.ccdc.cam.ac.uk/data_request/cif.

RESULTS AND DISCUSSION

$RTi(O\text{-}i\text{-}Pr)_3$ (R = Me, C_6H_5, C_6F_5) had been synthesized and characterized by ^1H NMR spectroscopy in the 1970s.[64] Other alkyltitanium compounds of $RTi(O\text{-}i\text{-}Pr)_3$ (R = Et, Pr, Bu, Hex, $CH_2CH_2CH{=}CH_2$, and CH_2Ph) had been prepared in situ for asymmetric addition reactions.[35,40,41] In this study, three alkyltitanium compounds of $RTi(O\text{-}i\text{-}Pr)_3$ [R = Cy (*c*-hexyl, **1a**), *i*-Bu (*i*-butyl, **1b**), and *n*-Bu (*n*-butyl, **1c**)] were prepared in good yields from a reaction of $ClTi(O\text{-}i\text{-}Pr)_3$ with corresponding alkyl Grignard reagents in THF or diethyl ether (Eq. 1). Among them, **1a** and **1b** are novel compounds. **1a** was obtained as a crystalline material, and **1b** and **1c** were liquids. **1b** and **1c** contained trace amounts of impurities and were used directly for the addition reactions. The HR-MS (high-resolution mass spectroscopy) revealed a monomeric species for **1b** and **1c** in the gas phase. However, similar to the structures of $[(3\text{-furyl})Ti(O\text{-}i\text{-}Pr)_3]_2$[43] and $[ArTi(O\text{-}i\text{-}Pr)_3]_2$,[50] **1a** has a dimeric structure in its solid

$$ClTi(O\text{-}i\text{-}Pr)_3 + RMgBr \xrightarrow[0\ ^\circ C,\ 3\ h]{THF\ or\ Et_2O} RTi(O\text{-}i\text{-}Pr)_3\ (1)$$

1a: R = Cy
1b: R = *i*-Bu
1c: R = *n*-Bu

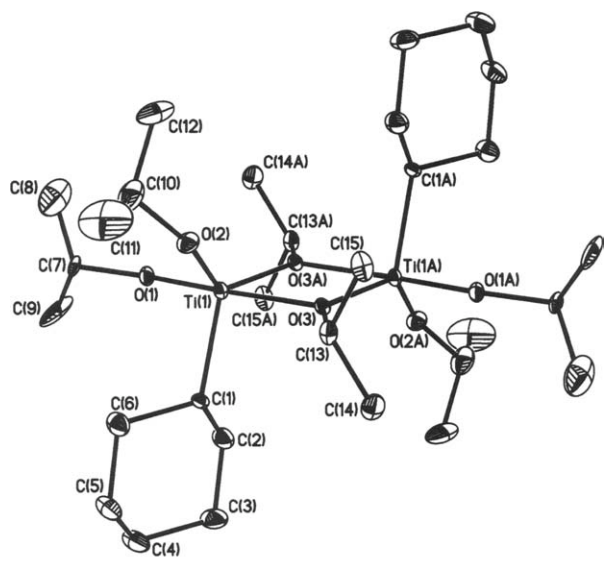


Fig. 1. The molecular structure of **1a**. Hydrogen atoms are omitted for clarity.

state (Fig. 1). **1a–1c** are stable enough to be stored under a dry nitrogen atmosphere for months.

Asymmetric reactions were first optimized on the additions of (Cy)Ti(O-*i*-Pr)$_3$ (**1a**) to benzaldehyde (**4a**) using a 10 mol % catalyst of [{(*R*)-H$_8$-BINOLate}Ti(O-*i*-Pr)$_2$]$_x$ ((*R*)-**2**),[65] [{(*R*)-BINOLate}Ti(O-*i*-Pr)$_2$]$_x$ ((*R*)-**3**), or [{(*S*)-BINOLate}Ti(O-*i*-Pr)$_2$]$_x$ ((S)-**3**)[38] (Eq. 2); the results are listed in Table 1. When the reaction was conducted at 0°C in THF using the catalytic system of (*R*)-**2**, but without an addition of Ti(O-*i*-Pr)$_4$, the addition of the cyclohexyl group to benzaldehyde proceeded slowly and produced addition product **5a** in a low conversion of 12%, but with a good enantioselectivity of 87% ee (entry 1). Though additions of Ti(O-*i*-Pr)$_4$ to the catalytic solution improved the enantioselectivities of up to 92% ee, conversions of **5a** were still low (11–25%, entries 2–5). The solvent effect was then investigated (entries 6–9) while keeping the amount of Ti(O-*i*-Pr)$_4$ at 2.0 equiv. Hexane was found to be the best solvent to afford **5a** in a 42% conversion. Increasing the amount of (*c*-hexyl)titanium reagent **1a** from 1.2 to 1.8 equiv resulted in increasing conversions of **5a** to 65% (entries 9–12). When the reaction was carried out at room temperature using 1.6 equiv of **1a**, a good 86% conversion of **5a** was obtained with a 92% ee (entry 13). Reducing the solvent amount of hexane to 2 mL further improved the conversion to 94% with the same enantioselectivity (entry 14). However, reducing the amount of (*R*)-**2** to 5 mol % produced **5a** in both a lower conversion of 88% and a lower enantioselectivity of 87% ee (entry 15). The in situ-formed titanium catalyst from mixing of 10 mol % (*R*)-H$_8$-BINOL ligand and 2.2 equiv Ti(O-*i*-Pr)$_4$ was also investigated, furnishing **5a** in an 83% conversion with an enantioselectivity of 91% ee (entry 16). The above results reveal that the preformed titanium catalytic system of (*R*)-**2** afforded the addition product in a somewhat better yield, but with similar enantioselectivity as compared with the in situ-formed titanium catalytic system of (*R*)-H$_8$-BINOL. Titanium complexes of (*R*)- and (*S*)-**3** containing simple BINOLate ligand were also examined, affording predominant (*R*)-**5a** and (*S*)-**5a** in somewhat lower conversions of 89 and 86% and lower enantioselectivities of 81% ee (entries 17 and 18).

The reaction scope was then studied on aromatic aldehydes, 2-furaldehyde, and (*E*)-cinnamaldehyde (Eq. 3) under optimized reaction conditions (Table 1, entry 14); the results are summarized in Table 2. The *c*-hexyl addition to benzaldehyde proceeded over 24 h to afford addition product **5a** in a 90% yield and a 92% ee (entry 1). For aromatic aldehydes bearing an electron-donating group and for naphthylaldehydes, the addition reactions required a reaction time of 36 h to

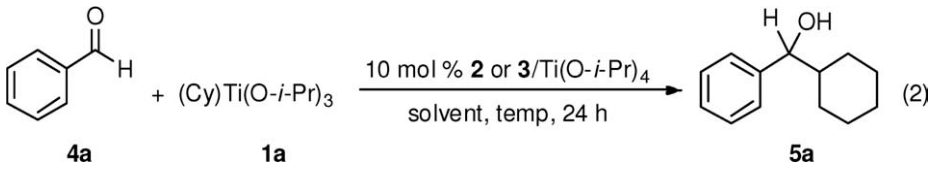


TABLE 1. Optimizations of asymmetric (Cy)Ti(O-*i*-Pr)$_3$ additions to benzaldehyde catalyzed by a titanium catalyst of (*R*)-H$_8$-BINOL, (*R*)-BINOL, or (*S*)-BINOL[a]

Entry	**1a** (equiv)	Ti(O-*i*-Pr)$_4$ (equiv)	Solvent	Temp (°C)	Conv.[b] (%)	Ee[c] (%)
1	1.2	0	THF	0	12	87 (*R*)
2	1.2	0.2	THF	0	11	84 (*R*)
3	1.2	1.0	THF	0	25	86 (*R*)
4	1.2	2.0	THF	0	22	92 (*R*)
5	1.2	2.5	THF	0	14	92 (*R*)
6	1.2	2.0	Et_2O	0	23	89 (*R*)
7	1.2	2.0	CH_2Cl_2	0	4	87 (*R*)
8	1.2	2.0	Toluene	0	20	87 (*R*)
9	1.2	2.0	Hexane	0	42	92 (*R*)
10	1.4	2.0	Hexane	0	45	92 (*R*)
11	1.6	2.0	Hexane	0	54	92 (*R*)
12	1.8	2.0	Hexane	0	65	90 (*R*)
13	1.6	2.0	Hexane	r.t.	86	92 (*R*)
14[d]	1.6	2.0	Hexane	r.t.	94	92 (*R*)
15[d,e]	1.6	2.0	Hexane	r.t.	88	87 (*R*)
16[d,f]	1.6	2.2	Hexane	r.t.	83	91 (*R*)
17[d,g]	1.6	2.0	Hexane	r.t.	89	81 (*R*)
18[d,h]	1.6	2.0	Hexane	r.t.	86	81 (*S*)

[a]Benzaldehyde/(*R*)-**2** = 0.50/0.050 mmol; solvent, 4 mL.
[b]Conversions of **5a** were determined by ^{1}H NMR.
[c]Ee values were determined by HPLC.
[d]2 mL of hexane.
[e]0.025 mmol of (*R*)-**2** (5 mol %).
[f](*R*)-H$_8$-BINOL, 0.050 mmol; Ti(O-*i*-Pr)$_4$, 1.1 mmol.
[g][{(*R*)-BINOLate}Ti(O-*i*-Pr)$_2$]$_x$ ((*R*)-**3**), 0.050 mmol.
[h][{(*S*)-BINOLate}Ti(O-*i*-Pr)$_2$]$_x$ ((*S*)-**3**), 0.050 mmol.

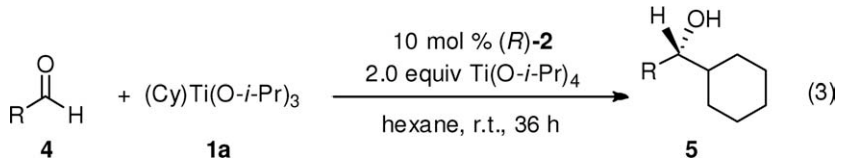


TABLE 2. Asymmetric (Cy)Ti(O-*i*-Pr)$_3$ additions to aldehydes catalyzed by the titanium catalyst of (*R*)-H$_8$-BINOL[a]

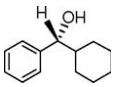
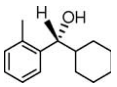
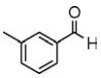
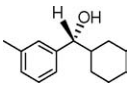
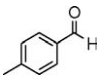
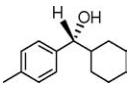
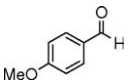
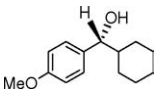
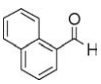
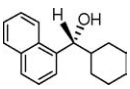
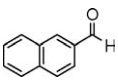
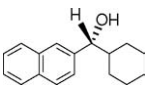
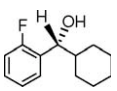
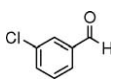
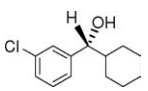
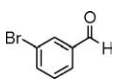
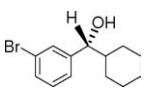
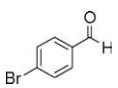
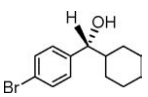
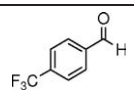
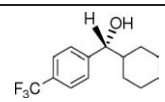
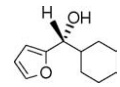
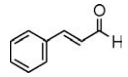
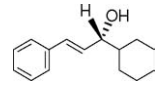
Entry	Substrate **4**		Product **5**		Yield[b] (%)	Ee[c] (%)
1[d]		**4a**		**5a**	90	92 (*R*)
2		**4b**		**5b**	67	90
3		**4c**		**5c**	80	90
4		**4d**		**5d**	83	90
5		**4e**		**5e**	80	90 (*R*)
6		**4f**		**5f**	68	90
7		**4g**		**5g**	73	91
8		**4h**		**5h**	66	93 (*R*)
9		**4i**		**5i**	81	91
10		**4j**		**5j**	80	91
11		**4k**		**5k**	81	85

TABLE 2. (Continued)

Entry	Substrate **4**		Product **5**		Yield[b] (%)	Ee[c] (%)
12		**4l**		**5l**	77	94
13		**4m**		**5m**	85	90
14		**4n**		**5n**	77	76 (*R*)

[a]**4**/**1a**/Ti(O-*i*-Pr)$_4$ = 0.50/0.80/0.050/1.0 mmol; hexane, 2 mL.
[b]Isolated yields of **5**.
[c]1Ee values were determined by HPLC.
[d]24 h.

produce corresponding secondary alcohols **5b–5g** in good yields and excellent enantioselectivities ranged from 90 to 91% ee (entries 2–7). In this study, a steric effect of the substrates was observed. The addition reactions of aromatic aldehydes with an *ortho*-substituent, such as 2-methylbenzaldehyde and 1-naphthylaldehyde, produced products **5b** (entry 2) and **5f** (entry 6) in moderate yields of 67 and 68%, respectively. The addition reactions of aromatic aldehydes containing an electron-withdrawing substituent afforded **5h–5l** in good yields and excellent enantioselectivities (entries 8–12) except a 66% yield for the addition reaction of 2-fluorobenzaldehyde (**4h**; entry 8). The addition reaction of heteroaromatic 2-furaldehyde furnished product **5m** in good yield with an excellent enantioselectivity of 90% ee (entry 13). However, the addition reaction of α,β-unsaturated (*E*)-cinnamaldehyde afforded **5n** in a moderate enantioselectivity of 76% ee (entry 14).

The addition reactions of primaryl alkyltitanium reagent of (*i*-Bu)Ti(O-*i*-Pr)$_3$ (**1b**) were subsequently investigated at 0°C (Eq. 4); the results are presented in Table 3. The solvent effect was first screened in the absence of Ti(O-*i*-Pr)$_4$ (entries 1–4), affording addition product **6a** in conversions ranging from 53 to 76%. Interestingly, it was found that THF is the best solvent for *i*-butyl addition reactions. Though conversions of **6a** vary in different solvents, the enantioselectivities

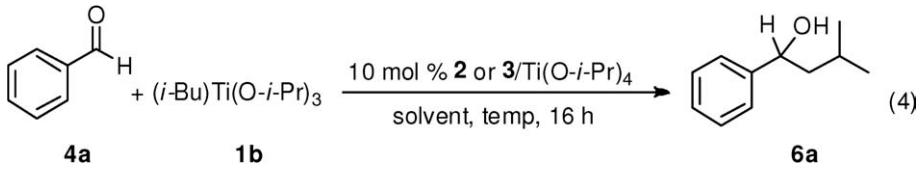


TABLE 3. Optimizations of asymmetric (*i*-Bu)Ti(O-*i*-Pr)$_3$ additions to benzaldehyde catalyzed by a titanium catalyst of (*R*)-H$_8$-BINOL, (*R*)-BINOL, or (*S*)-BINOL[a]

Entry	**1b** (equiv)	Ti(O-*i*-Pr)$_4$ (equiv)	Solvent	Temp. (°C)	Conv.[b] (%)	Ee[c] (%)
1	1.0	0	THF	0	76	93 (*R*)
2	1.0	0	toluene	0	63	91 (*R*)
3	1.0	0	hexane	0	66	93 (*R*)
4	1.0	0	CH_2Cl_2	0	53	91 (*R*)
5	1.1	0	THF	0	60	92 (*R*)
6	1.2	0	THF	0	72	92 (*R*)
7	1.0	0.2	THF	0	55	93 (*R*)
8	1.0	0.5	THF	0	24	93 (*R*)
9	1.0	0	THF	r.t.	81	94 (*R*)
10[d]	1.0	0	THF	r.t.	49	94 (*R*)
11[e]	1.0	0	THF	r.t.	48	94 (*S*)

[a]Benzaldehyde/(*R*)-**2**, (*R*)-**3**, or (*S*)-**3** = 0.50/0.050 mmol; solvent, 4 mL.
[b]Conversions of **6a** were determined by ^{1}H NMR.
[c]Ee values were determined by HPLC.
[d](*R*)-**3**, 0.050 mmol.
[e](*S*)-**3**, 0.050 mmol.

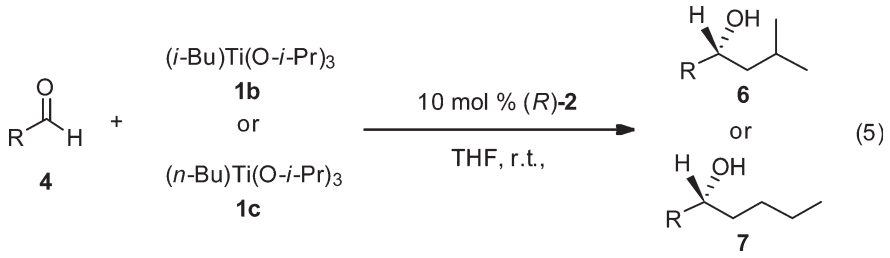
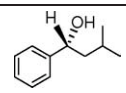
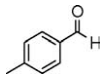
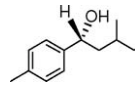
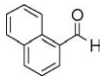
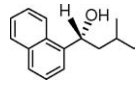
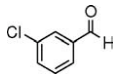
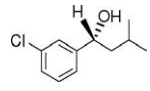
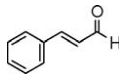
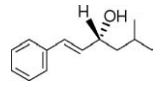
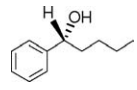
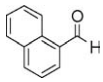
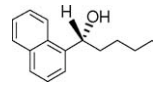
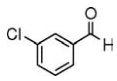
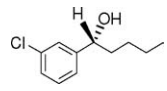
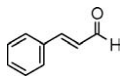
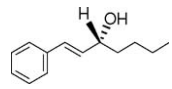


TABLE 4. Asymmetric (*i*-Bu)Ti(O-*i*-Pr)$_3$ or (*n*-Bu)Ti(O-*i*-Pr)$_3$ additions to aldehydes catalyzed by the titanium catalyst of (*R*)-H$_8$-BINOL[a]

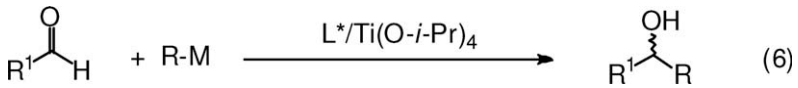
Entry	1	Substrate 4	Time (h)	Product 6 or 7		Yield[b] (%)	Ee[c] (%)
1	**1b**		16		**6a**	78	94 (*R*)
2	**1b**		16		**6b**	78	92 (*R*)
3	**1b**		24		**6c**	80	86 (*R*)
4	**1b**		20		**6d**	80	91 (*R*)
5	**1b**		20		**6e**	76	83 (*R*)
6	**1c**		16		**7a**	78	84 (*R*)
7	**1c**		24		**7b**	72	76 (*R*)
8	**1c**		16		**7c**	80	86 (R)
9	**1c**		20		**7d**	74	75 (*R*)

[a]**4**/**1b** or **1c**/(*R*)-**2** = 0.50/0.50/0.050; THF, 4 mL.
[b]Isolated yields.
[c]Ee values were determined by HPLC.

remain excellent from 91 to 93% ee in (*R*)-configuration. Increasing the amount of **1b** to 1.1 or 1.2 equiv did not improve the conversions of **6a** (entries 5 and 6). Additions of 0.2 or 0.5 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ to the catalytic reaction mixture suppressed the reactions with lower conversions of 55 and 24%, although the enantioselectivities remained an excellent 93% ee (entries 7 and 8). When the reaction was conducted at room temperature, the best enantioselectivity of 94% ee was obtained for **6a** with a good 81% conversion (entry 9). The *i*-butyl addition reactions using the simple BINOLate catalytic system of (*R*)- or (*S*)-**3** produced corresponding secondary alcohols of (*R*)- and (*S*)-**6a** in excellent enantioselectivities of 94% ee. However, conversions were low at 49 and 48% over a reaction time of 16 h (entries 10 and 11).

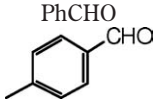
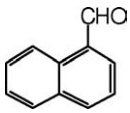
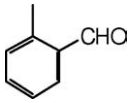
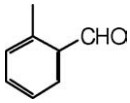
Asymmetric *i*-butyl or *n*-butyl addition reactions of some aldehydes were then carried out under optimized conditions of 10 mol % of the titanium catalytic system of (*R*)-**2**, 1.0 equiv of **1b** or **1c**, without the addition of $Ti(O\text{-}i\text{-}Pr)_4$, and in THF at room temperature (Eq. 5). The results are summarized in Table 4. Additions of *i*-butyl to aromatic aldehydes afforded (*R*)-**6a** to (*R*)-**6d** in good yields and excellent enantioselectivities of 91–94% ee (entries 1–4) except an 86% ee for the addition reaction of 1-naphthylaldehyde (entry 3). Similar to the *c*-hexyl addition reaction, the addition reaction of *i*-butyl to (*E*)-cinnamaldehyde furnished product (*R*)-**6e** in a lower 83% ee (entry 5). For addition reactions of the linear *n*-butyl nucleophile, it was found that lower enantioselectivities of 75–84% ee were obtained for products **7a–7d** (entries 6–9).

This study demonstrates features of differences on reaction conditions, reactivities, and enanatioselectivities in terms of nucleophiles' steric nature. First, for sterically hindered secondary alkyl of *c*-hexyl, addition reactions are slower with a longer reaction time of 36 h required (Table 2) as com-



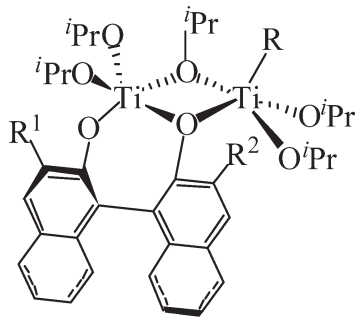
(6)

TABLE 5. The stereochemistry of organometallic additions to aldehydes catalyzed by titanium catalysts of BINOLs or BINOL derivatives

Entry		R—M	L*	Ee (%)	*Re*- or *Si*-addition	Ref.
1	PhCHO	$ZnEt_2$	(*S*)-BINOL	92 (*S*)	*Si*	66
2.	PhCHO	$ZnEt_2$	(*R*)-H_4-BINOL	91 (*R*)	*Re*	69
3	PhCHO	$ZnEt_2$	(*S*)-H_8-BINOL	98 (*S*)	*Si*	71
4		$ZnEt_2$	(*R*)-3-R-BINOL	94 (*R*)	*Re*	11
5		$ZnEt_2$	(*R*)-3,3′-R_2-BINOL	53 (*R*)	*Re*	67
6	PhCHO	*n*-BuMgBr	(*S*)-BINOL	92 (*S*)	*Si*	32
7	PhCHO	*n*-BuMgCl	(*R*)-3-R-BINOL	93 (*R*)	*Re*	30
8	PhCHO	Phenylacetylene/$ZnMe_2$	(*R*)-H_8-BINOL	92 (*S*)	*Re*	72
9	PhCHO	Phenylacetylene/$ZnEt_2$	(*S*)-BINOL	90 (*R*)	*Si*	73
10	PhCHO	$AlEt_3$	(*R*)-BINOL	81 (*R*)	*Re*	17
11	PhCHO	$AlEt_3$	(*S*)-H_8-BINOL	96 (*S*)	*Si*	17
12	PhCHO	*p*-tolylLi	(*R*)-3-R-H_8-BINOL	92 (*S*)	*Re*	34
13		$AlPh_3$(THF)	(*R*)-H_8-BINOL	96 (*R*)	*Re*	24
14		$AlPhEt_2$(THF)	(*R*)-H_8-BINOL	96 (*R*)	*Re*	28
15	PhCHO	(Cy)Ti(O-*i*-Pr)$_3$	(*R*)-H_8-BINOL	90 (*R*)	*Re*	This work
16	PhCHO	(*i*-Bu)Ti(O-*i*-Pr)$_3$	(*R*)-H_8-BINOL	94 (*R*)	*Re*	This work
17	PhCHO	(*n*-Bu)Ti(O-*i*-Pr)$_3$	(*R*)-H_8-BINOL	84 (*R*)	*Re*	This work

pared with reaction times of 16–24 h for addition reactions of the primary alkyl of *i*-butyl or *n*-butyl nucleophile (Table 4). This effect is attributed to the steric hindrance of secondary *c*-hexyl nucleophile on active metallic species that retards an access of the aldehyde substrate. Second, a larger amount of 1.6 equiv (Cy)Ti(O-*i*-Pr)$_3$ (**1a**) is required to ensure higher yields and enantioselectivities for the addition products (Tables 1 and 2) as compared with 1.0 equiv of **1b** or **1b** used for primary alkyl addition reactions (Tables 3 and 4). Third, additional Ti(O-*i*-Pr)$_4$ of up to 2.0 equiv is required to improve both conversion and enantioselectivity of the product derived from the addition of the secondary *c*-hexyl nucleophile. The above phenomenon is a general feature for titanium-catalyzed addition reactions of organozinc, organoaluminum, Grignard, or organolithium reagents to organic carbonyls.[5–34] In contrast, addition reactions of primary alkyls of *i*-butyl and *n*-butyl do not require the addition of Ti(O-*i*-Pr)$_4$ to the reaction mixture which is a feature observed for the asymmetric addition reactions of alkyltitanium reagents.[35,40,41] Fourth, hexane is the best solvent for *c*-hexyl addition reactions as compared with THF solvent for *i*-butyl or *n*-butyl addition reactions. THF's coordinating ability is unfavorable for the addition of bulkier *c*-hexyl toward aldehydes. Fifth, for addition reactions of primaryl alkyls, the addition reactions of linear *n*-butyl nucleophile to aldehydes furnish the addition products in enantioselectivities of ~10% ee lower than those of corresponding branched *i*-butyl addition products.

This study shows that the stereochemical nature of the addition products is governed by the steric configuration of the BINOLate ligands. To illustrate the generality of the stereochemical nature for addition products using different organometallic reagents, catalytic reactions of titanium complexes of BINOLs,[32,36,66] 3-substituted BINOLs,[11,30,67,68] 3,3′-disubstituted BINOLs,[67,68] H_4-BINOLs,[69,70] or H_8-BINOLs[71] were examined (Eq. 6). The stereochemical nature of products are summarized in Table 5. For addition reactions of $ZnEt_2$[11,66,67,69,71] or RMgX,[30–33] it is found that regardless of that the ligands are the simple BINOLs, 3-substituted BINOLs, 3,3′-disubstituted BINOLs, H_4-BINOLs, or H_8-BINOLs, the absolute structures of the predominant products are determined by the absolute configurations of the BINOLate ligands (entries 1–7). For catalysts of (*S*)-BINOL and its derivatives, the nucleophile adds to aromatic aldehydes predominantly from the *Si*-face to give the (*S*)-alcohols as major products, and the catalysts of (*R*)-BINOL and its derivatives produce major *R*-products from the *Re*-face addition of the nucleophile. Similarly, products from the *Re*-face or the *Si*-face addition of Zn-phenylacetylide[72,73] or $AlEt_3$[17] reagents have been obtained using the catalysts of (*R*)- or (*S*)-BINOL derivatives (entries 8–11), respectively. The same phenomena have also been observed for the aryl addition of *p*-tolylLi,[34] $AlPh_3$(THF),[24,27] or $AlPhEt_2$(THF)[28] to benzaldehyde or 2-methylbenzaldehyde (entries 13–15). This study shows that addition reactions of RTi(O-*i*-Pr)$_3$ produced desired products having the same stereochemistry (entries 15–17). The above observations illustrate that substituents at 3-position or 3,3′-positions of the BINOLate ligands do not affect the stereochemistry of the major products. The same phenamenon also applies to catalysts of H_4-BINOL or H_8-BINOL ligands. In addition, the same stereochemistry for products derived from addition reactions of organozinc, Grignard, organolithium, organoaluminum, or organotitanium compounds suggests that the catalytic reactions involve acitve species with similar structures which are proposed to be dititanium species **I** containing one BINOLate ligand and the nucleophile.[11,24,33,36,38]



I

CONCLUSIONS

Three alkyltitanium reagents of RTi(O-*i*-Pr)$_3$ (R = Cy, *i*-Bu, and *n*-Bu) were synthesized in high yields. Asymmetric RTi(O-*i*-Pr)$_3$ additions to aldehydes catalyzed by the titanium complexes of (*R*)-H_8-BINOL were investigated. The titanium catalyst of H_8-BINOL showed better reactivity and enantioselectivity than BINOL's catalysts. This study demonstrates that alkyltitanium addition reactions could be conducted under a mild condition at room temperature, affording secondary alcohols in good yields and good to excellent enantioselectivities of up to 94% ee. For the catalyst of (*R*)-H_8-BINOL or (*R*)-BINOL, alkyl nucleophiles added to the aldehydes from a *Re*-face to produce the (*R*)-products, and the catalyst of (*S*)-BINOL provided the (*S*)-product from a *Si*-face addition. Substrates' steric effect was observed, and lower yields of addition products were obtained for aromatic aldehydes bearing an *ortho*-substitutent. For RTi(O-*i*-Pr)$_3$ reagents, profound steric effects in terms of the bulkiness of R nucleophiles were observed. Addition reactions of the secondary *c*-hexyl nucleophile required the addition of 2.0 equiv of Ti(O-*i*-Pr)$_4$, the higher amount of 1.6 equiv (Cy)Ti(O-*i*-Pr)$_3$, the longer reaction time of 36 h, and the reaction conducting in noncoordinating hexane solvent. On the other hand, addition reactions of primary alkyl of *i*-butyl or *n*-butyl did not require the addition of Ti(O-*i*-Pr)$_4$ and were carried out in coordinating solvent of THF using 1.0 equiv (*i*-Bu)Ti(O-*i*-Pr)$_3$ or (*n*-Bu)Ti(O-*i*-Pr)$_3$ over shorter reaction times of 16–24 h. This study directly supports the argument of that titanium-catalyzed asymmetric additions of organozinc, organoaluminum, Grignard, or organolithium reagents to organic carbonyls involve the addition of organotitanium reagents.

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