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Enantioselective Additions of Aryltitanium Tris(isopropoxide) to Ketones: Structure of [(*i*-PrO)$_2$Ti{μ-(*S*)-BINOLate}(μ-O-*i*-Pr)TiPh(O-*i*-Pr)$_2$], Study of Mechanistic and Stereochemical Insights

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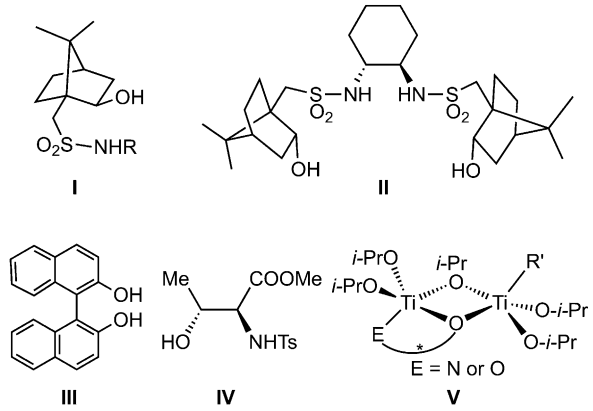
Abstract: Aryl addition reactions of ArTi(O-*i*-Pr)$_3$ to aromatic, heteroaromatic, or α,β-unsaturated ketones are described, producing tertiary alcohols in good to excellent enantioselectivities of up to 97% *ee*. The structure of the dititanium complex [(*i*-PrO)$_2$Ti{μ-(*S*)-BINOLate}(μ-O-*i*-Pr)TiPh(O-*i*-Pr)$_2$] [(*S*)-**4**] that simultaneously bears a chiral directing ligand and a nucleophile is reported. Complex (*S*)-**4** possesses a pocket structure and has been illustrated as the key active species for addition reactions of both aldehydes and ketones. Mechanistic and stereochemical insights concerning addition reactions of organometallic reagents to organic carbonyls are rationalized based on the pocket structure and pocket size of (*S*)-**4**.

Keywords: aryl addition; aryltitaniums; enantioselectivity; ketones; titanium



Introduction

Titanium-catalyzed asymmetric addition reactions of organometallic reagents to aldehydes have been established as one of the most powerful synthetic protocols for the synthesis of bioactive chiral secondary alcohols, and a wide variety of ligands has been demonstrated to be highly enantioselective.[1,2] By contrast, the construction of chiral tertiary alcohols *via* titanium-catalyzed addition reactions of ketones has been less reported. Only a few ligand types, such as camphorsulfonamide **I**,[3] camphordisulfonamide **II**,[4] BINOL **III**[5] or sulfonamide alcohol **IV**,[6] have proven to be effective when organozinc or organotin compounds are used as nucleophiles. Recently, we found that organoalanes[7] and organotitanium[2,8] reagents are excellent nucleophile sources for addition reactions of aromatic or α,β-unsaturated ketones employing the titanium catalyst derived from BINOLs. In addition, a few examples of addition reactions of organoboron or organozinc compounds to ketones have been reported.[9] Despite extensive studies on titanium-catalyzed addition reactions of aldehydes, the reactivity and stereochemical insights have not been well explored. Previous studies have suggested that the titanium-catalyzed addition reactions of aldehydes involve a dititanium active species **V** containing only one bidentate chiral ligand and a nucleophile R′.[3b,10] In terms of stereochemistry, titanium catalysts of (*R*)-BINOLate derivatives, such as (*R*)-BINOL,[11] 3-substituted (*R*)-BINOL,[12] 3,3′-disubstituted (*R*)-BINOL,[13] (*R*)-H$_4$-BINOL[14] as well as (*R*)-H$_8$-BINOL,[2,7e,10e,15] induce a *Re*-face addition to aldehydes, and the catalysts of (*S*)-BINOLate derivatives direct an *Si*-face addition.[11,16] By contrast, studies of titanium-catalyzed organoalanes[7] or (3-furyl)Ti(O-*i*-Pr)$_3$[8] addition reactions of aromatic/heteroaromatic or α,β-

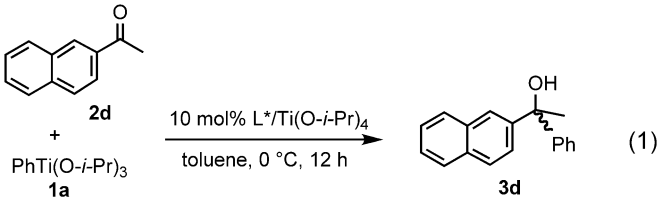
unsaturated ketones reveal a reverse stereochemical nature, such as a *Re*-face addition from a titanium catalyst of (*S*)-BINOL. Furthermore, in terms of reactivity and enantioselectivity, the excellent titanium catalyst of H_8-BINOLate for addition reactions of aldehydes does not work well for ketones,[2] and the titanium/BINOL systems are not good catalysts for aliphatic ketones.[7,8] Given the above observations, two questions are raised. First, is the dititanium active species **V** established for nucleophilic addition reactions of aldehydes also an active species for addition reactions of ketones? If the answer is yes, then the second question is what would be the key structural feature of the active species that causes the dramatic changes in stereochemistry and reactivity toward aldehydes and ketones?

To explore the mechanistic and stereochemical insights of titanium-catalyzed addition reactions of organic carbonyls, we here report asymmetric addition reactions of ArTi(O-*i*-Pr)$_3$[17] (**1**) to ketones. The addition reactions of aromatic or α,β-unsaturated ketones afforded tertiary alcohols in good to excellent enantioselectivities of up to 97% *ee*. Importantly, the structure of dititanium complex of [(*i*-PrO)$_2$Ti{μ-(*S*)-BINOLate}(μ-O-*i*-Pr)TiPh(O-*i*-Pr)$_2$] [(*S*)-**4**] is reported. The reverse stereochemical nature for addition reactions of ketones as compared to aldehydes and the mechanistic insights are rationalized based on the structure and stoichiometric reactions of (*S*)-**4**.

Results and Discussion

The reaction was first optimized for the addition of PhTi(O-*i*-Pr)$_3$ (**1a**) to 2′-acetonaphthone (**2d**) [Table 1, Eq. (1)] employing 10 mol% titanium complexes of (*R*)-BINOL, (*S*)-BINOL or (*R*)-H_8-BINOL, and the results are summarized in Table 1. When using 1.5 equivalents of PhTi(O-*i*-Pr)$_3$ and in the absence of Ti(O-*i*-Pr)$_4$, the catalysts of (*S*)- or (*R*)-BINOL produced addition product **3d** in similar conversions of 96 and 94% (entries 1 and 2) over a reaction time of 12 h. Enantioselectivities of **3d** were comparable for 89 and 88% *ee* but have the opposite absolute structures. By contrast, the titanium catalyst of (*R*)-H_8-BINOL was sluggish, furnishing **3d** in a low conversion of 32% and a low enantioselectivity of 18% *ee* (entry 3). Reducing or increasing the amounts of PhTi(O-*i*-Pr)$_3$ afforded **3d** in somewhat lower conversions or lower enantioselectivities (entries 4–6). The effects of temperature and addition of 0.25, 0.50, or 0.75 equiv. of Ti(O-*i*-Pr)$_4$ to the catalytic solution were subsequently investigated (entries 7–10), and it was found that the optimized reaction conditions were 1.5 equiv. PhTi(O-*i*-Pr)$_3$, 0.50 equiv. Ti(O-*i*-Pr)$_4$, and a reaction temperature of 0 °C, producing **3d** in a 94% conversion and a 93% *ee* (entry 8). This study

Table 1. Optimizations of titanium catalytic systems of addition reactions of PhTi(O-*i*-Pr)$_3$ to 2′-acetonaphthone.[a]



(1)

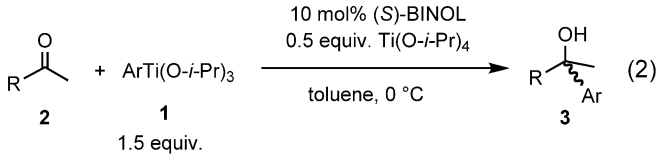
Entry	L*	**1a** (equiv.)	Ti(O-*i*-Pr)$_4$ (equiv.)	Conv.[b] [%]	*ee*[c] [%]
1	(*S*)-BINOL	1.5	0	96	89
2	(*R*)-BINOL	1.5	0	94	88
3	(*R*)-H_8-BINOL	1.5	0	32	18
4	(*S*)-BINOL	1.0	0	83	91
5	(*S*)-BINOL	1.25	0	92	91
6	(*S*)-BINOL	2.0	0	97	86
7	(*S*)-BINOL	1.5	0.25	94	92
8	(*S*)-BINOL	1.5	0.50	94	93
9	(*S*)-BINOL	1.5	0.75	89	93
10[d]	(*S*)-BINOL	1.5	0.50	100	71

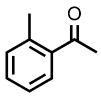
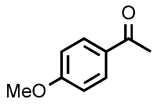
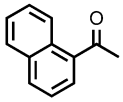
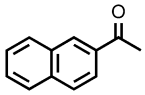
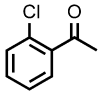
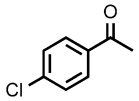
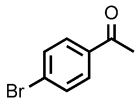
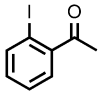
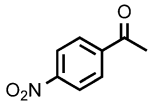
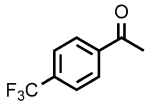
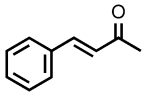
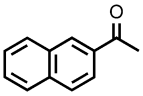
[a] **2d**, 0.50 mmol; toluene, 7 mL.
[b] Conversions were calculated based on ^{1}H NMR spectra of the product.
[c] The *ee* values were determined by HPLC using an appropriate chiral column.
[d] Room temperature.

has demonstrated that the titanium catalyst of BINOL is an efficient system for nucleophilic addition reactions of aromatic/heteroaromatic or α,β-unsaturated ketones in terms of reactivity and enantioselectivity, compared to systems demonstrated in previous studies.[3–6]

The reaction scope of aryl additions of ArTi(O-*i*-Pr)$_3$ to representative ketones under the optimized conditions was then examined [Table 2, Eq. (2)], and results summarized in Table 2. Similar to the AlAr$_x$Et$_{3-x}$(THF)[7a,e] ($x=3$ or 1) addition reactions, the titanium catalyst of (*S*)-BINOL worked well for ArTi(O-*i*-Pr)$_3$ addition reactions of aromatic ketones, affording products **3** in excellent enantioselectivities of ≥90% *ee* (entries 1–10) except for 2′-methylacetophenone (**2a**). The addition of PhTi(O-*i*-Pr)$_3$ to the steric hindered substrate of **2a** was rather slow, and the reaction over 48 h furnished **3a** in only a 50% yield with an enantioselectivity of 85% *ee* (entry 1). It is a general feature that addition reactions of the sterically hindered *ortho*-substituted aromatic ketones, such as **3a**, **3e** or 1′-acetonaphthone (**3c**), require longer reaction times in order to achieve products in satisfactory yields. In order to determine the stereochemistry of addition products, the phenyl addition to 2′-iodoacetophenone (**2h**) was conducted over 168 h to furnish **3h** in a 45% yield but with an excellent enantioselectivity of 94% *ee* (entry 8). The absolute

Table 2. Titanium-(*S*)-BINOLate-catalyzed addition reactions of $ArTi(O\text{-}i\text{-}Pr)_3$ to ketones.[a]



Entry	**2**	Ar	Time [h]	**3**	Yield[b] [%]	*ee*[c] [%]
1		Ph	48	**3a**	50	85
2		Ph	24	**3b**	47	90
3		Ph	48	**3c**	40	90
4		Ph	16	**3d**	95	93
5		Ph	16	**3e**	43	94
6		Ph	16	**3f**	89	92
7		Ph	16	**3g**	91	91
8		Ph	168	**3h**	45[d]	94 (*R*)
9		Ph	16	**3i**	90	97
10		Ph	16	**3j**	90	90
11		Ph	16	**3k**	87	84
12		Ph	48	**3l**	75	82
13		Ph	16	**3m**	70	32
14		4-MeC_6H_4	16	**3n**	89	93
15		4-$MeOC_6H_4$	16	**3b**	91	93
16		2-naphthyl	16	**3d**	90	94
17		4-ClC_6H_4	48	**3f**	81	86

[a] Ketone/(*S*)-BINOL/$ArTi(O\text{-}i\text{-}Pr)_3$/$Ti(O\text{-}i\text{-}Pr)_4$ = 0.50/0.050/0.75/0.25 mmol; toluene, 7 mL.
[b] Isolated yield.
[c] The *ee* values were determined by HPLC using appropriate chiral columns.
[d] 54% conversion.

structure of **3h** was confirmed as the *R*-configuration[7a,18] that is derived from a *Re*-face addition of the phenyl nucleophile to the carbonyl carbon of **2h**. However, the same titanium catalyst of (*S*)-BINOL induces an opposite *Si*-face addition of the nucleophiles to the aldehydes.[2]

This catalytic system also applied to addition reactions of α,β-unsaturated (*E*)-1-phenyl-1-buten-3-one or heterocyclic 2-acetylfuran, producing **3k** or **3l** in 84 and 82% *ee* (entries 11 and 12). However, the phenyl addition to aliphatic ketone 2-methyl-3-butanone (**2m**) produced addition product **3m** in a low enantioselectivity of 32% *ee* (entry 13). $ArTi(O\text{-}i\text{-}Pr)_3$ [Ar = 4-MeC_6H_4 (**1b**), 4-$MeOC_6H_4$ (**1c**), 2-naphthyl (**1d**), or 4-ClC_6H_4 (**1e**)] additions to aromatic ketones were also studied to furnish diarylethanols in enantioselectivities ranging from 86 to 94% *ee* (entries 14–17).

To explore the mechanistic insights, $PhTi(O\text{-}i\text{-}Pr)_3$ addition reactions of 2′-acetonaphthone in the presence of 0, 20, 40, 60, 80, or 100% *ee* (*S*)-BINOL afforded the product **3d** in enantioselectivities of 1.7, 16.8, 37.8, 54.3, 75.5, and 91.5% *ee*, respectively. The linear plot of *ee* values of the BINOL ligand *vs.* *ee* values of **3d** (Figure 1) suggests that the active metallic species involves only one BINOLate ligand. The linear effect was also observed for $ArTi(O\text{-}i\text{-}Pr)_3$ addition reactions of aldehydes catalyzed by the titanium derivative of (*R*)-H_8-BINOL,[2a] indicating that addition reactions of both aldehydes and ketones might involve the active species having a similar geometric structure. However, the reverse stereochemistry of

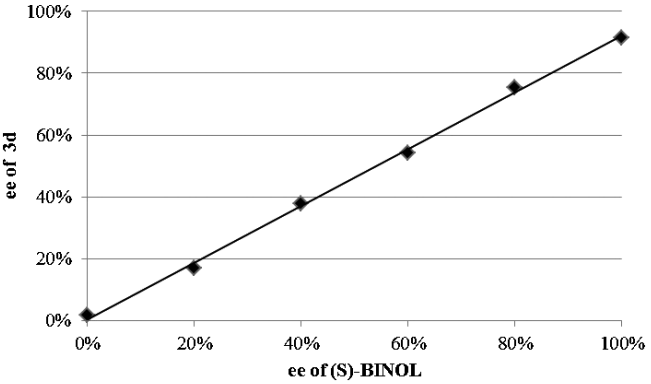


Figure 1. The linear plot of *ee* values of **3d** *vs. ee* values of (*S*)-BINOL.

the nucleophilic addition to ketones was observed, compared to the addition reactions of aldehydes.[2]

To rationalize the stereochemical nature, [Ti{(*S*)-BINOLate}(O-*i*-Pr)$_2$]$_x$[10c] was reacted with one equivalent of PhTi(O-*i*-Pr)$_3$, affording a dititanium complex of formula [(*i*-PrO)$_2$Ti{μ-(*S*)-BINOLate}(μ-O-*i*-Pr)TiPh(O-*i*-Pr)$_2$] [(*S*)-**4**] as an orange crystalline solid. The molecular structure of (*S*)-**4** (Figure 2) shows a dititanium species bearing one (*S*)-BINOLate ligand, and is the first dititanium structure simultaneously containing a chiral ligand and a nucleophile. Even though the solid state structure and elemental analysis confirmed a dititanium species for (*S*)-**4**, the ^{1}H and ^{13}C NMR spectra are quite complicated, suggesting an equilibrium process among (*S*)-**4**, [{(*S*)-BINOLate}Ti(O-*i*-Pr)$_2$]$_x$, and PhTi(O-*i*-Pr)$_3$ in $CDCl_3$ solution.[10b,d,19] Thus, we examined the ^{13}C NMR spectra of PhTi(O-*i*-Pr)$_3$ (**1a**), [Ti{μ-(*S*)-BINOLate}(O-*i*-Pr)$_2$]$_x$, and (*S*)-**4** in CD_2Cl_2 and $CDCl_3$ solutions.

The phenyl reagent **1a** has a dimeric structure of [PhTi(O-*i*-Pr)$_2$(μ-O-*i*-Pr)]$_2$ in CD_2Cl_2 at low temperatures, showing two sets of ^{13}C NMR signals for bridging and terminal O-*i*-Pr ligands. The phenyl characteristic ^{13}C NMR signal of **1a** in $CDCl_3$ at 20 °C appears at $\delta = 187.5$ ppm and a broad methine ^{13}C NMR peak is found at $\delta = 77.3$ ppm [Figure 3 (a)]. Since the solid state structures of both dimeric [Ti{μ-(*S*)-BINOLate}-(O-*i*-Pr)$_2$]$_2$ and trimeric [Ti{μ-(*S*)-BINOLate}(O-*i*-Pr)$_2$]$_3$ species are known,[10c] the ^{13}C NMR spectrum of [{(*S*)-BINOLate}Ti(O-*i*-Pr)$_2$]$_x$ is very complicated at low temperatures. Fortunately, the spectrum of [{(*S*)-BINOLate}Ti(O-*i*-Pr)$_2$]$_x$ in $CDCl_3$ solution at 20 °C exhibits only 10 naphtholate ^{13}C NMR signals [Figure 3 (b)], indicating a dynamic exhange process of the bridging and the terminal naphtholate moieties of the (*S*)-BINOLate ligand. The ^{13}C NMR spectrum of (*S*)-**4** is shown in Figure 3 (c). Close examination of the spectrum reveals that the solution contains [{(*S*)-BINOLate}Ti(O-*i*-Pr)$_2$]$_x$, suggesting that (*S*)-**4** partially dissociates in solution to afford [{(*S*)-BINOLate}Ti-

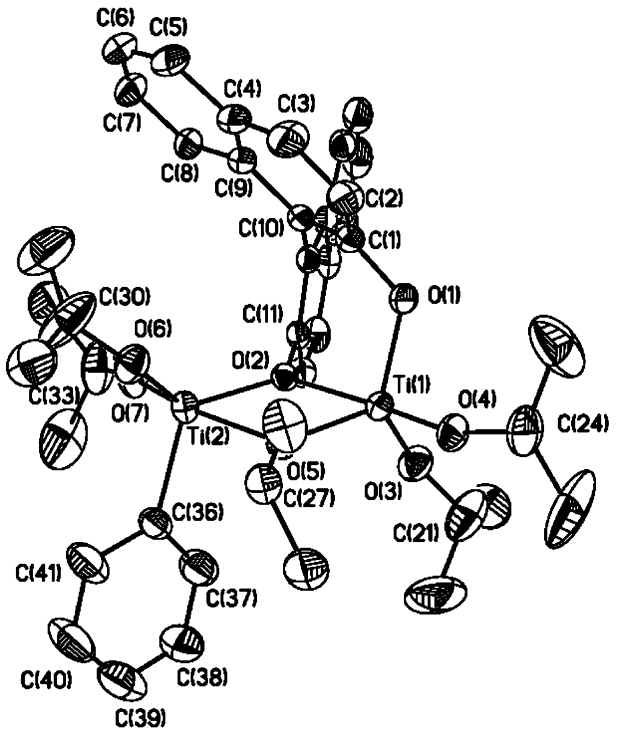


Figure 2. The molecular structure of (*S*)-**4**. Hydrogens are omitted for clarity.

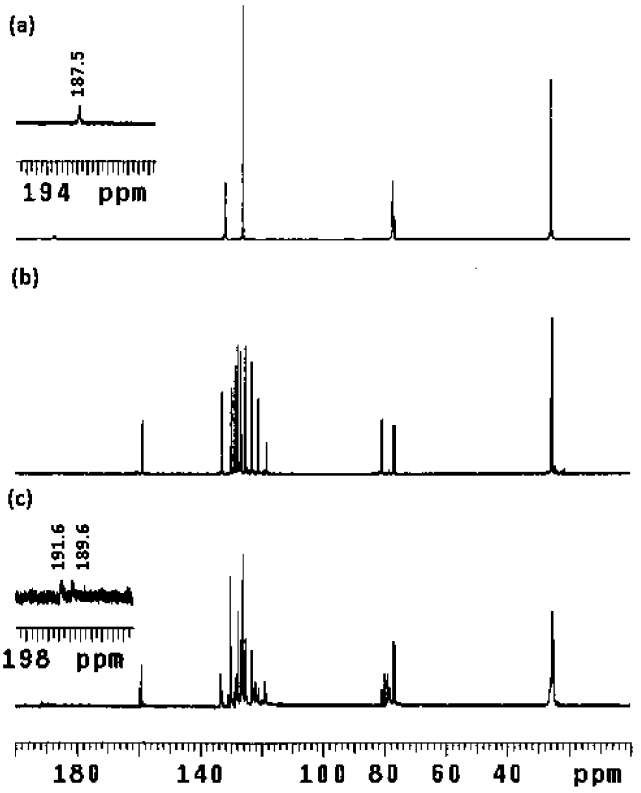


Figure 3. ^{13}C NMR spectra of (a) PhTi(O-*i*-Pr)$_3$, (b) [{(*S*)-BINOLate}Ti(O-*i*-Pr)$_2$]$_x$ and (c) (*S*)-**4** in $CDCl_3$ at 20 °C.

$(O\text{-}i\text{-}Pr)_2]_x$ and $[PhTi(O\text{-}i\text{-}Pr)_2(\mu\text{-}O\text{-}i\text{-}Pr)]_2$. In addition to the naphthyl ^{13}C NMR signals, two characteristic phenyl peaks at $\delta = 191.6$ and 189.6 ppm and 4 methine ^{13}C NMR peaks at $\delta = 80.9$, 80.1, 79.0 and 78.5 ppm are observed for (*S*)-**4**, indicating the presence of two phenyl-containing species in solution. The methine ^{13}C NMR peak at $\delta = 80.9$ ppm belongs to the signal of $[\{(S)\text{-BINOLate}\}Ti(O\text{-}i\text{-}Pr)_2]_x$. However, the above mentioned phenyl and methine ^{13}C NMR characteristic signals do not match to signals of $[PhTi(O\text{-}i\text{-}Pr)_2(\mu\text{-}O\text{-}i\text{-}Pr)]_2$. One characteristic phenyl peak is attributed to the signal of (*S*)-**4**. The other phenyl resonance might be due to an unknown species or a species of trititanium complex containing one BINOLate ligand resulting from a further reaction of $[PhTi(O\text{-}i\text{-}Pr)_2(\mu\text{-}O\text{-}i\text{-}Pr)]_2$ with (*S*)-**4** since the trititanium/BINOLate $[Ti_3\{3,3'\text{-}(MeOCH_2)_2BINOLate\}(\mu\text{-}O)(O\text{-}i\text{-}Pr)_8]$ structure has been reported recently.[20]

Although the possibility of the trititanium species (or unknown species) being the active catalyst is not ruled out based on the linear effect of the catalytic reaction, we propose, for two reasons, that the dititanium (*S*)-**4** is the active catalyst. First, structures of dititanium complexes of $[Ti_2(\mu\text{-BINOLate})(OR)_6]$[10c] and $[Ti_2(\mu\text{-}H_8\text{-BINOLate})(OR)_6]$[21] are well known in addition to the structure of (*S*)-**4**. Second, previous mechanistic studies of titanium catalysts of BINOLate, diolate, and *N*-sulfonylated β-amino alcoholate suggested that the dititanium species containing one chiral ligand are involved in the catalytic addition reactions.[10]

To demonstrate that (*S*)-**4** is the key active species for addition reactions of both aldehydes and ketones, a stoichiometric reaction of (*S*)-**4** with 2-naphthylaldehyde produced the secondary (*S*)-2-naphthylphenylmethanol in an 80% *ee*, compared to the 77% *ee* obtained from the catalytic reaction,[2a] and a reaction with 2′-acetonaphthone afforded tertiary diarylethanol **3d** in an 88% *ee*, compared to the 89% *ee* from the catalytic reaction (Table 1, entry 1). The above results support the argument that the (*S*)-**4** complex is the active species for aryl addition reactions of both aldehydes and aromatic ketones. The structure of (*S*)-**4** that contains a chiral ligand is also consistent with the observations of the linear effect of *ee* values of BINOLate ligands *vs.* *ee* values of products in addition reactions of either aldehydes or aromatic ketones. Stoichiometric reactions of (*S*)-**4** with 2-naphthylaldehyde or 2′-acetonaphthone rule out the possibility of pi-pi interactions for directing the reverse stereochemistry since both substrates have a naphthalene moiety for pi-pi interaction with the BINOLate ligand.

To account for differences in reactivity and stereochemistry toward aldehydes and ketones, the following issues need to be further elucidated. First, how does the (*S*)-**4** structure direct opposite facial additions toward aldehydes and aromatic ketones? Second, why does the (*S*)-**4** not induce high enantioselectivities for addition reactions of aliphatic ketones? Third, why is the titanium catalyst of $(R)\text{-}H_8$-BINOL sluggish for addition reactions of ketones? To rationalize the above observations, we examined the pocket sizes of the dititanium complex of (*S*)-**4** and the structures of $[(i\text{-}PrO)_2Ti\{\mu\text{-}(rac)\text{-BINOLate}\}(\mu\text{-}O\text{-}i\text{-}Pr)Ti(O\text{-}i\text{-}Pr)_3]$[10c] [(*rac*)-**5**] and $[(CyO)_2Ti\{\mu\text{-}(R)\text{-}H_8\text{-BINOLate}\}(\mu\text{-OCy})Ti(OCy)_3]$[21] [(*R*)-**6**] (Cy = cyclohexyl) reported by Walsh et al. Since the naphthyl ring of the BINOLate ligand is planar, the closest contacts of the pocket are from the alkoxide methine hydrogen to the naphthyl carbon atoms. They are 3.109 Å in (*S*)-**4** and 3.315 Å in (*rac*)-**5**. For the dititanium complex of $(R)\text{-}H_8$-BINOLate [(*R*)-**6**], the shortest contact is from a methine hydrogen of one cyclohexyl oxide ligand to the CH_2 hydrogen atoms of the puckered H_4-naphthyl ring, and the distance is only 2.545 Å, which is about 0.6 ~ 0.8 Å shorter than the distances in the BINOLate complexes. All of the above questions can be reasonably rationalized in terms of the pocket sizes of the dititanium species. The small pocket size of the titanium catalysts of H_8-BINOLate accommodates the small hydrogen atom of the aldehydes, accounting for the excellent enantioselectivities of the addition products. By contrast, the aliphatic or aromatic groups of ketones are too large to fit in the small pocket size, resulting in the low reactivity and low enantioselectivity of the tertiary alcohols. For titanium catalysts of BINOLate, the planar aromatic, heteroaromatic, or α,β-unsaturated moiety fits the pocket for inducing high enantioselectivities of tertiary alcohols. Based on the observed reversal of stereochemistry, the small hydrogen atom inserts into the pocket of (*S*)-**4** predominantly for an *Si*-face addition of the nucleophile [Figure 4 (a)]. Conversely, for addition reactions of ketones, the planar group of the aromatic, heteroaromatic, or α,β-unsaturated unit in-

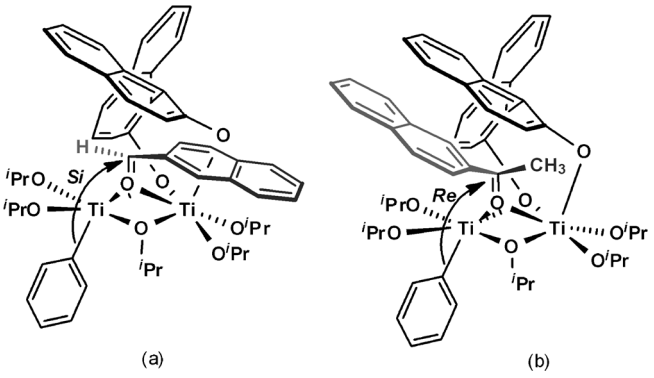


Figure 4. (a) The *Si*-face addition of the phenyl nucleophile in (*S*)-**4** to 2-naphthylaldehyde; (b) The *Re*-face addition of Ph to 2′-acetonaphthone.

serts into the pocket of (*S*)-**4** for a *Re*-face addition [Figure 4 (b)]. In addition, the pocket size of (*S*)-**4** is not large enough for aliphatic groups, and thus a low yield and enantioselectivity were observed for the product derived from the addition reaction of aliphatic ketone (Table 2, entry 13).

Conclusions

In summary, a simple and highly enantioselective aryl addition reaction of ArTi(O-*i*-Pr)$_3$ to ketones is reported. The titanium catalyst of BINOL is the best performing system for aromatic/heteroaromatic or α,β-unsaturated ketones. But the same system does not work well for aliphatic ketones, and the titanium system of H_8-BINOL is sluggish for addition reactions of ketones. The most important feature of this study is a report of the first dititanium structure of (*S*)-**4** that simultaneously bears the chiral directing BINOLate ligand and the phenyl nucleophile. Stoichiometric reactions of (*S*)-**4** with aromatic aldehyde or ketone support the argument that (*S*)-**4** is an active species in the crucial and final step of the catalytic addition reaction of organic carbonyl compounds. The pocket structure and pocket sizes of the dititanium species reasonably account for all reaction features of the titanium-catalyzed addition reactions, including the reverse stereochemistry of addition faces of nucleophiles to the aldehydes and to the aromatic ketones, the sluggish reactions and low enantioselectivities of the titanium catalysts of BINOLate toward the aliphatic ketones, and the poor reactivity and stereocontrol of the titanium catalysts of H_8-BINOLate for ketones. The mechanistic and stereochemical features described in this study also apply to titanium catalysts of C_2-symmetric diols and C_1-symmetric *N*-sulfonylated amino alcohols. Furthermore, the mechanistic insights illustrated in this study may also apply to titanium-catalyzed nucleophilic addition reactions of organic carbonyls employing organometallic reagents of organozinc, organoalanes, organolithium, Grignard, and organotitanium reagents as well.

Experimental Section

General Remarks

ArTi(O-*i*-Pr)$_3$[17] was prepared according to literature procedures. Ti(O-*i*-Pr)$_4$ was freshly distilled prior to use. (*R*)-BINOL, (*S*)-BINOL, and (*R*)-H_8-BINOL were obtained commercially. All syntheses and manipulations were carried out under a dry nitrogen atmosphere using standard Schlenk techniques or in a glovebox. Solvents were dried by refluxing for at least 24 h over P_2O_5 (dichloromethane) or sodium/benzophenone (THF, *n*-hexane or toluene) and were freshly distilled prior to use. ^{1}H NMR spectra were obtained with a Varian Mercury-400 (400 MHz) or an INOVA-600 (600 MHz) spectrometer, and ^{13}C NMR spectra were recorded with the Varian Mercury-400 (100.70 MHz) or the INOVA-600 (150 MHz). ^{1}H and ^{13}C chemical shifts were measured relative to TMS (0.00 ppm) as the internal reference. Elemental analyses were performed using a Heraeus CHN-O-RAPID instrument.

General Procedures for the Asymmetric ArTi(O-*i*-Pr)$_3$ Addition Reaction of Ketone

Under a dry nitrogen atmosphere, (*S*)-BINOL (0.0143 g, 0.0500 mmol), PhTi(O-*i*-Pr)$_3$ (0.227 g, 0.750 mmol), and Ti(O-*i*-Pr)$_4$ (0.075 mL, 0.25 mmol) were mixed in dry toluene (6 mL) at room temperature. The mixture was cooled to 0 °C and treated with a ketone (0.500 mmol) in 1 mL toluene. The mixture was allowed to react at 0 °C for a given period and quenched with 2 M aqueous NaOH (1 mL). The aqueous phase was then extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by column chromatography to give the desired product **3**. Enantiomeric excesses of products were determined by HPLC using suitable chiral columns.

Synthesis of [{(*S*)-BINOLate}Ti(O-*i*-Pr)$_2$]$_x$[10c]

To a solution of (*S*)-BINOL (1.43 g, 5.00 mmol) in 50 mL toluene, Ti(O-*i*-Pr)$_4$ (1.50 mL, 5.00 mmol) was added at room temperature under a dry nitrogen atmosphere. After reacting for 2 h, the toluene was removed under reduced pressures to give a quantitative yield of [{(*S*)-BINOLate}Ti-(O-*i*-Pr)$_2$]$_x$ as a dark red solid which was used directly without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, J = 8.0 Hz, 2H), 7.51–7.47 (m, 2H), 7.38–7.34 (m, 2H), 7.18–7.14 (m, 4H), 6.78–6.71 (m, 2H), 4.51 (sept, J = 6.0 Hz, 2H), 1.10 (d, J = 6.0 Hz, 6H), 1.04 (d, J = 6.0 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 158.9, 133.0, 130.0, 128.8, 128.0, 126.9, 125.4, 123.3, 121.1, 118.5, 80.9, 25.7, 25.4.

Synthesis of [(*i*-PrO)$_2$Ti{μ-(*S*)-BINOLate}(μ-O-*i*-Pr)-TiPh(O-*i*-Pr)$_2$] [(*S*)-4]

To a solution of [{(*S*)-BINOLate}Ti(O-*i*-Pr)$_2$]$_x$ (4.50 g, 10.0 mmol based on the formula of {(*S*)-BINOLate}Ti(O-*i*-Pr)$_2$ in 30 mL hexane, PhTi(O-*i*-Pr)$_3$ (4.53 g, 15.0 mmol) in 30 mL hexane was added at room temperature under a dry nitrogen atmosphere. After reacting for 1 h, the solution was concentrated to about 30 mL under reduced pressures. The resulting concentrated solution was allowed to stand at room temperature for 12 h to afford (*S*)-**4** as an orange crystalline solid; yield: 5.51 g (73.2%). The ^{1}H and ^{13}C NMR spectra of (*S*)-**4** reveal complicated patterns. Anal. calcd. for $C_{41}H_{52}O_7Ti_2$: C 65.43, H 6.96%; found: C 65.34, H 6.43%.

X-Ray Crystallography of (*S*)-4

The X-ray diffraction study of suitable crystals of (*S*)-**4** was performed on an Oxford Xcalibur Sapphire3 diffractometer using graphite-monochromated *Mo*-K_α radiation (λ = 0.71073 Å), temperature 100(2) K, and φ and ω scan technique, and semi-empirical absorption was applied in the

data corrections. The structure was solved by direct methods (SHELXTL-97),[22] completed by subsequent difference Fourier syntheses, and refined by full-matrix least squares calculations based on F^2 (SHELXTL-97). Crystal data: $C_{41}H_{52}O_7Ti_2$, MM = 752.63 g mol^{-1}, orthorhombic, space group $P2_12_12_1$, a = 9.9334(2) Å, b = 18.8692(3) Å, c = 21.1612(4) Å, V = 3966.36(13) Å^3, Z = 4, absorption coefficient = 0.449 mm^{-1}, total reflections collected 29237, unique 7790 (R_{int} = 0.0486), goodness of fit indicator = 1.034, R_1 = 0.0458, wR_2 = 0.1188, absolute structure parameter = 0.08(2). CCDC 880452 contains the supplementary crystallographic data for this paper [compound (*S*)-**4**]. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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