ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 11668–11670

www.rsc.org/chemcomm

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Instantaneous room-temperature and highly enantioselective ArTi(O-*i*-Pr)$_3$ additions to aldehydes†

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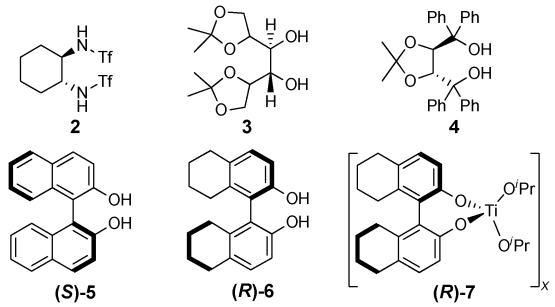
Received 15th August 2011, Accepted 19th September 2011
DOI: 10.1039/c1cc15059f

Direct asymmetric additions of ArTi(O-*i*-Pr)$_3$ to aldehydes catalyzed by a titanium catalyst of (*R*)-H$_8$-BINOL are reported. The reactions proceed instantaneously at room temperature, affording alcohols in ≥ 90% ee. Importantly, the ArTi(O-*i*-Pr)$_3$ reagent differentiates the ligand effectiveness in an order of H$_8$-BINOL > BINOL > TADDOL > diol 3 > disulfonamide 2.

The highly enantioselective addition reactions of arylzinc reagents to aldehydes have been extensively explored in the past decade for the synthesis of diarylmethanols,[1] which are key intermediates leading to bioactive compounds such as neobenodine[2] and cetirizine hydrochloride.[3] A variety of arylzinc sources, such as $ZnPh_2$,[4] mixtures of $ZnR_2/ZnPh_2$,[5] arylzinc reagents from transmetallation of arylboronic acid or arylboron with $ZnEt_2$,[6] and arylzinc from reactions of aryl nucleophile with dialkylzinc or zinc halides,[7] have been introduced for this purpose. The commercially available $ZnPh_2$ and the mixed $ZnPh_2/ZnR_2$ (R = Me or Et) reagents produce the phenyl addition products only. Later, the *in situ*-prepared arylzinc compounds have extended the reaction scope to addition reactions of various aryl nucleophiles.

Recent studies have demonstrated that $AlAr_xEt_{3-x}(THF)$ (x = 3 or 1),[8,9] ArMgX[10] and ArLi[11] compounds are efficient aryl sources for titanium-catalyzed asymmetric aryl addition reactions of organic carbonyls, and excess amounts of $Ti(OR)_4$ are required to ensure the high stereocontrol of the addition products.[12] Roles of excess $Ti(OR)_4$ have been suggested as to generate the dititanium active species bearing a chiral ligand and to facilitate a removal of the product.[13] It has been suggested that the reactions involve the additions of organotitanium species, which are *in situ*-generated from reactions of organometallic compounds with $Ti(OR)_4$. However, direct asymmetric additions of organotitanium reagents have been demonstrated only in a couple of catalytic systems with the reactions being conducted at an initial low temperature of −78 °C[13a,14] or at temperatures ≤ −15 °C.[15] In contrast, our recent study found that the 3-furyl addition of (3-furyl)Ti(O-*i*-Pr)$_3$ to ketones could be conducted at a mild reaction temperature of 0 °C.[16] The above study prompted us to explore direct addition reactions of ArTi(O-*i*-Pr)$_3$ (Ar = Ph (**1a**); *p*-tolyl (**1b**); 4-MeOC$_6$H$_4$ (**1c**); 2-naphthyl (**1d**); 4-ClC$_6$H$_4$ (**1e**); 4-TMSC$_6$H$_4$ (**1f**)) which are effective reagents in late-transition metal-catalyzed asymmetric reactions[17] and coupling reactions.[18]

Addition reactions of PhTi(O-*i*-Pr)$_3$ to 2-naphthaldehyde (**8g**) were first screened using chiral ligands of (1*R*,2*R*)-*N*,*N*′-bis(trifluoromethylsulfonyl)-1,2-cyclohexanediamine (**2**),[19] 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**3**),[20] α,α,α′,α′-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol (**4**, TADDOL),[21] (*S*)-BINOL (**5**),[22] and (*R*)-H$_8$-BINOL (**6**)[23] and complex (*R*)-**7**[24] (eqn (1)); the results are summarized in Table 1. Compounds **2**–**6** are known as highly enantioselective ligands for titanium-catalyzed organozinc addition reactions of aldehydes.



2 **3** **4**

(*S*)-**5** (*R*)-**6** (*R*)-**7**

In the absence of Ti(O-*i*-Pr)$_4$ and at 0 °C, the titanium catalyst of disulfonamide **2** or diol **3** produced 2-naphthylphenylmethanol (**9g**) in 100% conversions over 10 min, but racemic or a low enantioselectivity of 24% ee of **9g** were obtained (entries 1 and 2). The TADDOL **4** yielded **9g** in a 47% ee (entry 3). The catalytic system of (*S*)-BINOL ((*S*)-**5**) produced (*S*)-**9g** in a 77% ee (entry 4), while a catalyst of (*R*)-H$_8$-BINOL ((*R*)-**6**) afforded (*R*)-**9g** in an excellent 92% ee (entry 5). The preformed titanium catalyst of (*R*)-**7** along with 1.2 equiv. PhTi(O-*i*-Pr)$_3$ also afforded (*R*)-**9g** in a similar 93% ee (entry 6). The above results reveal that both the *in situ*-formed titanium catalyst of (*R*)-H$_8$-BINOL and the preformed (*R*)-**7** afford the product in

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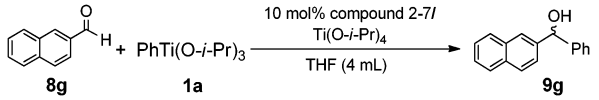
† Electronic supplementary information (ESI) available: General procedures, HPLC conditions and chromatograms, and ^{1}H and ^{13}C NMR spectroscopic data of addition products. See DOI: 10.1039/c1cc15059f

Table 1 Optimizations of asymmetric PhTi(O-*i*-Pr)$_3$ addition to 2-naphthylaldehyde[a]



8g 1a 9g

Entry	Compound	**1a** (equiv.)	T/°C	Time/min	Conv[b] (%)	Ee[c] (%)
1	**2**	1.4	0	10	100	*rac*
2	**3**	1.4	0	10	100	24 (*R*)
3	**4**	1.4	0	10	100	47 (*R*)
4	(*S*)-**5**	1.4	0	10	100	77 (*S*)
5	(*R*)-**6**	1.4	0	10	100	92 (*R*)
6	(*R*)-**7**	1.2	0	10	100	93 (*R*)
7[d]	(*R*)-**7**	1.2	0	10	100	92 (*R*)
8[e]	(*R*)-**7**	1.2	0	10	100	93 (*R*)
9	(*R*)-**7**	1.2	rt	10	100	93 (*R*)
10	(*R*)-**7**	1.2	rt	1	100	93 (*R*)
11[f]	(*R*)-**7**	1.2	rt	—	100	94 (*R*)

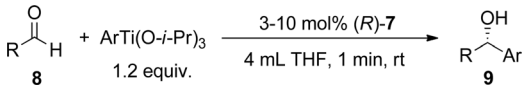
[a] 2-Naphthylaldehyde/**2–7** = 0.50/0.050 mmol; equiv. of PhTi(O-*i*-Pr)$_3$ is relative to 2-naphthylaldehyde. [b] Conversions were determined based on ^{1}H NMR spectra. [c] ee values were determined by HPLC using suitable columns. [d] 0. 25 equiv. Ti(O-*i*-Pr)$_4$ was added. [e] 0.50 equiv. Ti(O-*i*-Pr)$_4$ was added. [f] The reaction was quenched immediately.

the best enantioselectivities. The effect of Ti(O-*i*-Pr)$_4$ was also studied, and additions of 0.25 or 0.50 equiv. of Ti(O-*i*-Pr)$_4$ did not improve the stereoselectivity of the product (entries 7 and 8). To our surprise, the reactions could be carried out at room temperature (entries 9–11) and completed instantaneously, producing (*R*)-**9g** in 94% ee (entry 11). In terms of stereochemistry, the catalyst of (*S*)-BINOL catalyzed the phenyl addition of **8g** from a *Si*-face to yield (*S*)-**9g** (entry 4) predominantly as compared to (*R*)-**9g** obtained from a *Re*-face addition by the catalyst of (*R*)-H$_8$-BINOL (entries 5 and 6).

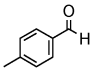
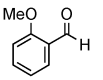
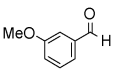
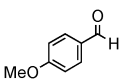
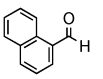
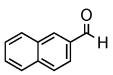
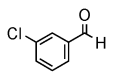
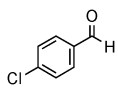
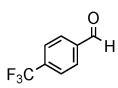
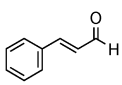
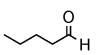
In terms of reactivity and enantioselectivity, this study clearly reveals that the titanium catalyst of the H$_8$-BINOL is currently the most efficient system. In contrast, catalysts of ligand **2–4** are not good enough to attain high enantioselectivities for the PhTi(O-*i*-Pr)$_3$ addition reaction. The low enantioselectivities are attributed to higher levels of background reaction of PhTi(O-*i*-Pr)$_3$. Thus PhTi(O-*i*-Pr)$_3$ differentiates the ligand effectiveness in an order of H$_8$-BINOLs (**6**) > BINOLs (**5**) > TADDOL (**4**) > diol **3** > disulfonamide **2** (Table 1, entries 1–5).

Addition reactions of aromatic, vinylic, heterocyclic and aliphatic aldehydes were subsequently studied with the reaction time kept at 1 min (eqn (2)); the results are listed in Table 2. For aromatic aldehydes with either an electron-donating or an electron-withdrawing substituent at 2-, 3-, or 4-position, PhTi(O-*i*-Pr)$_3$ addition reactions employing 3–10 mol% of (*R*)-**7** afforded chiral secondary diarylmethanols **9a–9k** in >90% yields and ≥ 90% ee (entries 1–11). It is worth noting that 3 mol% of (*R*)-**7** was effective enough for 4-methoxybenzaldehyde (entry 5), and 5 mol% of (*R*)-**7** was used for 1- or 2-naphthaldehyde (entries 6 and 7). The catalytic system applied equally well to (*E*)-cinnamaldehyde or 2-furaldehyde (entries 12 and 13), affording products **9l** and **9m** in 90 and 93% ee. Regardless of the steric bulk of aliphatic aldehydes, the addition reactions of linear pentanal or of bulkier 2-methylpropanal or 2,2-dimethylpropanal furnished secondary alcohols **9n–p** in good to excellent yields and excellent

Table 2 ArTi(O-*i*-Pr)$_3$ addition reactions of aldehydes catalyzed by the catalytic system of (*R*)-**7**[a]



8 9

Entry	RCHO	Ar	(*R*)-**7** (mol%)	Product	Yield[b] (%)	Ee[c] (%)
1		Ph	10	(*R*)-**9a**	94	99
2		Ph	10	(*R*)-**9b**	95	94
3		Ph	10	(*R*)-**9c**	92	90
4		Ph	10	(*R*)-**9d**	95	95
5		Ph	3	(*R*)-**9e**	91	90
6		Ph	5	(*R*)-**9f**	94	95
7		Ph	5	(*R*)-**9g**	94	91
8		Ph	10	(*R*)-**9h**	94	94
9		Ph	10	(*R*)-**9i**	92	94
10		Ph	10	(*R*)-**9j**	95	98
11		Ph	10	(*R*)-**9k**	96	97
12		Ph	10	(*S*)-**9l**	93	90
13		Ph	10	(*R*)-**9m**	94	93
14		Ph	10	(*S*)-**9n**	90	92
15		Ph	10	(*S*)-**9o**	88	95
16		Ph	10	(*S*)-**9p**	90	93
17	PhCHO	*p*-Tolyl	10	(*S*)-**9b**	96	95
18	PhCHO	4-MeOC$_6$H$_4$	10	(*S*)-**9e**	94	95
19	PhCHO	2-Naphthyl	10	(*S*)-**9g**	86[d]	94
20	PhCHO	4-ClC$_6$H$_4$	10	(*S*)-**9l**	92	90
21	PhCHO	4-TMSC$_6$H$_4$	10	(*S*)-**9q**	95	94[e]

[a] Aldehyde/(*R*)-**7**/ArTi(O-*i*-Pr)$_3$ = 0.50/0.015–0.050/0.60 mmol. [b] Isolated yield. [c] Determined by HPLC using appropriate chiral columns. [d] 91% conversion. [e] (*S*)-**9q** was converted to (4-BrC$_6$H$_4$)CH(OH)Ph for a determination of the ee value.

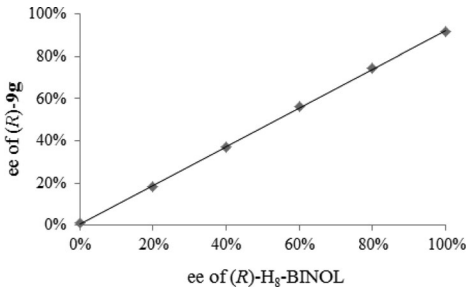


Fig. 1 Linear plot of ee of (*R*)-**9g** *vs.* ee of (*R*)-H_8-BINOL.

enantioselectivities of $\geq$ 92% ee (entries 14-16). The additions of aryl nucleophiles of ArTi(O-*i*-Pr)$_3$ (Ar = *p*-tolyl, 4-MeOC$_6$H$_4$, 2-naphthyl, 4-ClC$_6$H$_4$, or 4-TMSC$_6$H$_4$) to benzaldehyde were also studied, affording aryl addition products in $\geq$ 90% ee (entries 17–21) but in opposite absolute structure as compared to products from additions of the phenyl nucleophile to aryl aldehydes.

To explore the mechanistic insight, PhTi(O-*i*-Pr)$_3$ additions to **8g** in the presence of 0, 20, 40, 60, 80, or 100% ee of (*R*)-H_8-BINOL were conducted, producing (*R*)-**9g** in 1.3, 18.1, 36.8, 56.3, 74.5, and 91.6% ee, respectively. A linear plot of ee of (*R*)-**9g** *vs.* ee of (*R*)-H_8-BINOL (Fig. 1) suggests that the metallic active species involves only one H_8-BINOL.[25] To study the autocatalysis, 0.60 mmol of PhTi(O-*i*-Pr)$_3$ and 50% of (*R*)-**9g** (0.25 mmol, 91.6% ee) were mixed in the absence of (*R*)-H_8-BINOL followed by an addition of 50% substrate of **8g** (0.25 mmol). The reaction over 2 h furnished (*R*)-**9g** in a 96% conversion with an 84.7% ee. The result did show autocatalysis with an improvement of 38.9% ee relative to the 45.8% ee of the pre-added (*R*)-**9g** in the case of no autocatalysis. However, the slower reaction and the linear effect of the catalytic system indicate that the autocatalysis of the chiral alcohol product is negligible as compared to the catalytic reaction.

In summary, the most efficient and direct aryl additions of ArTi(O-*i*-Pr)$_3$ to aldehydes catalyzed by the titanium catalyst of (*R*)-H_8-BINOL are reported. This study demonstrates several important features. First, the ArTi(O-*i*-Pr)$_3$ addition reactions complete instantaneously at room temperature. Second, excess amounts of Ti(O-*i*-Pr)$_4$ are not necessary along with 0.2 equiv. excess of ArTi(O-*i*-Pr)$_3$ used, revealing the atomic efficiency of the Ti–H_8-BINOLate catalytic system. Third, the ligand effectiveness in terms of stereocontrol is in the order of H_8-BINOLs > BINOLs > TADDOL **4** > diol **3** > disulfonamide **2**.

Financial support from the National Science Council of Taiwan, ROC, under the grant number of NSC99-2113-M-005-005-MY3 is appreciated.

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