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Remarkably Efficient Enantioselective Titanium(IV)−(*R*)-H_8-BINOLate Catalyst for Arylations to Aldehydes by Triaryl(tetrahydrofuran)aluminum Reagents

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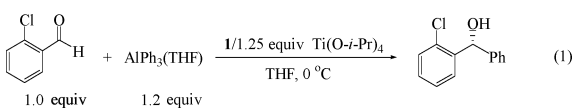
Organozinc is one of the most widely used reagents in the past decade for asymmetric C−C bond formation reactions due to its mild and controllable characteristics for inducing high enantioselectivity.[1] Recently, chiral diaryl alcohols,[2] propargyl alcohols,[3] and allyl alcohols[4] are increasingly demanded as intermediates for important bio-active compounds.[5] For asymmetric aryl additions to aldehydes, the catalytic reaction was first reported by Seebach and co-worker, employing a highly reactive PhTi(O-*i*-Pr)$_3$ reagent at −78 °C.[6] After the works of direct $ZnPh_2$ addition by Fu et al.,[7] considerable progresses in arylation reactions were developed.[8] To improve stereoselectivities, an addition of $ZnEt_2$ to the catalytic system was first discovered by Pu and co-worker,[9] and it was later found by Bolm and co-workers that the quantity of the expensive $ZnPh_2$ can be reduced to 0.65 equiv.[10] Bolm and co-worker further developed arylzinc reagents from reactions of dialkylzinc and arylboronic acids.[11] This study extends the scope of phenylation to arylation reactions, and several catalytic systems[5d,12] were reported to induce excellent stereoselectivities, including systems using other arylboron reagents.[13] In the most recent papers, Pu and co-workers reported direct $ZnPh_2$ additions to both aromatic and aliphatic aldehydes, employing a modified H_8-BINOL ligand,[14] and Walsh and co-worker reported in situ-formed arylzinc reagents from reactions of aryllithiums and $ZnCl_2$ for asymmetric arylations to aldehydes.[15]

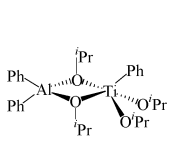
In contrast, organoaluminum reagents are excellent nucleophiles for organic reactions due to their higher reactivity and a greater Lewis acidity of the metal center.[16] Moreover, the industrial bulk aluminum alkyls or hydrides insert into unsaturated C−C bonds,[17] and aluminum reagents can even deprotonate a hydrogen from sp or sp^2 carbons[16h,18] to furnish diversified organoaluminum reagents for further reactions. Additional advantages include low toxicities and considerable stabilities for preservation under inert atmosphere or even in air.[19] Nevertheless, their applications to asymmetric catalysis are still limited. The first asymmetric catalytic application of organoaluminum reagents was developed by Chan and co-workers involving triethylaluminum additions to aldehydes[20] followed by methylation reactions by Carreira et al.[21] and Woodward et al.,[19] and ethylation or allylation reactions by Alexakis et al.[22] and by us.[23] In addition, asymmetric alkynylation reactions to a cyclic enone were demonstrated by Corey and co-worker.[24]

We here report novel asymmetric additions of easily prepared triaryl(tetrahydrofuran)aluminum $AlAr_3$(THF)[25] to aldehydes catalyzed by a titanium(IV) complex of (*R*)-H_8-BINOL. Optimizations of reaction conditions were conducted on 2-chlorobenzaldehyde and catalyst precursor [Ti{(*R*)-H_8-BINOLate}(O-*i*-Pr)$_2$]$_x$ (**1**)[26] (eq 1).



(1)

It was found that the reaction employing 1.2 equiv of $AlPh_3$(THF) and 1.25 equiv of Ti(O-*i*-Pr)$_4$ afforded the product in 100% yield in 12 h with the best enantioselectivity of 93% ee (Table 1, entry 1). Under the optimized conditions but without the catalyst precursor, we surprisingly found that the background reaction afforded the racemic product in 73% yield in 10 min (entry 2), suggesting that the catalytic reaction should be complete within 10 min. Indeed, the catalytic reaction gave the product in 98% yield with a comparable enantioselectivity of 92% ee in 10 min (entry 3), and in 5 min, the product was obtained in 86% yield with 90% ee (entry 4). In 1 min, the reaction afforded the product in 43% yield with 88% ee (entry 5). Catalytic reactions with lower catalyst loading at 5 and 2.5 mol % were then examined to give the product in 96 and 95% yields with enantioselectivities of 90 and 86% ee (entries 6 and 7), respectively.



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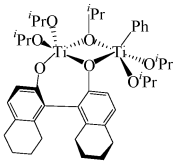
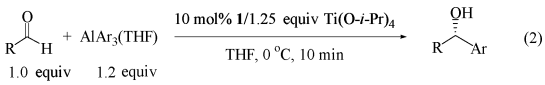


3

To elucidate roles of $AlPh_3$(THF) and Ti(O-*i*-Pr)$_4$ in the reaction, an immediate formation of a bimetallic complex **2** was obtained from mixing equal molar equivalents of the two reagents. The catalytic phenyl addition using reagent **2** gave the product in the same 93% ee. To clarify how the complex **2** transfers the phenyl group, a stoichiometric reaction of **1**, 2-chlorobenzaldehyde, and PhTi(O-*i*-Pr)$_3$ was examined to afford the product in 96% ee, suggesting that the complex **2** probably transfers the PhTi(O-*i*-Pr)$_3$ moiety to the Ti−H_8-BINOLate complex to give an active bimetallic species **3** having a structure similar to structures of bimetallic titanium complexes of H_8-BINOL[26] and of N-sulfonylated β-amino alcohol.[27]

Generalities of the catalytic system in a reaction time of 10 min were examined on a variety of aldehydes (eq 2), and results are listed in Table 2.



(2)

The catalytic system applies to aromatic aldehydes with an electron-donating or an electron-withdrawing substituent at the 2-, 3-, or 4-position to give chiral diarylmethanols in excellent isolated yields, and excellent enantioselectivities ranged from 92 to 97% ee (entries 1−10). For 1- or 2-naphthylaldehyde, 96 and 94% ee (entries 11 and 12) were obtained, respectively. The catalyst works equally well for both linear and branched aliphatic aldehydes and for poly-functional aldehydes, such as 2-furylaldehyde and vinyl aldehydes with enantioselectivities ranging from 91 to 99% ee (entries 13−18). Additions to poly-functional carbonyls are important reactions

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Table 1. Optimizations of Asymmetric Phenyl Addition of $AlPh_3(THF)$ to 2-Chlorobenzaldehyde Catalyzed by the In Situ-Formed **1**/Ti(O-*i*-Pr)$_4$ Systems[a]

entry	**1** (mol%)	time	yield (%)[b]	ee (%)[c]
1	10	12 h	100	93
2		10 min	73	
3	10	10 min	98	92
4	10	5 min	86	90
5	10	1 min	43	88
6	5	10 min	96	90
7	2.5	10 min	95	86

[a] 2-Chlorobenzaldehyde/$AlPh_3(THF)$/Ti(O-*i*-Pr)$_4$ = 0.5/0.6/0.625 mmol. [b] Yields were based on ^{1}H NMR spectra. [c] Enantioselectivities were determined by HPLC.

Table 2. Asymmetric $AlAr_3(THF)$ Addition to Aldehydes Catalyzed by the In Situ-Formed **1**/Ti(O-*i*-Pr)$_4$ Catalyst[a]

entry	RCHO	Ar	yield (%)[b]	ee (%)[c]
1	2-ClC_6H_4CHO	Ph	93	92 (*R*)
2	3-ClC_6H_4CHO	Ph	90	94 (*R*)
3	4-ClC_6H_4CHO	Ph	92	95 (*R*)
4	2-MeC_6H_4CHO	Ph	92	96 (*R*)
5	3-MeC_6H_4CHO	Ph	96	94 (*R*)
6	4-MeC_6H_4CHO	Ph	95	95 (*R*)
7	2-(MeO)C_6H_4CHO	Ph	96	95 (*R*)[d]
8	3-(MeO)C_6H_4CHO	Ph	94	94 (*R*)
9	4-(MeO)C_6H_4CHO	Ph	96	97 (*R*)
10	4-$(CF_3)C_6H_4CHO$	Ph	94	96 (*R*)
11	1-naphthylaldehyde	Ph	90	96 (*R*)
12	2-naphthylaldehyde	Ph	92	94 (*R*)
13	*n*-BuCHO	Ph	90	91 (*S*)
14	*i*-PrCHO	Ph	89	96 (*S*)
15	*t*-BuCHO	Ph	70	99 (*S*)
16	2-furylaldehyde	Ph	89	94 (*R*)
17	(*E*)-PhCH=CHCHO	Ph	95	91 (*S*)[d]
18	(*E*)-*n*-PrCH=CHCHO	Ph	91	92 (*S*)
19	PhC≡CCHO	Ph	93	95 (*R*)
20	*n*-BuC≡CCHO	Ph	96	97 (*R*)
21	C_6H_5CHO	*p*-tolyl	88	94 (*S*)
22	C_6H_5CHO	4-(MeO)C_6H_4	80	90 (*S*)
23	C_6H_5CHO	4-(TMS)C_6H_4	87	93 (*S*)[e]
24	C_6H_5CHO	2-naphthyl	90	92 (*S*)
25	C_6H_5CHO	1-naphthyl	52	72 (*S*)

[a] Substrate/$AlAr_3(THF)$/**1**/Ti(O-*i*-Pr)$_4$ = 0.5/0.6/0.05/0.625 mmol. [b] Isolated yields. [c] Enantioselectivities were determined by HPLC using suitable chiral column from Daicel. [d] Ti(O-*i*-Pr)$_4$, 0.75 mmol. [e] The enantioselectivity was determined after conversion the TMS product into the bromo product.

to afford corresponding alcohols as building blocks for further reactions, and asymmetric alkynyl additions to α,β-unsaturated aldehydes have been demonstrated in a recent paper by Trost and co-workers.[28] To our knowledge, only one example of a phenyl addition to the acetylenyl aldehyde, TIPSC≡CCHO, was reported to afford the propargyl alcohol in 85% ee.[8c] Our system also applies to phenylacetylenyl and *n*-butylacetylenyl aldehydes to afford propargyl alcohols in 95 and 97% ee (entries 19 and 20). Entries 21−24 demonstrate additions of substituted aryl to afford desired products with excellent stereoselectivities from 90 to 94% ee. The additions of substituted aryl to benzaldehyde afforded products in reverse *S*-configurations in contrast to the *R*-products obtained by the phenyl addition to the substituted benzaldehydes. However, the addition by the more hindered 1-naphthyl to benzaldehyde gave the product in only 52% yield with 72% ee (entry 25). In entry 23, the resulted phenyl 4-(trimethylsilyl)phenyl methanol is an important product since the TMS substituent can be easily converted into other functional groups such as a bromo, an iodo, or a boron dichloride substituent for further applications.[29] In this study, the product was demonstrated to transform into the phenyl 4-bromophenyl methanol.[30]

In summary, novel asymmetric aryl additions of $AlAr_3(THF)$ to aldehydes catalyzed by the Ti(IV) catalyst of (*R*)-H_8-BINOL are reported. Important features demonstrated in this study include an easy processing relative to previous studied systems, both easily prepared simple and substituted arylaluminum reagents used to afford chiral alcohols in excellent enantioselectivities, and the catalytic system applying to the most diversified aldehydes to date. Moreover, diarylmethanols in both *R*- and *S*-configurations can be obtained. Most importantly, the catalytic system is extremely efficient with the reactions completing within 10 min, and the suppression of the background reaction is not required.

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Supporting Information Available: Synthesis of compounds and HPLC analytical conditions of chiral products. This material is available free of charge via the Internet at http://pubs.acs.org.

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