



Catalytic asymmetric addition of aldehydes using organolithium reagents in the presence of commercial available chiral diol ligands



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ABSTRACT

An efficient method for the catalytic asymmetric additions to aldehydes using organolithium reagents and titanium(IV) isopropoxide in the presence of commercially available and relatively inexpensive diol ligands, such as (*S*)-BINOL or *D*-TADDOL has been developed. Good to excellent yields (up to 92%) and enantioselectivities (up to 94%) of the corresponding secondary alcohol products can be obtained following a simple procedure at relatively mild reaction temperatures.

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1. Introduction

The asymmetric addition of organometallic reagents to aldehydes is recognized as one of the most efficient transformations for preparing optically active secondary alcohols with numerous biological activities.¹ Organolithium reagents are very commonly used reagents in organic laboratory work and even in industry procedures.² Due to the high reactivity of organolithium reagents, previous studies mainly preferred to use more than stoichiometric amounts of catalysts and the products were mainly obtained with moderate to high *ee* at low temperatures (normally $-78\text{ }^{\circ}\text{C}$).³ Until recently only a few successful examples of highly catalytic asymmetric transformations for organolithium reagents had been reported,⁴ while great progress has been made in the catalytic asymmetric addition of diorganozinc reagents,^{5,6} organoaluminium reagents,⁷ organomagnesium reagents⁸ and organotitanium reagents⁹ to aldehydes, and in the catalytic enantioselective reduction of ketones.¹⁰

In 1994, Seebach et al. reported their pioneering work on the catalytic asymmetric addition of organolithium reagents to aldehydes using *L*-TADDOL (Fig. 1, I) as a chiral ligand. In order to achieve high levels of enantioselectivity, alkyl triisopropoxy titanium reagents from organolithium reagents with $\text{CITi}(\text{Oi-Pr})_3$ with very careful removal of Lewis acid salts (centrifugation of LiCl and addition of 12-crown-4) was used, and the reaction was carried at very low temperature ($-78\text{ }^{\circ}\text{C}$).¹¹ In 2009, Walsh et al. employed ZnCl_2 and aryllithium reagents to generate arylzinc reagents at

$-78\text{ }^{\circ}\text{C}$ and tetraethylethylene diamine was used to chelate the LiCl by-product, which may cause a background reaction, to achieve excellent yields and *ee* of the corresponding secondary alcohols when using (*-*)-MIB (Fig. 1, II) as chiral ligand.¹² In 2011, Harrison-Marchand and Maddaluno et al. reported the first substoichiometric version of the catalytic asymmetric addition of methyllithium to *o*-tolualdehyde at $-78\text{ }^{\circ}\text{C}$. The secondary alcohol product was obtained with 80% yield and 80% *ee* using chiral diamine (Fig. 1, III); it should be noted that 0.33 equiv of LiCl must be added as an additive to keep the catalytic cycle running.¹³ Subsequently, Macia and Yus et al. reported examples of chiral diol ligands IV and V in the catalyzed enantioselective addition of organolithium reagents to aromatic aldehydes, to achieve excellent *ees* of the corresponding products under relatively mild temperature ($-40\text{ }^{\circ}\text{C}$) using simple procedures.¹⁴ It was reported by Harada et al. that the aryl triisopropoxy titanium reagent could be generated in situ from organolithium with $\text{CITi}(\text{Oi-Pr})_3$ at $-78\text{ }^{\circ}\text{C}$, with only 2% chiral ligand VI without the removal of the in situ generated LiCl, although it should be noted that the aryl triisopropoxy titanium reagent had to be added very slowly over 2 h to achieve excellent *ees*.¹⁵ Very recently, Da et al. transferred aryllithium reagents to triarylaluminiums and then to an aryl titanium reagent, using (*S*)- H_8 -BINOL VII as chiral ligand, to achieve excellent yields and *ees*; TMEDA was found to be useful in enhancing the enantioselectivity.¹⁶

Harsh reaction conditions, strict operational procedures and complicated systems seem necessary for achieving high yield and excellent enantioselectivity in most of these reported reactions, some of which required elaborate chiral ligands that demand multistep syntheses. Herein, we report our exploration of operationally convenient (without removing the Lewis acid formed from the

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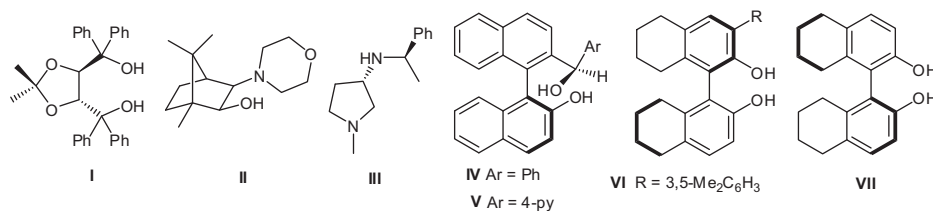


Figure 1. Structures of chiral ligands.

metathesis) catalytic asymmetric addition reactions of organolithium reagents to various aldehydes with the use of commercially available and relatively inexpensive chiral ligands, such as chiral TADDOL^{9a,11,17} and BINOL,^{6d,8j,18} which are very efficient chiral ligands in many catalytic asymmetric reactions, and relatively mild reaction temperatures for the economical synthesis of optical secondary alcohols without using any additives. This approach could obviously lower the cost and make it more promising for industrial applications.

2. Results and discussion

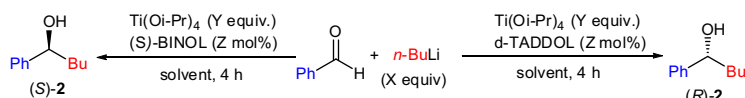
We started with the model reaction of the catalytic asymmetric addition of *n*-BuLi to benzaldehyde (Eq. 1 in Table 1) using *D*-TADDOL as a chiral ligand to optimize the reaction conditions. The results are listed in Table 1. When 20 mol % of *D*-TADDOL, 3.2 equiv of *n*-BuLi and 6.0 equiv of Ti(Oi-Pr)₄ at –60 °C were used, the desired alcohol product was obtained in 50% yield and with 66% *ee* (Table 1, entry 1). The effect of temperature was first investigated. The yield and *ee* increased when the temperature was raised to –30 °C (Table 1, entry 2). When increasing the temperature further, the yield of the product remained at the same level while the enantioselectivity dropped dramatically (entries 3 and 4). The ratio of *n*-BuLi to Ti(Oi-Pr)₄ was also studied. Decreasing the amount of *n*-BuLi to 1.6 equiv, led to excellent yield and *ee* of the product

when the ratio of *n*-BuLi/Ti(Oi-Pr)₄ was 1:3 or 1:2 (entries 5–6), however very low yield and *ee* of the product was afforded if 1:1 of *n*-BuLi/Ti(Oi-Pr)₄ was used (entry 7). In the absence of Ti(Oi-Pr)₄, very high yield but no *ee* of the product was observed (entry 8). These results indicated that *n*-Bu group may be transformed by the excess amount of Ti(Oi-Pr)₄. Different solvents such as CH₂Cl₂, MTBE, Et₂O, hexane and heptane were also evaluated and heptane was found to be the best solvent (entries 9–14), giving 92% yield with 92% *ee* of the product. If 10 mol % *D*-TADDOL was used, the yield and *ee* of the product decreased to 82% and 85% respectively (entry 15). When 30 mol % *D*-TADDOL was used, the yield and *ee* remained at the same level as to when 20 mol % *D*-TADDOL was used (entry 16). Under the same optimized conditions, when 20% (*S*)-BINOL was used as chiral ligand, the alcohol product was obtained in 92% yield and with 88% *ee* (entry 17).

With the optimized conditions in hand, we next investigated the substrate scope and limitation of the catalytic reaction system using both (*S*)-BINOL and *D*-TADDOL as chiral ligands, and the results are listed in Table 2.

As shown in Table 2, almost the same level and variation trend of yields and enantioselectivities of the corresponding alcohol products were obtained in the catalytic asymmetric addition of *n*-butyl lithium to aldehydes (entries 1–9 and entries 15–23). The electronic effect of the substituent was investigated using a series of substituted benzaldehydes. It can be seen from entries 2–5 and

Table 1
Catalytic asymmetric addition of *n*-BuLi to benzaldehyde using *D*-TADDOL or (*S*)-BINOL as chiral ligand^a



Entry	Ligand	X (equiv)	Y (equiv)	Z (mol %)	Temp (°C)	Solvent	Yield ^b (%)	<i>ee</i> ^c (%)
1	<i>D</i> -TADDOL	3.2	6	20	–60	Toluene	50	66
2	<i>D</i> -TADDOL	3.2	6	20	–30	Toluene	93	82
3	<i>D</i> -TADDOL	3.2	6	20	–20	Toluene	94	66
4	<i>D</i> -TADDOL	3.2	6	20	–10	Toluene	95	48
5	<i>D</i> -TADDOL	1.6	4.8	20	–30	Toluene	92	87
6	<i>D</i> -TADDOL	1.6	3.2	20	–30	Toluene	90	88
7	<i>D</i> -TADDOL	1.6	1.6	20	–30	Toluene	15	6
8	<i>D</i> -TADDOL	1.6	0	20	–30	Toluene	91	0
9	<i>D</i> -TADDOL	1.6	3.2	20	–30	CH ₂ Cl ₂	45	79
10	<i>D</i> -TADDOL	1.6	3.2	20	–30	MTBE	51	51
11	<i>D</i> -TADDOL	1.6	3.2	20	–30	THF	11	20
12	<i>D</i> -TADDOL	1.6	3.2	20	–30	Et ₂ O	35	83
13	<i>D</i> -TADDOL	1.6	3.2	20	–30	Hexane	91	89
14	<i>D</i> -TADDOL	1.6	3.2	20	–30	Heptane	92	92
15	<i>D</i> -TADDOL	1.6	3.2	10	–30	Heptane	82	85
16	<i>D</i> -TADDOL	1.6	3.2	30	–30	Heptane	93	92
17 ^d	(<i>S</i>)-BINOL	1.6	3.2	20	–30	Heptane	90	88

^a Unless otherwise noted, all reactions were carried out with benzaldehyde on a 1 mmol scale.

^b Isolated yields.

^c Determined by chiral GC analysis; the absolute configuration was assigned by comparison of the sign of the specific rotation value with the literature value.

^d (*S*)-BINOL was used as the chiral ligand and (*S*)-1-phenylpentan-1-ol was obtained.

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