

# Highly active bifunctional salenTi(IV) catalysts for asymmetric cyanosilylation of aldehydes and TMSCN

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## Abstract

A novel enantiopure salen ligand bearing a diphenylphosphine oxide on the 3-position of one aromatic ring was synthesized and combined with  $\text{Ti}(\text{O}i\text{-Pr})_4$  as a monometallic bifunctional catalyst for asymmetric cyanosilylation reaction of aldehydes with trimethylsilyl cyanide (TMSCN). The catalyst system exhibited excellent activity and moderate enantioselectivity. The addition of TMSCN to 4-nitrobenzaldehyde in the presence of 1 mol% catalyst loading could complete within 10 min at ambient temperature. An intramolecularly cooperative catalysis was observed in this system wherein the central metal Ti(IV) is suggested to play a role of Lewis acid to activate aldehydes while the appended diphenylphosphine oxide worked as Lewis base to activate TMSCN.

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Asymmetric catalytic formation of C–C bonds is a basic and vital method in organic synthesis [1]. Cyanosilylation reaction of carbonyl compounds with TMSCN has attracted much attention due to the easy construction of new chiral center. Numerous catalyst systems including Lewis acids [2], Lewis bases [3], *N*-heterocyclic carbenes [4], metal complexes [5], inorganic salts [6] and bifunctional catalysts [7–11] have been developed for the reaction of carbonyl compounds with trimethylsilyl cyanide (TMSCN). Among them bifunctional catalysts are more fascinating. Shibasaki and co-workers first reported the use of BINOL-based Lewis acid–Lewis base bifunctional catalyst **1** for cyanosilylation of aldehydes [7]. In this system, activation of both substrates and nucleophiles occurs simultaneously at the Lewis acid and the Lewis base moiety in the catalyst **1** (Fig. 1). Following this study, Nájera et al. designed a monometallic bifunctional catalyst BINOLAM- $\text{AlCl}_3$  **2** for this reaction [8]. Other backbones, such as PyBOX derivatives [9], and *N*-oxide containing ligand [10], were also used as ligands for catalyzing asymmetric cyanosilylation reaction to afford cyanohydrins with high enantiomeric excess.

Salen ligands based on diimine-diphenolate bearing a linkage between two imine donors have emerged as one of the most versatile synthetic ligands [11]. SalenTi(IV) complexes were reported as active catalyst for asymmetric addition of TMSCN to aldehydes [2,10,12]. Recently, we have reported bifunctional metal-salen catalysts for the coupling reaction of  $\text{CO}_2$  and epoxides to yield the corresponding organic carbonates with excellent activity [13,14]. Herein, we designed a new salen ligand L3 in which a phosphine oxide was attached on the 3-position of one aromatic

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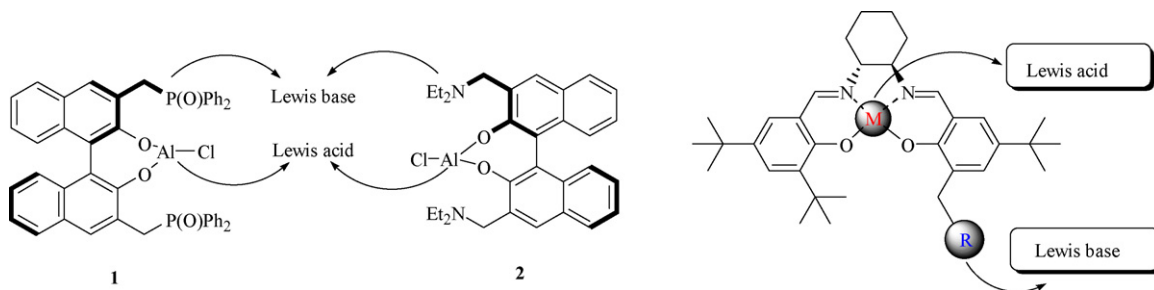


Fig. 1. Design of Lewis acid–base bifunctional catalyst.

ring through a methylene. The ligand, in combination with  $\text{Ti}(\text{O}i\text{-Pr})_4$ , proved to be effective in catalyzing the addition of TMS-CN to aldehydes. In this catalyst system, the phosphine oxide is suggested to play a role of Lewis base to activate nucleophile, while the central metal ion acted as Lewis acid to activate electrophile (Fig. 1).

## 1. Results and discussion

The chiral ligand L3 bearing a phosphine oxide on the 3-position of one aromatic ring was first synthesized. In order to illustrate our speculation, symmetrical ligand L4 that possessed phosphine oxide groups on both 3- and 3'-position and ligand L5 in which the phosphine oxide group was appended on the 5-position of one aromatic ring have also been synthesized (Fig. 2).

We delightedly found that the catalyst system based on L3 showed excellent activity and moderate enantioselectivity, and up to 98% yield was achieved at 4 h with 1 mol% catalyst loading (Table 1, entry 1). Interestingly, the catalyst system with regard to L4 also exhibited very high activity for this reaction, but the enantioselectivity of the resulting cyanosilylation product is only 48% ee (entry 2). It is tentatively ascribed to the attack of TMS-CN at both *Re*- and *Si*-faces of the coordinated benzaldehyde, owing to the symmetrical structure of the ligand.

For demonstrating the intramolecularly cooperative catalysis of the catalyst system of L3 in conjunction with  $\text{Ti}(\text{O}i\text{-Pr})_4$ , we also set out some control experiments. Firstly, ligand L5 in which diphenylphosphine oxide was connected on 5-position of one aromatic ring was chosen for a comparison purpose. Under the same condition, cyanosilylation product was obtained in 70% yield and 37% ee after 24 h (entry 3), whereas 70% ee was obtained with the catalyst system regarding L3. It is tentatively ascribed to the far distance between the Lewis acid and Lewis base in the system concerning L5, which is unfavourable to bring the activated TMS-CN into appropriate position for attacking aldehyde coordinating to titanium. Interestingly, when 1 mol%  $\text{Ph}_3\text{PO}$  was added to the system of L3/ $\text{Ti}(\text{O}i\text{-Pr})_4$ , lower enantioselectivity was observed in the resultant product (entry 4).

Although the catalyst system consisting of cyclohexane-1,2-diamine derived salen ligand and  $\text{Ti}(\text{O}i\text{-Pr})_4$  had been reported to be active on the asymmetric cyanosilylation of carbonyl compounds with TMS-CN in 1996 [15], further mechanistic investigation demonstrated that the actual catalytic species was dinuclear (salen)titanium

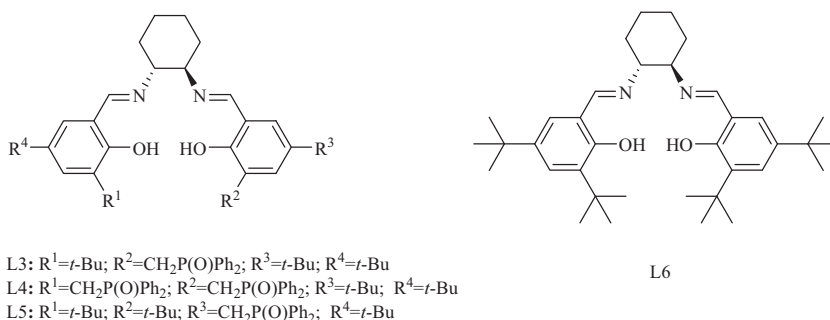


Fig. 2. Chiral ligands used for asymmetric cyanosilylation.

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