Journal of Organometallic Chemistry 768 (2014) 50–55

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Investigation of catalytic activity and catalytic mechanism of chiral amino diol tridentate ligands in the asymmetric addition of aldehydes in the present of methyllithium reagent

An-Lin Zhang, Li-Wen Yang*, Nian-Fa Yang*, Da-Cai Liu

Key Laboratory of Environmentally Friendly Chemistry and Applications of Ministry of Education, College of Chemistry, Xiangtan University, Hunan 411105, PR China

ARTICLE INFO

Article history:
Received 7 February 2014
Received in revised form
18 May 2014
Accepted 16 June 2014
Available online 28 June 2014

Keywords:
Organolithium
Asymmetry
Alkylation
Enantioselectivity

ABSTRACT

Several highly modular chiral amino diol tridentate ligands were found to be effective for the asymmetric alkylation reaction of aromatic aldehydes in the presence of methyllithium reagent, providing up to 96% ee values and up to 94% yields under relatively mild conditions. The investigation of the catalytic activity of these ligands shows a correlation of enantioselectivities of ligands with steric properties of substituent N-alkyl and nucleophilic Li-alkyl. With the addition of Ti(O-*i*-Pr)$_4$ to the ligand **3c**, the ^{1}H NMR spectrum reveals a hexa-coordinate Ti transition state complex with only one Ti metal center generated in solution.

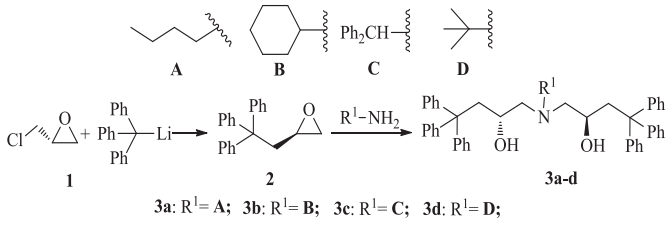
Introduction

β-amino alcohols are the most often used chiral auxiliaries. In recent years, aromatic and aliphatic amino diols bearing a 1, 2- or a 1, 3-amino alcohol moiety have proven to be useful building blocks [1–3]. They have been applied as chiral catalysts or starting materials in the stereoselective synthesis of compounds of pharmacological interest. In addition to their synthetic importance, amino diols can also be applied as chiral ligands and auxiliaries in enantioselective transformations [4–6]. In this regard, the asymmetric addition of organometallic reagents to aldehydes has become a highly investigated model reaction, with the application of chiral promoters such as 1,2- or 1,3-difunctionalized ligands [7–9]. Although numerous enantiopure chelating ligands have been prepared, there is still a need for new types obtainable by concise syntheses from inexpensive starting materials. Enantiopure epichlorohydrin (ECH) is a key chiral synthon and building block for preparing chiral pharmaceuticals and agrochemicals such as pheromones, L-carnitine and *β*-blockers [10,11]. (*R*)-ECH are commercially available enantiopure epoxides that has been underutilized in organic synthesis. It is also well known that enantioselectivities of chiral ligand-catalyzed reactions are always related to the steric effects of ligands besides their electronic effects [12,13]. Thus, it should be of interest to explore the catalytic ability of bulky amino diol ligands derived from (*R*)-ECH.

Over the past decades, an overwhelming majority of chiral catalysts have been developed and applied for the reaction of organolithium reagents with aromatic aldehydes, while most of the ligands could not simultaneously show good yields and enantioselectivities in the organolithium additions to a broad range of aromatic substrates [14–19], and successful methods often require non-ideal conditions (temperatures < −100 °C and equimolar quantities of chiral ligand) [20]. In addition, The catalytic enantioselective addition of terminal alkynes to aldehydes has recently generated a tremendous amount of interest [21,22]. The resulting propargylic alcohols are versatile building blocks for fine chemicals, pharmaceuticals, and natural products [23,24]. However, on the one hand, in the wonderful studies [25,26], synthetic chiral ligands served for metals, while on the other hand, there is only few reports of high enantioselectivity for the alkynylation of carbonyl compound in the presence of organolithium rather than organozinc [27–29], Herein, we report a highly efficient catalytic system (Scheme 1) for the asymmetric additions of several organometallic reagents to aldehydes using chiral amino diol tridentate ligands **3a**–**d** with bulky substituent and Ti(O-*i*-Pr)$_4$ as cocatalysts.

* Corresponding authors.
E-mail addresses: yangliwen_0519@163.com (L.-W. Yang), nfyang@xtu.edu.cn, xtu1986xtu@gmail.com (N.-F. Yang).

http://dx.doi.org/10.1016/j.jorganchem.2014.06.012
0022-328X/



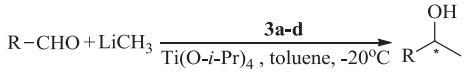
Scheme 1. Synthetic strategy for the synthesis of chiral amino diol tridentate ligands.

Results and discussion

The synthesis of new amino diol ligands **3a**–**d** is straightforward (Scheme 1). Considering the strongly rigidity nature of triphenylmethyl, we speculated that the introduction of bulky and rigid triphenylmethyl group on the side chains can make the structure of amino diols become more rigid. One possible reason is that the strong repulsive interaction between the bulky and rigid triphenylmethyl group and the alkyl on the nitrogen atom of the amino diol chain leads to this tetrahedral structure that is a stable conformation. Another reason is due to formation of an intramolecular hydrogen bond [30], which further prevents nitrogen inversion. The stable rigid structures could be beneficial to the investigation of catalytic activity and catalytic mechanism of amino diol ligands.

Given these, the new amino diol ligands were initially applied in the enantioselective addition of methyllithium to benzaldehyde in toluene. As shown, **3a**–**d** derived from (*R*)-ECH gave good yields and good enantioselectivities under the optimal reaction conditions (Table 1, entries 1–4). The enantioselectivity depended on the rigidity of R^1 on the nitrogen atom of the amino diol, namely, the order was **A** < **B** < **C** < **D**, which indicated that increase in the bulkiness of the achiral auxiliary increased the enantioselectivity of the reaction. The ee value of product increased with increasing bulkiness of the N-alkyl group (R^1) in the following order: **3a**(*n*-Bu) < **3b**(cyclohexyl) < **3c**(Ph_2CH_2) < **3d**(*tert*-Bu), i.e., there was a trend among ligands **3a**, **3b**, **3c**, **3d** that the catalytic enantioselectivity was higher with more sterically hindered substituting group at the amide nitrogen (Table 1, entries 1–4). According to the obtained ee values and isolated yields, **3c** was considered as the most effective ligand among these amino diol ligands, affording the best asymmetric activity with 80% ee and 90% yield (Table 1, entry 3). The ligand **3c** was then used for the addition of methyllithium to several aromatic aldehydes under the optimal reaction conditions (Table 1, entries 5–11). The reactions were performed using 10% mol of the catalyst in toluene. With regard to the additions of $LiCH_3$ to various aromatic aldehydes with electron-donating group or electron-withdrawing group, good enantioselectivities and good chemoselectivities were observed (Table 1, entries 5–9). As can be seen from the summarized results (Table 1), this method was highly efficient for all of aromatic aldehydes studied; the *sec*-alcohols were obtained with 80–86% ee value and up to 80–92% yield. It was worth mentioning that, in previous reports, when chiral β-amino alcohols were used as catalysts for the asymmetric addition of organolithium to aldehydes, the reaction had to be performed in the presence of chiral ligand at a lower temperature in order to obtain good yields and good enantioselectivities because of the increased reactivity of organolithium with raising the reaction temperature [15,31].

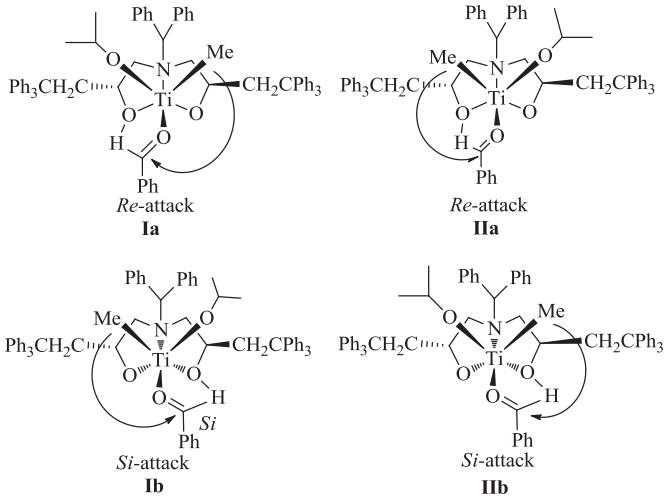
Table 1
The chiral induction ability of **3a**–**d** toward the reaction of methyllithium reagents with aromatic aldehydes.[a]



Entry	Ligand	RCHO	Yield/%[b]	E.e.(%)[c]	Config.[d]
1	**3a**	Benzaldehyde	85	70	*R*
2	**3b**	Benzaldehyde	90	75	*R*
3	**3c**	Benzaldehyde	90	80	*R*
4	**3d**	Benzaldehyde	80	82	*R*
5	**3c**	*p*-Methoxybenzaldehyde	80	85	*R*
6	**3c**	*p*-Methylbenzaldehyde	90	86	*R*
7	**3c**	*m*-Methoxybenzaldehyde	80	84	*R*
8	**3c**	*p*-Chlorobenzaldehyde	82	82	*R*
9	**3c**	*p*-Nitrobenzaldehyde	82	80	*R*
10	**3c**	1-Naphthaldehyde	91	85	*R*
11	**3c**	Cinnamaldehyde	92	81	*R*

[a] RCHO: 1 mmol; reaction time: 24 h; reaction temperature: −20 °C; $n(R_1CHO)/n(\mathbf{3c})/n(Ti(O\text{-}i\text{-}Pr)_4)/n(LiCH_3) = 1/0.1/1.5/2$.
[b] The isolated yield.
[c] The e.e. of the product was determined by chiral HPLC.
[d] the absolute configurations of the products were determined by comparing their rotation sign with that reported by literatures [32,33].

For picture simplicity, addition of methyllithium to benzaldehyde in the presence of amino diol **3c** is analyzed (Scheme 2). In the model **Ia** and **IIa** *re* attack leads to products with the observed configuration *R*, opposite to that observed in experiments. In models **Ib** and **IIb** the *si* attack leads to the absolute configuration *S*, but the apical position of the bulky isopropoxy group in the model **IIa** and **Ib** are not very likely, due to a steric hindrance from triphenylmethyl. In all four we postulate the presence of hydrogen



Scheme 2. Stereochemical models for a methylation of aldehydes.