

Highly enantioselective hetero-Diels–Alder reaction between *trans*-1-methoxy-2-methyl-3-trimethylsiloxybuta-1,3-diene and aldehydes catalyzed by (*R*)-BINOL–Ti(IV) complex

Bo Gao, Zhengyan Fu, Zhipeng Yu, Lan Yu, Yaozong Huang and Xiaoming Feng*

Key Laboratory of Green Chemistry and Technology (Sichuan University), Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China

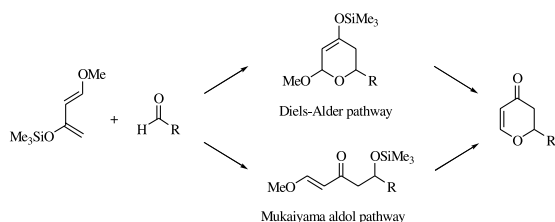
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Abstract—An efficient enantioselective approach to 2,5-disubstituted dihydropyrones was developed. Some easily accessible inexpensive diol ligand metal complexes were employed, and [(*R*)-BINOL]₂-Ti(OiPr)₄ complex was found to be the most effective catalyst (up to 99% yield and 99% ee in the presence of 5 mol% catalyst) for the hetero-Diels–Alder reaction between *trans*-1-methoxy-2-methyl-3-trimethylsiloxybuta-1,3-diene (**1**) and aldehydes. The potential and generality of this catalyst were evaluated by a variety of aldehydes including aromatic, heteroaromatic, α,β -unsaturated and aliphatic aldehydes. Based on the isolated intermediate from the reaction of benzaldehyde being confirmed by ¹H, ¹³C NMR and HRMS data, the mechanism was proposed as a Mukaiyama aldol pathway. © 2005 Elsevier Ltd. All rights reserved.

1. Introduction

Recent advance of asymmetric reactions in synthetic organic chemistry has been well documented and excellent stereoselective reactions have been successfully established.¹ Among these reactions, asymmetric hetero-Diels–Alder (HDA) reaction allows the direct formation of carbon–carbon bond and carbon–oxygen bond with up to two stereogenic centers in one convergent step from simple achiral precursors. In this context, it has attracted much attention over the past two decades. Following the development of chiral Lewis acids² and organocatalysts,^{2b,3} considerable progress on this reaction has been achieved.



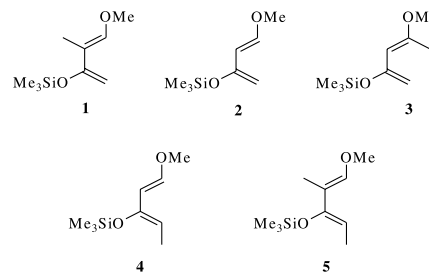
Scheme 1. Two possible pathways for the HDA reaction of Danishefsky's diene.

Keywords: Asymmetric catalysis; Dihydropyrene; Hetero-Diels–Alder reaction; Titanium (IV) complex.

* Corresponding author. Tel./fax: +86 28 8541 8249; e-mail: xmfeng@scu.edu.cn

When Lewis acid catalyzed HDA reaction is considered, two mechanistic pathways have generally been taken into account, namely that a given Lewis acid will catalyze this reaction by either a traditional Diels–Alder type cycloaddition or a Mukaiyama aldol pathway (Scheme 1). In the course of mechanism investigation, identification of reaction intermediate⁴ and semi-empirical calculation⁵ are two practical approaches.

Dihydropyrones are highly versatile synthetic intermediates for the preparation of biologically important compounds,^{4j,6} including carbohydrates,^{6a–i} antibiotics,^{6k} and toxins.^{4j,6l,m} Asymmetric HDA reaction of activated diene, such as Danishefsky's diene and its derivatives (Scheme 2),⁷ is a synthetically powerful approach to these heterocycles. Enantioselective HDA reaction between diene **1** and benzaldehyde using chiral auxiliary-chiral catalyst



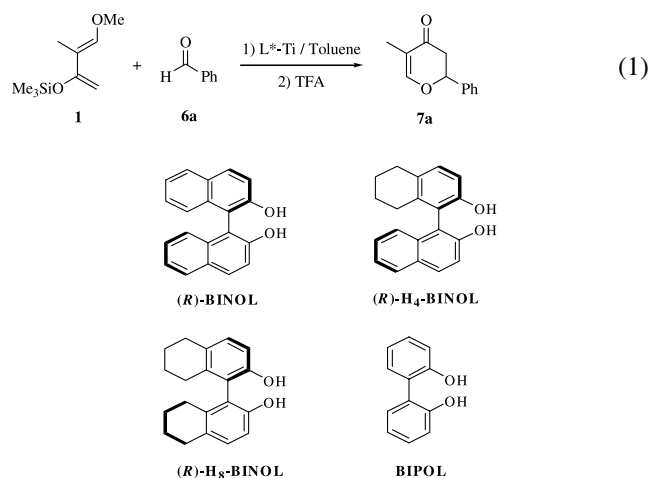
Scheme 2. Danishefsky's diene and its derivatives.

combination strategy (84% ee) was firstly reported by Danishefsky and co-workers.^{6j} Recently, we reported our preliminary efforts on the asymmetric HDA reaction of diene **1** catalyzed by (*R*)-BINOL–Ti(O*i*Pr)₄ (2:1 ratio) complex,⁸ which provided an efficient and enantioselective approach to 2,5-disubstituted dihydropyrone. The present paper, describes our studies on catalyst optimization, substrate generality and mechanistic investigation for this reaction.

2. Results and discussion

2.1. Optimization of the catalysts

During the course of catalyst optimization, how to make the chiral ligand, metallic ion, substrate, etc. into a perfect match is a key point for a highly enantioselective reaction. To achieve a perfect chiral match, some concepts in asymmetric catalysis must be taken into account, such as ‘asymmetric amplification’,^{9a} ‘chiral poisoning’,^{9b} ‘asymmetric activation’,^{9c,9d} ‘ligand-accelerated catalysis’,^{9e} ‘chiral environment amplification’,^{9f} and ‘asymmetric autocatalysis’.^{9g} Based on the principle of these concepts, which make the combination of two different ligands with a metallic ion into a practicable approach for increasing the activity and stereospecificity of a target reaction theoretically, some homo- and hetero-combinations of easily accessible diol ligands with titanium(IV) isopropoxide were tested as catalysts for the HDA reaction of *trans*-1-methoxy-2-methyl-3-trimethylsilyloxybuta-1,3-diene (**1**) with benzaldehyde (Eq. 1) (Scheme 3).



Scheme 3. Diols used as ligands for the catalysts survey.

According to the results shown in Table 1, the yield and enantiomeric excess of dihydropyrone **7a** were greatly affected by the catalyst used. (*R*)-BINOL/Ti^{IV}/*(R)*-BINOL, (*R*)-BINOL/Ti^{IV}/*(R)*-H₄-BINOL, (*R*)-BINOL/Ti^{IV}/*(R)*-H₈-BINOL and (*R*)-H₄-BINOL/Ti^{IV}/*(R)*-H₄-BINOL promoted this reaction smoothly to give product **7a** in reasonable yields with high enantioselectivities (Table 1, entries 1–3, and 5). However, (*R*)-H₄-BINOL/Ti^{IV}/*(R)*-H₈-BINOL complex, an exceptionally efficient catalyst for solvent-free enantioselective HDA reaction of Danishefsky’s diene,¹⁰ showed lower catalytic activity to give dihydropyrone **7a**

Table 1. Asymmetric hetero-Diels–Alder reaction of diene **1** with benzaldehyde catalyzed by chiral diol titanium(IV) complexes^a

| Entry | Catalyst ^b | Yield (%) ^c | ee (%) ^d |
|-------|---|------------------------|---------------------|
| 1 | (<i>R</i>)-BINOL/Ti ^{IV} / <i>(R)</i> -BINOL | 99 | 87 |
| 2 | (<i>R</i>)-BINOL/Ti ^{IV} / <i>(R)</i> -H ₄ -BINOL | 99 | 88 |
| 3 | (<i>R</i>)-BINOL/Ti ^{IV} / <i>(R)</i> -H ₈ -BINOL | 89 | 87 |
| 4 | (<i>R</i>)-BINOL/Ti ^{IV} /BIPOL | 49 | 78 |
| 5 | (<i>R</i>)-H ₄ -BINOL/Ti ^{IV} / <i>(R)</i> -H ₄ -BINOL | 99 | 89 |
| 6 | (<i>R</i>)-H ₄ -BINOL/Ti ^{IV} / <i>(R)</i> -H ₈ -BINOL | 38 | 79 |
| 7 | (<i>R</i>)-H ₄ -BINOL/Ti ^{IV} /BIPOL | 43 | 24 |
| 8 | (<i>R</i>)-H ₈ -BINOL/Ti ^{IV} / <i>(R)</i> -H ₈ -BINOL | 25 | 71 |
| 9 | (<i>R</i>)-H ₈ -BINOL/Ti ^{IV} /BIPOL | 37 | 45 |

^a All reactions were carried out at 0 °C in toluene using 10 mol% catalyst, in the presence of 120 mg 4 Å MS, over 48 h, concentration of benzaldehyde = 0.25 M.

^b The chiral catalyst was generated by combining a diol ligand with Ti(O*i*Pr)₄ and an alternative diol ligand (1:1:1) in parallel style.

^c Isolated yield.

^d The ee values were determined by HPLC using Chiralcel OJ column.

with 38% yield and 79% ee (Table 1, entry 6). And chiral (*R*)-H₈-BINOL/Ti^{IV}/*(R)*-H₈-BINOL complex also revealed lower catalytic activity in this reaction (Table 1, entry 8). These results showed that a much larger dihedral angle value of axial biaryl groups ((*R*)-H₈-BINOL > (*R*)-H₄-BINOL > (*R*)-BINOL) on titanium (IV) complex was disadvantageous for the activity of catalyst in this system. It was obviously different from what had been observed in titanium (IV) complexes catalyzed HDA reaction of Danishefsky’s diene, in which the reactivity and enantioselectivity of catalyst increased with the dihedral angle value.^{11b}

Then, other (*R*)-BINOL–metal complexes were screened in the HDA reaction of diene **1** with benzaldehyde. As shown in Table 2, among these catalysts, (*R*)-BINOL–Al^{III} complexes (Table 2, entries 5–7), and (*R*)-BINOL–Yb^{III} complex (Table 2, entry 8) could promote this reaction slowly, but gave racemic products. (*R*)-BINOL–Zr^{IV} complexes (Table 2, entries 3 and 4) revealed moderate reactivity and lower enantioselectivity. Only (*R*)-BINOL–Ti^{IV} complexes (Table 2, entries 1 and 2) catalyzed the reaction with high enantioselectivities. However, (*R*)-BINOL–TiCl₄ complex was much more sluggish than (*R*)-BINOL–Ti(O*i*Pr)₄ (Table 2, entry 2 vs 1).

Table 2. Effects of Lewis acids on asymmetric hetero-Diels–Alder reaction of diene **1** with benzaldehyde^a

| Entry | Metal compound ^b | Yield (%) ^c | ee (%) ^d |
|-------|--------------------------------|------------------------|---------------------|
| 1 | Ti(O <i>i</i> Pr) ₄ | 99 | 87 |
| 2 | TiCl ₄ | 29 | 82 |
| 3 | Zr(O <i>t</i> Bu) ₄ | 87 | 40 |
| 4 | ZrCl ₄ | 77 | 9 |
| 5 | AlEt ₃ | 16 | <5 |
| 6 | AlEt ₂ Cl | 18 | <5 |
| 7 | Al(O <i>i</i> Pr) ₃ | 20 | 0 |
| 8 | Yb(OTf) ₃ | 16 | 0 |

^a All reactions were carried out at 0 °C in toluene using 10 mol% catalyst, in the presence of 120 mg 4 Å MS, over 48 h, concentration of benzaldehyde = 0.25 M.

^b (*R*)-BINOL was used as chiral ligand, and the ratio of (*R*)-BINOL to metal compound was 2:1.

^c Isolated yield.

^d The ee values were determined by HPLC using Chiralcel OJ column.

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