Tetrahedron Letters 50 (2009) 7388–7391

Contents lists available at ScienceDirect

Tetrahedron Letters

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

C_2-Symmetric bipyrrolidines as organocatalysts for asymmetric Diels–Alder reactions

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ARTICLE INFO

Article history:
Received 16 September 2009
Revised 14 October 2009
Accepted 16 October 2009
Available online 21 October 2009

Keywords:
Bipyrrolidines
C_2-Symmetry
Organocatalyst
Diels–Alder reaction

ABSTRACT

A new class of C_2-symmetric 3,3′-dialkoxy-2,2′-bipyrrolidines have been designed and developed for asymmetric organocatalytic Diels–Alder reactions of α,β-unsaturated aldehydes. The bipyrrolidines combined with $HClO_4$ were found to be effective organocatalysts for enantioselective Diels–Alder reactions. The catalysis mode has been demonstrated by NMR and X-ray crystallographic studies for diiminium intermediate.

In the last decade organocatalysis has been witnessed a tremendous growth in the field of asymmetric synthesis.[1] The development of new chiral organocatalysts to carry out efficient asymmetric transformations plays a crucial role in this area. Since the great success of proline-catalyzed asymmetric reactions,[2] a large number of chiral pyrrolidine-type organocatalysts have been developed to achieve various asymmetric transformations.[3] The majority of catalyst design strategies rely on the introduction of various proton-donor groups, Lewis-bases or bulky groups at the 2-position of pyrrolidine ring. In our search for the new highly effective chiral organocatalysts, we were interested in C_2-symmetric bipyrrolidine **1** (see Fig. 1),[4] which has no application in organocatalysis as a catalyst.[5] It is well known that the C_2-symmetric chiral ligands have played a significant role in the advancement of transition-metal-catalyzed asymmetric reactions.[6] However, C_2-symmetric organocatalysts have rarely been reported.[7] Herein, we present our newly designed C_2-symmetric organocatalysts, 3,3′-disubstuted 2,2′-bipyrrolidines **2**, which are successfully applied in asymmetric Diels–Alder reaction of α,β-unsaturated aldehydes.

The enantioselective Diels–Alder reaction is one of the most powerful synthetic methods for the construction of cyclohexane frameworks, and is a versatile synthetic tool for the preparation of various important chiral building blocks and total synthesis of bioactive natural products.[8] Since the first report by MacMillan and co-workers on metal-free organocatalytic asymmetric Diels–Alder reactions,[9] several efforts have been devoted to develop new organocatalytic systems to achieve this important transformation.[10,11] Recently, several diamine salts have also been used to catalyze Diels–Alder reaction.[11] Ha and co-workers reported bisammonium salts derived from 1,2-diamino-1,2-diphenylethane (DPEN) as catalysts for asymmetric Diels–Alder reaction of α,β-unsaturated aldehydes with cyclopentadiene.[11a] The catalysts showed high catalytic activity, but moderate enantioselectivities were observed in the reaction. Most recently, Maruoka and co-workers reported asymmetric Diels–Alder reactions using C_2-symmetric binaphthyl-based diamines as catalysts.[11b,f] However, low reaction temperature (−20 °C) and long reaction time (40–160 h) are necessary to obtain good yields and high levels of enantiomeric enrichment.

It has been demonstrated that the rate-determining step of organocatalytic Diels–Alder reaction is an iminium ion formation. Additionally, the geometry of iminium intermediate plays a crucial role in the enantioselection. Our hypothesis is that the C_2-symmetric bipyrrolidines **2** could form diiminium intermediate **4** with cinnamaldehyde (Fig. 2), which can potentially accelerate the reaction rate by providing two identical reaction sites. In addition, as revealed in Newman projection of intermediate **4**, the two

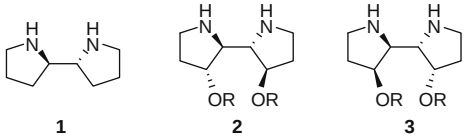

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Figure 1. Structure of C_2-symmetric bipyrrolidines catalysts.

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doi:10.1016/j.tetlet.2009.10.067

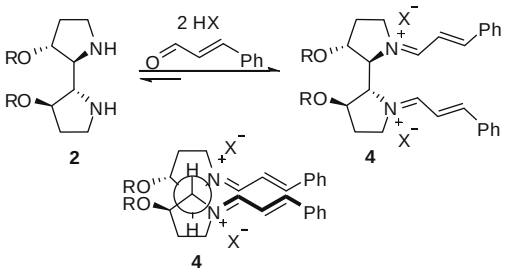
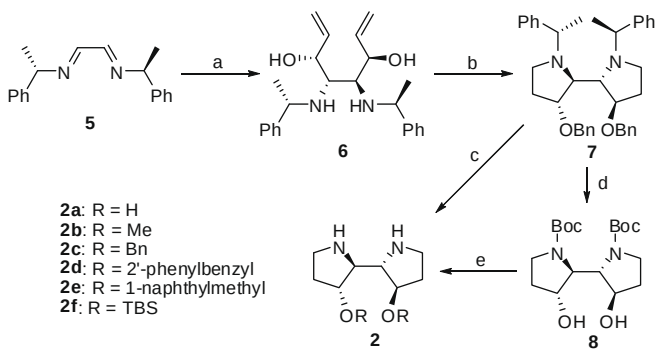


Figure 2. Proposed diiminium intermediate **4** formed from **2** and cinnamaldehyde.

conjugated iminiums faced each other in a parallel fashion, and two *Si* faces of the diiminium are facing each other with the two *Re* faces exposed for cycloaddition resulting in high enantiofacial discrimination. The OR groups at 3,3′-positions may additionally influence the conformational flexibility of intermediate **4** through a *gauche* steric interaction.

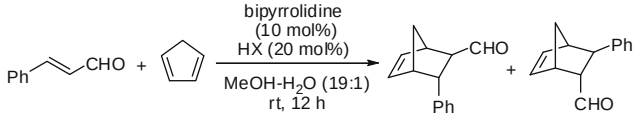
With these design concepts in hand, bipyrrolidines **2** have been readily synthesized from chiral diimine **5** (Scheme 1). Diastereoselective addition of propenylzinc reagent to diimine **5** led to optically pure diamino diol compound **6** in accordance with a previous literature report.[12] Protection of diol **6** with benzyl bromide, hydroboration of terminal alkenes with 9-BBN followed by mesilation in the presence of excess triethylamine gave cyclized bipyrrolidine **7** in 80% yield over three steps. Interestingly, hydrogenolysis of **7** with $Pd(OH)_2/C$ under 20 bar hydrogen pressure only afforded N-debenzylated product **2c** in quantitative yield. However, under the hydrogenolysis reaction conditions, addition of Boc anhydride furnished O-debenzylated, *N*-Boc protected product **8** in 96% yield. Direct deprotection of compound **8** gave (3*R*,2*S*,2′*S*,3′*R*)-3,3′-dihydroxy-2,2′-bipyrrolidine (**2a**) in 95% yield. To test our hypothesis in catalyst design, a number of substituents on oxygen were introduced. O-Alkylation or silylation of compound **8** with NaH and alkyl halide or silyl chloride in DMF followed by deprotection afforded bipyrrolidine catalysts **2b–f** in 70–86% yields. In order to examine the configuration effect, the diastereomer (3*S*,2*S*,2′*S*,3′*S*)-3,3′-dibenzyloxy-2,2′-bipyrrolidine (**3c**) was also synthesized by Mitsunobu inversion of diol **8**.

A model experiment was conducted with (*E*)-cinnamaldehyde and cyclopentadiene in the presence of 10 mol % bipyrrolidine **2c** and 20 mol % TfOH cocatalyst in aqueous MeOH at room temperature for 12 h. As expected, the catalyst showed high catalytic activity giving the cyclic adduct in 95% isolated yield with good enantioselectivity and moderate *exo*-selectivity (Table 1, entry 1). The Brønsted acid cocatalysts had little effect on the reaction (entries 2–4). The



Scheme 1. Synthesis of bipyrrolidines **2**. Reagents and conditions: (a) Ref. 12; (b) (i) BnBr, NaH, DMF, 98%; (ii) 9-BBN, THF, $NaOH/H_2O_2$, 95%; (iii) MsCl, Et_3N, CH_2Cl_2, 86%; (c) $Pd(OH)_2/C$, H_2, $MeOH/CH_2Cl_2$, 99%; (d) $Pd(OH)_2/C$, H_2, Boc_2O, MeOH, 96%; (e) (i) RX, NaH, DMF; (ii) AcCl, EtOH, and then NaOH, 70–86%.

Table 1
Asymmetric Diels–Alder reaction between cinnamaldehyde and cyclopentadiene catalyzed by bipyrrolidines[a]

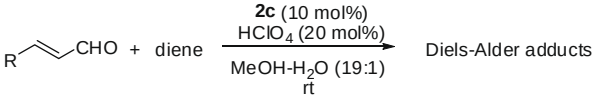


Entry	Cat.	HX	Yield[b] (%)	*exo*:*endo*[c]	*exo* ee[d] (%)	*endo* ee[d] (%)
1	**2c**	TfOH	95	2.3:1	88	78
2	**2c**	HCl	95	2.9:1	88	80
3	**2c**	TsOH	75	2.9:1	89	83
4	**2c**	$HClO_4$	93	2.5:1	91	83
5[e]	**1**	$HClO_4$	10	2.1:1	79	60
6[f]	**3c**	$HClO_4$	32	2.6:1	63	48
7	**2a**	$HClO_4$	94	2.5:1	90	83
8	**2b**	$HClO_4$	84	2.4:1	89	82
9	**2d**	$HClO_4$	84	2.5:1	90	85
10	**2e**	$HClO_4$	66	2.6:1	89	80
11	**2f**	$HClO_4$	93	2.3:1	90	88

[a] All the reactions were carried out with 0.25 mmol of cinnamaldehyde, 0.75 mmol of cyclopentadiene, 0.025 mmol of bipyrrolidine, and 0.05 mmol of acid at room temperature in $MeOH–H_2O$ (19:1, 0.25 M) for 12 h.
[b] Isolated yield of a mixture of *exo* and *endo* isomers.
[c] Determined by ^1H NMR.
[d] The ee was determined by chiral HPLC analysis.
[e] The reaction time is 17 h.
[f] The reaction time is 20 h.

reaction using $HClO_4$ gave Diels–Alder adduct in 93% yield with the best enantioselectivity (*exo* 91% ee, *endo* 83% ee, *exo*:*endo* = 2.5:1, and entry 4). Using bipyrrolidine **1** in combination with $HClO_4$ as a catalyst resulted in low conversion and poor enantioselectivity (entry 5). This result demonstrates the importance of 3,3′-dialkoxy groups for reactivity and enantioselectivity. To evaluate configurational effects of the catalyst, diastereomer **3c** was tested in the reaction. However, lower yield and stereoselectivity were observed (entry 6) which indicates that the configuration of catalysts **2** is matched in this Diels–Alder reaction. The effect of the O-substituent

Table 2
Asymmetric Diels–Alder reactions between various dienophiles and dienes catalyzed by bipyrrolidine **2c**[a]



Entry	R	Diene	*T* (h)	Yield[b] (%) (*exo*:*endo*)[c]	ee[d] (%) *exo*, *endo*
1	Ph	CP	12	93 (2.5:1)	91, 83
2	2-NO_2–Ph	CP	24	75 (0.9:1)	85, 91
3	4-NO_2–Ph	CP	12	94 (2.0:1)	83, 77
4	4-OMe–Ph	CP	12	55 (2.7:1)	89, 83
5	4-Cl–Ph	CP	7	95 (2.2:1)	89, 88
6	4-Br–Ph	CP	7	95 (2.1:1)	84, 83
7	*n*-Pr	CP	12	95 (1.1:1)	82, 85
8	COOEt	CP	36	95 (1.5:1)	84, 83
9	COOEt	CHD	12	95 (0.5:1)	85, 84
10	COOEt	DMB	24	87	70

[a] All the reactions were carried out with 0.25 mmol of dienophile, 0.75 mmol of diene, 0.025 mmol of catalyst **2c**, and 0.05 mmol of $HClO_4$ at room temperature in $MeOH–H_2O$ (19:1, 0.25 M).
[b] Isolated yield of a mixture of *exo* and *endo* isomers.
[c] Determined by ^1H NMR.
[d] The ee was determined by chiral HPLC analysis. CP: cyclopentadiene; CHD: cyclohexadiene; DMB: 2,3-dimethylbutadiene.

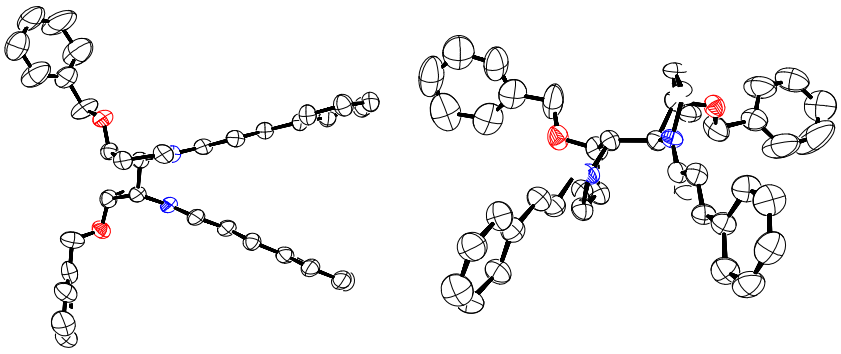


Figure 3. X-ray structure of diiminium intermediate **4**.

was also investigated. However, it has almost no effect on enantioselectivity and diastereoselectivity even though there is a small influence on reactivity (entries 7–11).

To explore the generality of the Diels–Alder reaction, the cycloadditions between various dienophiles and dienes using **2c** and $HClO_4$ cocatalyst have been investigated (Table 2). Substituted cinnamaldehyde dienophiles were subjected to the cycloaddition reaction with cyclopentadiene and Diels–Alder adducts were produced in good to excellent yields and selectivities (entries 1–6). Alkyl-substituted acrolein is also a suitable dienophile under the reaction conditions giving the product in excellent yield and good enantioselectivity (entry 7). The Diels–Alder reaction between (*E*)-ethyl 4-oxo-2-butenoate and various dienes was also examined. The reaction with cyclopentadiene gave high yield with good enantioselectivity (entry 8, 95% yield, *exo* 84% ee, and *endo* 83% ee). The reaction with cyclohexadiene resulted primarily in the formation of *endo*-product (entry 9). Acyclic diene, 2,3-dimethylbutadiene is also a suitable diene giving Diels–Alder adduct in high yield with good enantioselectivity (entry 10).

To elucidate the origin of the rate acceleration and stereoselectivity in the bipyrrolidine-catalyzed Diels–Alder reaction, we tried to make iminium intermediate by mixing catalyst **2c** with 2 equiv $HClO_4$ and 2 equiv cinnamaldehyde in MeOH. After stirring for 10 min, we observed that a substantial amount of cinnamaldehyde was consumed and diiminium intermediate **4** was formed on the basis of ^1H NMR spectroscopic studies. To gain further evidence for the catalytic mode of the Diels–Alder reaction, a single crystal of diiminium intermediate **4** was grown from methanol and ethyl acetate (20:1, v/v) and submitted for X-ray analysis. As we proposed, two conjugated iminiums faced each other in nearly a parallel fashion, and two *Si* faces of the diiminium are facing each other giving each other the same enantiofacial discriminations (Fig. 3). The crystal structure shows the two benzyloxy groups pointing away from two pyrrolidine rings. This fact may explain why modifying alkoxy groups at the 3,3′-positions did not have much influence on the enantioselectivity in the Diels–Alder reaction. However, the 3,3′-dialkoxy or dihydroxy groups of catalysts **2** likely have a positive effect on conformation of the reaction intermediate to give better reactivities and enantioselectivities when compared to the result of the cyclization reaction using catalyst **1**.

In summary, we have designed and developed a new class of C_2-symmetric 3,3′-dialkoxy-2,2′-bipyrrolidine catalysts for asymmetric organocatalytic Diels–Alder reactions of α,β-unsaturated aldehydes. The catalysts **2** showed excellent reactivity in the cyclization reactions giving Diels–Alder adducts with high enantioselectivities. The catalytic mode has been demonstrated by NMR and X-ray crystallographic studies for diiminium intermediate **4**. Further studies on modification of catalyst structure based on the crystal structure of diiminium intermediate **4** and other asymmetric transformations using C_2-symmetric bipyrrolidine catalysts will be described shortly.

Acknowledgments

This research was supported by the National Natural Science Foundation of China, and Shanghai Jiao Tong University (Chenxing Program).

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