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Tetrahedron Letters 46 (2005) 1803–1806

Tetrahedron Letters

Catalytic asymmetric aza Diels–Alder reactions of hydrazones using a chiral zirconium catalyst

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Received 29 December 2004; revised 21 January 2005; accepted 24 January 2005

Dedicated to Professor Iwao Ojima on the occasion of his 60th birthday

Abstract—Catalytic asymmetric aza Diels–Alder reactions of acylhydrazones with Danishefsky's dienes have been developed. A chiral zirconium complex derived from zirconium propoxide and 3,3′,6,6′-I_4BINOL was found to be effective in this reaction, and the desired optically active 2,3-dihydro-4-pyridone derivatives were obtained with high enantioselectivities. Asymmetric formal synthesis of a natural product, coniine, was conducted using this catalytic asymmetric reaction as a key step.

Development of efficient methods for constructing nitrogen-containing heterocycles is among the most important tasks in organic synthesis as well as medicinal chemistry, because the heterocycles are key building blocks for the preparation of biologically important alkaloids, peptides, and aza sugars, etc. Aza Diels–Alder reactions of imines with activated dienes, such as 1-alkoxy-3-siloxy-1,3-butadienes and its derivatives (Danishefsky's dienes),[1] opened an efficient way to functionalized piperidines, 2,3-dihydro-4-pyridone derivatives.[2] Recently, catalytic asymmetric versions of the aza Diels–Alder reactions have been explored, and high enantioselectivities were attained in some cases.[3,4] However, substrate generality of the reactions is still limited, especially in the reactions of unstable imines derived from aliphatic aldehydes.[4]

Acylhydrazones are stable imine equivalents, those derived from aromatic, α,β-unsaturated, and even aliphatic aldehydes are stable crystals easy to handle at room temperature. We have already reported that benzoylhydrazones reacted with several nucleophiles, such as silicon enolates and allylating agents, etc., in the presence of a catalytic amount of a Lewis acid to afford the corresponding adducts in high yields.[5] However, whereas aza Diels–Alder reaction of α,β-unsaturated hydrazones as dienes with olefins has been investigated,[6] the reactions of hydrazones as dienophiles with dienes, to the best of our knowledge, have never been reported regardless of its potential usefulness. In particular, such reactions would provide powerful methods when the N–N bonds of the products are cleaved under reductive conditions to afford N-unprotected piperidine derivatives. In this letter, we describe catalytic asymmetric aza Diels–Alder reactions of hydrazones with Danishefsky's dienes using a chiral zirconium catalyst.

In a preliminary investigation, we examined the aza Diels–Alder reaction of benzoylhydrazone **1a** derived from 3-phenylpropionaldehyde with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene **2a** in the presence of an achiral Lewis acid. It was found that boron trifluoride·diethyl ether ($BF_3{\cdot}OEt_2$) was an effective promoter for this reaction, affording the desired product **3a** in high yield (Scheme 1).[7]

Encouraged by this result, we decided to develop asymmetric aza Diels–Alder reactions of hydrazones with Danishefsky's dienes using a chiral Lewis acid catalyst.

We have already investigated catalytic asymmetric reactions of benzoylhydrazones and found that chiral zirconium Lewis acids were effective for achieving high enantioselectivity.[8] First, a chiral zirconium catalyst prepared from zirconium propoxide–propanol complex and 3,3′,6,6′-tetraiodo-1,1′-binaphthalen-2,2′-diol

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Keywords: Zirconium; Lewis acid; Asymmetric; Hydrazone; Aza Diels–Alder reaction.

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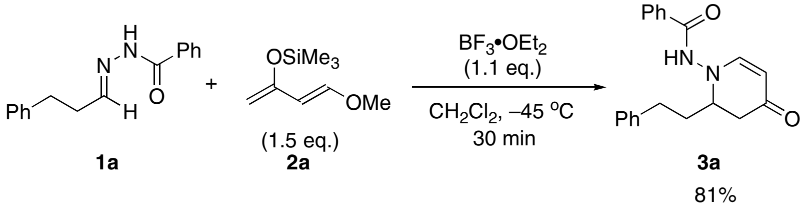
0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.01.111



Scheme 1.

(3,3′,6,6′-I$_4$BINOL) was tested. The catalyst was previously shown to be effective for asymmetric [3+2] cycloaddition of hydrazones with olefins.[8b,c] In the reaction of **1a** with **2a** in toluene at 0 °C, the desired product **3a** was obtained with high enantioselectivity but in low yield in the presence of 20 mol% of the catalyst (Table 1, entry 1). During this reaction there formed methanol, which was generated by decomposition of the intermediate with free propanol and was supposed to prevent the reaction by affecting the catalyst structure (an exchange of the propoxy group for the methoxy group). We then employed diene **2b** containing a *tert*-butyloxy group instead of the methoxy group, and found that the yield of the reaction was slightly improved to 35% with keeping high enantioselectivity (entry 2). The effect of substituents on the benzoyl moiety of the hydrazone was also examined; however, both electron-donating (MeO) and electron-withdrawing groups (Cl, CF$_3$) had no good effect on the yield (entries 3–5).

Next, we searched for a suitable solvent for this reaction (Table 2). At first, mixed solvent systems with toluene were examined, and slight improvement of the yield was observed in a toluene–*tert*-butyl methyl ether (TBME) system (entry 3).[9] Further increase of the yield was observed when TBME was used as the sole solvent (entry 4). Cyclopentyl methyl ether (CPME) was also gave a better yield than other ether-type solvents, Et$_2$O and ^{i}Pr$_2$O (entries 5–7). These results showed that the solvent polarity was a key factor for improving the yield. We then investigated further addition of aprotic polar solvents to the reaction system. We employed CH$_3$CN, THF, and DME as co-solvents of TBME. The yields reached up to 81% with maintaining the enantioselectivities (entries 8–11). In this reaction system, the catalyst loading was reduced to 10 mol% without significant loss of the yield and enantioselectivity (entry 12).

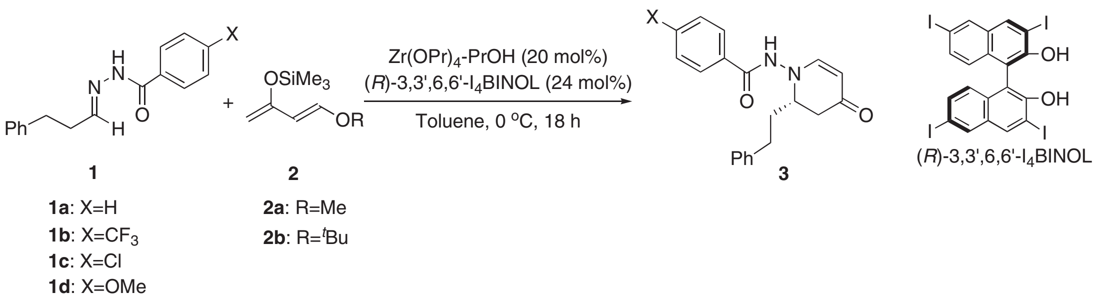
Other substrates were then subjected to this reaction (Table 3). The hydrazone derived from *n*-butanaldehyde also gave the desired product in good yield with high enantioselectivity (entry 2). On the other hand, the hydrazones derived from β- and α-branched aldehydes,

Table 2. Asymmetric aza Diels–Alder reactions of benzoylhydrazone **1a** with diene **2b**[a]

Entry	Solvent	Yield (%)	ee (%)
1	Toluene	35	93
2	Toluene/CH$_2$Cl$_2$ (2/1)	10	85
3	Toluene/^{t}BuOMe (2/1)	39	92
4	^{t}BuOMe	57	92
5	CPME[b]	56	93
6	^{i}Pr$_2$O	16	81
7	Et$_2$O	28	88
8	^{t}BuOMe/CH$_3$CN (2/1)	76	88
9	^{t}BuOMe/THF (2/1)	81	88
10	^{t}BuOMe/DME (2/1)	73	92
11	^{t}BuOMe/DME (4/1)	78	91
12[c]	^{t}BuOMe/DME (4/1)	70	91

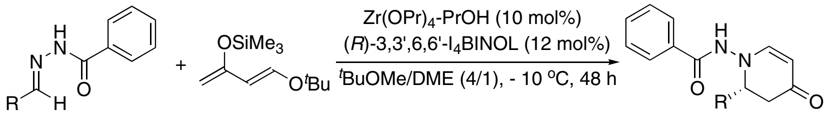
[a] The reactions were performed at 0 °C for 18 h in the presence of the zirconium catalyst (20 mol%).
[b] Cyclopentyl methyl ether.
[c] Using Zr catalyst (10 mol%) at −10 °C for 48 h.

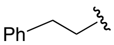
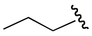
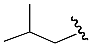
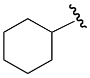
Table 1. Asymmetric aza Diels–Alder reactions of benzoylhydrazones **1** with diene **2** in the presence of a chiral zirconium complex



Entry	1	2	Yield (%)	ee (%)
1	**1a**	**2a**	19	90
2	**1a**	**2b**	35	93
3	**1b**	**2b**	17	53
4	**1c**	**2b**	22	85
5	**1d**	**2b**	<10	–

Table 3. Substrate generality



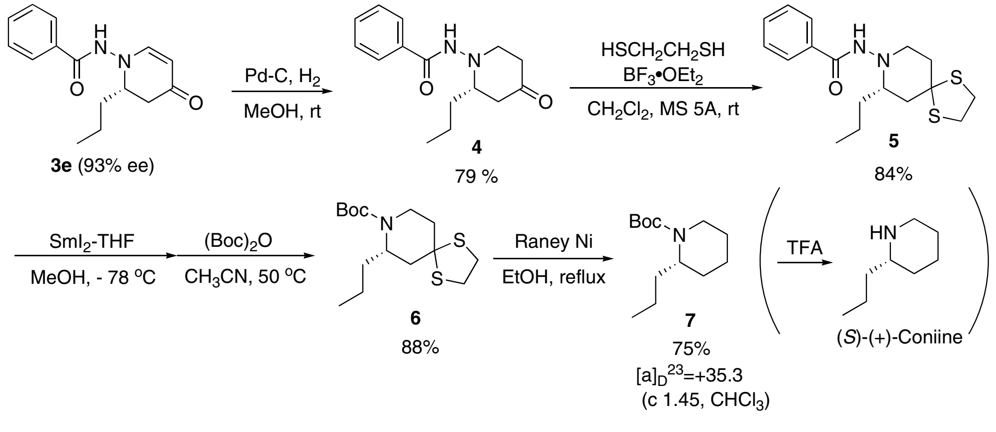
Entry	R	Yield (%)	ee (%)
1	 **(1a)**	70	91
2	 **(1e)**	70	93
3	 **(1f)**	31	92
4		50[a]	91
5	 **(1g)**	44	89
6		50[a]	95

[a] Using Zr catalyst (20 mol%) in ^{t}BuOMe.

3-methylbutanaldehyde and cyclohexancarboxyaldehyde, showed lower reactivity, albeit with high enantioselectivities (entries 3–6). From those results, it turned out that the present chiral zirconium catalyst system worked well in the reactions of hydrazones derived from various aliphatic aldehydes. This is a significant advantage of the catalytic asymmetric aza Diels–Alder reactions, because most reactions so far reported provided [4+2] products derived from aromatic or α,β-unsaturated imines or surrogates.[4] In the present system, hydrazones derived from benzaldehyde and α,β-unsaturated aldehydes were also tested; however, the reaction proceeded sluggishly, presumably due to high stability of the conjugated hydrazones.

An experimental procedure is described for the reaction of **1a** with **2b** (Table 2, entry 12): under argon atmosphere, to a suspension of (*R*)-3,3′,6,6′-I$_4$BINOL (39 mg, 0.049 mmol) in TBME (0.2 mL) was added a zirconium propoxide-propanol complex (17 mg, 77% purity, 0.041 mmol) in TBME (0.2 mL) at room temperature, and the mixture was stirred for 3 h. The zirconium catalyst solution was transferred into the flask in which hydrazone **1a** (103 mg, 0.41 mmol) was placed, and the zirconium flask was rinsed with TBME (0.2 mL). The whole was cooled at −10 °C, and diene **2b** (132 mg, 0.61 mmol) was added using TBME (0.2 mL) and DME (0.2 mL). The mixture was stirred for 48 h at the same temperature and was quenched with saturated aqueous NaHCO$_3$. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The organic layers were combined and dried over anhydrous Na$_2$SO$_4$. After filtration and concentration under reduced pressure, the crude mixture was purified by silica gel column chromatography to afford the desired product **3a** (92 mg, 70% yield). The enantiomeric excess was determined by HPLC analysis using Daicel CHIRALPAK AD (91% ee).

The reaction was applied to the synthesis of a natural compound, coniine, which was isolated from the pitcher plant, *Sarracenia flava*.[10] The aza Diels–Alder product **3e** was hydrogenated in the presence of Pd/C to afford compound **4**. Its carbonyl group was then protected with 1,2-ethanedithiol, and the N–N bond was cleaved with SmI$_2$.[11] After the Boc protection of the nitrogen atom, the dithioacetal moiety was cleaved by Raney Ni to afford Boc-protected coniine **7** in good yield. All physical data of synthetic **7** were completely consistent with the reported data of Boc-protected (*S*)-(+)-coniine ($[\alpha]_D^{23} = +35.3$ (*c* 1.45, CHCl$_3$); lit.[10c], $[\alpha]_D^{23} = +33.5$ (*c* 0.43, CHCl$_3$)) (Scheme 2).



Scheme 2. Formal synthesis of (*S*)-(+)-coniine.

In conclusion, we have developed catalytic asymmetric aza Diels–Alder reactions of hydrazones with Danishefsky's dienes. A chiral zirconium complex was found to be effective in this reaction, and the desired optically active 2,3-dihydro-4-pyridone derivatives were obtained with high enantioselectivities. Choice of solvents was an important factor for the reactivity, and better reactivity was obtained in mixed solvent systems containing aprotic polar solvents. Asymmetric formal synthesis of coniine was conducted, and Boc-protected (*S*)-(+)-coniine was obtained in good yield. Further application of this aza Diels–Alder reaction to the synthesis of biologically interesting compounds is under investigation.

Acknowledgements

This work was partially supported by CREST, SORST, and ERATO, Japan Science and Technology Corporation (JST), and a Grant-in-aid for Scientific Research from Japan Society of the Promotion of Science.

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