Diels-Alder Reactions

The First Organocatalytic Enantioselective Inverse-Electron-Demand Hetero-Diels–Alder Reaction**

*Karsten Juhl and Karl Anker Jørgensen**

The use of chiral amines as catalysts for organic reactions has emerged as a new and important field in chemistry and several new reactions have been developed.[1] Among the amines studied, L-proline and (*S*)-2-(1-pyrrolidinylmethyl)-pyrrolidine have been successfully applied as chiral catalysts for reactions of aldehydes or ketones in aldol,[2] Mannich,[3] Michael,[4] and α-amination reactions.[5] The mechanisms for these reactions are presumed to go via the enamine intermediate, that is, the aldehyde or ketone reacts with the amine to form an enamine, which then adds as a nucleophile to the C=O-, C=N-, C=C-, or N=N-moiety, respectively. Simultaneously, MacMillan and co-workers have developed organocatalytic cycloaddition reactions of electron-poor alkenes with dienes[6] or 1,3 dipoles[7] and 1,4-addition of aromatic compounds.[8]

Herein we present the development of a new organocatalytic reaction. We envisioned that chiral enamines, generated from aldehydes and chiral pyrrolidines, could act as electron-rich alkenes and undergo an enantioselective hetero-Diels–Alder (HDA) reaction with enones via the catalytic cycle outlined in Scheme 1:[9,10] In situ generation of a chiral enamine **2** from a chiral pyrrolidine **1** and an aldehyde **3** followed by a stereoselective HDA reaction with enone **4** would give the aminal **5**. Hydrolysis of aminal **5** would then give hemiacetal **6** and release the chiral catalyst **1** to complete the catalytic cycle.

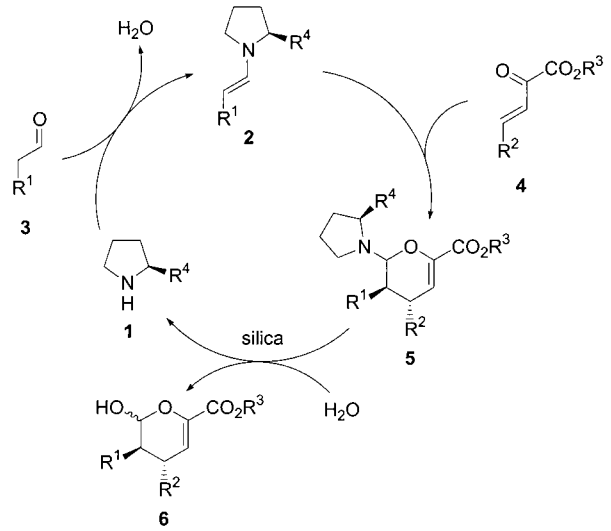
A key step in the catalytic cycle is the hydrolysis of the aminal **5**. We have found that the reaction of a stoichiometric

[*] Prof. Dr. K. A. Jørgensen, Dr. K. Juhl
The Danish National Research Foundation: Center for Catalysis
Department of Chemistry, Aarhus University
8000 Aarhus C (Denmark)
Fax: (+45) 8619-6199
E-mail: kaj@chem.au.dk

[**] This work was made possible by a grant from The Danish National Research Foundation. Thanks are expressed to Dr. R. G. Hazell for solving the X-ray crystal structure of **8bb**.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

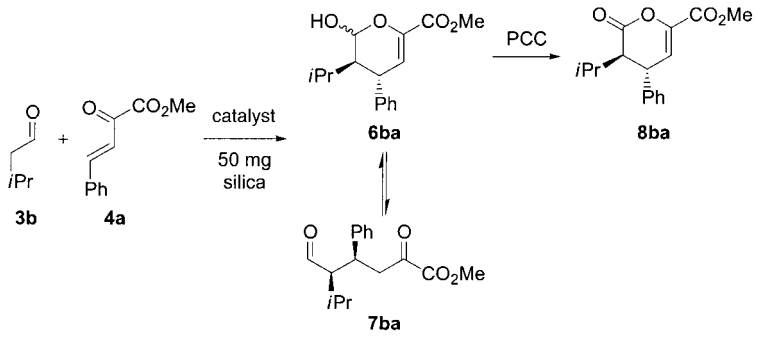
  DOI: 10.1002/ange.200250652



Scheme 1. Catalytic cycle for the organocatalytic hetero-Diels–Alder reaction.

amount of a chiral enamine **2** with enone **4** gives only one diastereomer of **5** and in attempts to purify **5** we found that the cycloaddition adduct was easily hydrolyzed by silica gel to give a mixture of the two anomers of hemiacetal **6** and aldehyde **7** (e.g. see Scheme 2).[11] Thus, the presence of silica would facilitate the hydrolysis step in the catalytic cycle.

Indeed, the enamine of isovaleraldehyde **3b** generated in situ reacted with the electron-poor enone **4a** in a HDA reaction eventually yielding a mixture of the two anomers of hemiacetal **6ba** and aldehyde **7ba** (Scheme 2). Oxidation of this mixture with pyridine chlorochromate (PCC) yielded lactone **8ba** as a single diastereomer.

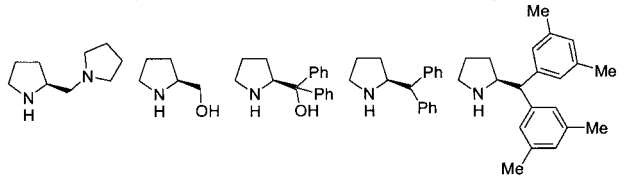


Scheme 2. The HDA reaction of aldehyde **3b** and enones **4a** in the presence of a chiral pyrrolidine catalyst yields the two anomers of hemiacetal **6ba** and aldehyde **7ba**.

Catalytic turnover was accomplished by the addition of silica (50 mg on a 0.5 mmol scale) to the reaction mixture. Table 1 shows representative results from the optimization of this reaction using different substituted (2*S*)-pyrrolidines **1a–e** as catalysts.

(*S*)-2-(1-Pyrrolidinylmethyl)pyrrolidine (**1a**) worked well as a catalyst yielding the HDA adduct in 69% with 51% *ee*

Table 1: Optimization of the organocatalytic hetero-Diels–Alder reaction of isovaleraldehyde **3b** with enone **4a** with various catalysts **1**.



1a **1b** **1c** **1d** **1e**

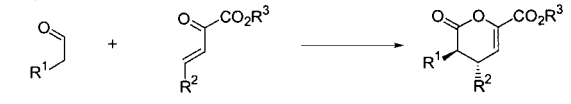
Entry	Catalyst (mol%)	Enone [equiv]	Solvent[a]	T[b]	Yield[c] [%]	*ee*[d] [%]
1	**1a** (20)	1.1	CH_2Cl_2	RT	69	51
2	**1b** (20)	1.1	CH_2Cl_2	RT	54	56
3	**1c** (20)	1.1	CH_2Cl_2	RT	6	97
4	**1d** (20)	1.1	CH_2Cl_2	RT	46	88
5	**1e** (10)	2	CH_2Cl_2	RT	71	87
6	**1e** (10)	1.5	CH_2Cl_2	−15 °C→RT	70	91
7	**1e** (10)	2	CH_2Cl_2	−15 °C→RT	93	89
8	**1e** (10)	2	toluene	−15 °C→RT	77	90
9	**1e** (10)	2	$CDCl_3$	−15 °C→RT	69	92
10	**1e** (10)	2	$ClCH_2CH_2Cl$	−15 °C→RT	74	90
11	**1e** (10)	2	MeCN	−15 °C→RT	59	90

[a] Solvent (0.5 mL). [b] RT = room temperature. [c] Combined yield of **6ba** and **7ba**. [d] The *ee* values were determined by HPLC.

(Table 1, entry 1). Use of the chiral prolinol (**1b**) resulted in a similar yield and selectivity (Table 1, entry 2), whereas the diphenylprolinol (**1c**) promoted a highly enantioselective HDA reaction, providing **8ba** with 97% *ee* (Table 1, entry 3). Unfortunately, the increased steric bulk of the substituent at C2 led to a low yield. However, the two phenyl groups of **1c** were required to obtain the high enantioselectivity. We therefore anticipated that the dehydroxylated catalyst **1d** would maintain high enantioinduction, whereas the smaller size of the substituent at C2 would lead to higher yield. Application of catalyst **1d** did, indeed, lead to a higher yield but also to a slight decrease in enantioselectivity (Table 1, entry 4). Catalyst **1e** was also applied and similar enantioselectivity was observed. The catalytic turnover was even more efficient, and the catalyst loading could be decreased to 10 mol% (Table 1, entry 5). Mixing the reagents and the catalyst at −15 °C and allowing the reaction mixture to warm to room temperature resulted in a cleaner reaction and higher yield. Under these reaction conditions, different solvents were tested (Table 1, entries 7–11). The highest yield (93%) was obtained with CH_2Cl_2 as solvent, and up to 92% *ee* could be reached in $CHCl_3$.

The scope of the enantioselective organocatalytic HDA reaction was demonstrated by the reaction of various aldehydes (**3a–c**) and enones **4a–c** and the results are presented in Table 2. The β,γ-unsaturated-α-ketoesters with aromatic substituents in the γ-position, **4a,b**, and the β,γ-unsaturated-α-ketoesters with an aliphatic substituent such as methyl in the γ-position, **4c**, all underwent the HDA reaction smoothly with both very high diastereo-[12] and enantioselectivity. The aliphatic aldehydes were also varied and different substitution patterns were

Table 2: Scope of the organocatalytic hetero-Diels–Alder reaction catalyzed by **1e**.[a]



3a R^1 = Et **4a** R^2 = Ph, R^3 = Me
3b R^1 = *i*Pr **4b** R^2 = 4-ClC_6H_4, R^3 = Me
3c R^1 = Bn **4c** R^2 = Me, R^3 = Et

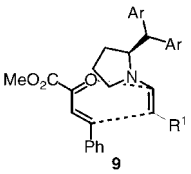
8

Entry	3	4	8	Yield [%][b]	*ee* [%][c]
1	**a**	**a**	**aa**	69	84
2	**b**	**a**	**ba**	93	89
3[d]	**b**	**a**	**ba**	69	92
4[e]	**c**	**a**	**ca**	65	86
5[f]	**a**	**b**	**ab**	79	85
6[f]	**b**	**b**	**bb**	70	90
7[e,f]	**c**	**b**	**cb**	62	80
8	**a**	**c**	**ac**	81	86
9	**b**	**c**	**bc**	75	94
10[e]	**c**	**c**	**cc**	72	89

[a] Reaction conditions (0.5 mmol scale): 1) **1e** (10 mol%), silica (50 mg), −15 →RT, CH_2Cl_2 (0.5 mL), 17 h; 2) PCC, CH_2Cl_2. [b] Combined yield of **6** and **7**. [c] The *ee* values were determined by HPLC or GC (entries 8 and 9) of **8**. [d] $CDCl_3$ used as solvent. [e] Reaction time = 40 h. [f] Solvent (2 mL).

allowed. In general, good yields were observed (62–93%) and the enantioselectivities were as high as 94% *ee*.

The absolute and relative stereochemistry of the outcome of the organocatalytic HDA reaction was determined on the basis of the X-ray crystal structure of the HDA adduct **8bb**.[13] The configuration of the HDA adduct was assigned to be 4*S*,5*R*. The observed absolute and relative stereochemistry is consistent with the proposed transition state model **9**. The electronic properties of the enamine govern the regioselectivity, while the 2,2-diarylmethyl substituent on the pyrrolidine ring shields the *Si* face of the enamine. Thus, the 2,2-diarylmethyl substituent of the enamine intermediate controls the addition of the enone to the *Re* face of the alkene fragment in an *endo*-selective fashion. At the present stage of investigations we have no direct evidence for a concerted versus a stepwise cycloaddition reaction; the latter reaction path would take place by an initial Michael addition followed by a ring-closure reaction.



9

In conclusion, we have developed a new concept in organocatalysis—the use of a chiral enamine intermediate as an alkene in catalytic asymmetric cycloaddition reactions. The present work presents the catalytic asymmetric hetero-Diels–Alder reaction of aldehydes with enones to give highly functionalized, optically active molecules with excellent diastereo- and enantioselectivity.

Received: November 28, 2002 [Z50652]

Keywords: aldehydes · amines · asymmetric catalysis · cycloaddition · enones

[1] a) H. Gröger, J. Wilken, *Angew. Chem.* **2001**, *113*, 545; *Angew. Chem. Int. Ed.* **2001**, *40*, 529; b) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840; *Angew. Chem. Int. Ed.* **2001**, *40*, 3709; c) B. List, *Tetrahedron* **2002**, *58*, 5573.

[2] For example, see: a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395; b) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260; c) A. Córdova, W. Notz, C. F. Barbas III, *J. Org. Chem.* **2002**, *67*, 301; d) A. Bøgevig, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Commun.* **2002**, 620; e) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386; f) L. Hoang, S. Bahmanyar, K. N. Houk, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 16; g) B. List, P. Polarjiev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423; h) A. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798.

[3] For example, see: a) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336; b) B. List, P. Polarjiev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827; c) A. Córdova, S.-i. Watanabe, F. Tanaka, W. Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1842; d) A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1866; e) S.-I Watanabe, A. Córdova, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2002**, *4*, 4519.

[4] For example, see: a) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737; b) D. Enders, A. Seki, *Synlett*, **2002**, 26; see also: c) S. Hanessian, V. Pham, *Org. Lett.* **2000**, *2*, 2975; d) A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611; e) N. Halland, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 8331; f) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 685; *Angew. Chem. Int. Ed.* **2003**, *42*, 661; g) B. List, P. Polarjiev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423; h) A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964; i) M. Yamaguchi, T. Shiraishi, M. Hirami, *J. Org. Chem.* **1996**, *61*, 3520; j) D. J. Gurin, S. J. Miller, *J. Am. Chem. Soc.* **2002**, *124*, 2134.

[5] a) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem.* **2002**, *114*, 1868; *Angew. Chem. Int. Ed.* **2002**, *41*, 1790; b) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656; c) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254.

[6] a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243; b) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458.

[7] a) W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874; see also: b) S. Karlsson, H.-E. Högberg, *Tetrahedron: Asymmetry* **2002**, *13*, 923.

[8] a) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172; b) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370; c) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 7894.

[9] The Lewis acid catalyzed enantioselective hetero-Diels–Alder reaction of electron-rich alkenes with electron-poor enones has been developed: a) K. A. Jørgensen, *Angew. Chem.* **2000**, *112*, 3702; *Angew. Chem. Int. Ed.* **2000**, *39*, 3559; b) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325; c) K. A. Jørgensen, M. Johannsen, S. Yao, H. Audrain, J. Thorhauge, *Acc. Chem. Res.* **1999**, *32*, 605; see also: d) K. Gademann, D. E. Chavez, E. N. Jacobsen, *Angew. Chem.* **2002**, *114*, 3185; *Angew. Chem. Int. Ed.* **2002**, *41*, 3059.

[10] The stoichiometric HDA reaction of achiral enamines with β,γ-unsaturated-α-ketoesters has been reported earlier: F. Eiden, W. Winkler, *Arch. Pharm.* **1986**, *319*, 704. Schreiber et al. have used a stoichiometric asymmetric enamine–enal cycloaddition for the synthesis of a series of brefeldin isomers: S. L. Schreiber, H. V. Meyers, *J. Am. Chem. Soc.* **1988**, *110*, 5198.

[11] B. B. Snider, *Tetrahedron Lett.* **1980**, *21*, 1133.

[12] In all cases, only one diastereomer of **8** was detected, with the exception of **8ac** (d.r. = 45:1).

[13] CCDC-198535 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

