The first highly enantioselective catalytic hetero-Diels–Alder reaction of ketones

Mogens Johannsen, Sulan Yao and Karl Anker Jørgensen*

Center for Metal Catalyzed Reactions, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

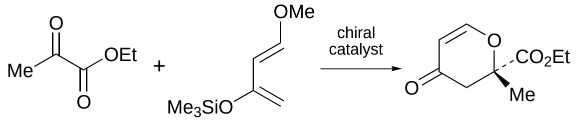
The first highly enantioselective catalytic hetero-Diels–Alder reaction of various aliphatic and aromatic ketones with an activated conjugated diene catalysed by chiral copper(II) complexes with enantiomeric excesses up to 99% is presented.

The hetero-Diels–Alder (HDA) reaction of carbonyl compounds with conjugated dienes is one of the cornerstone reactions in organic chemistry and has wide application for the synthesis of important compounds.[1] One of the most useful reactions in this field is the HDA reaction of aldehydes with activated conjugated dienes, such as Danishefsky's diene, leading to highly valuable oxygenated products.[2]

In recent years interest has been focused on the development of metal-catalysed enantio- and diastereo-selective HDA reactions of aldehydes with conjugated dienes.[3] Great progress has been made in the HDA reaction between activated conjugated dienes and simple unactivated aldehydes.[4] Recently, we have been involved in developing highly enantioselective HDA reactions of aldehydes, such as glyoxylates, with unactivated conjugated cyclic and acyclic dienes catalysed by bisoxazoline–copper(II) and –zinc(II) complexes[5] and BINOL-aluminium(III) complexes.[6]

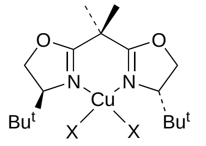
The challenge is to develop the metal-catalysed enantioselective HDA reaction of ketones with conjugated dienes, as this reaction will have wide potential in organic chemistry. Here we present the first highly enantioselective HDA reaction of both aliphatic and aromatic ketones with an activated conjugated diene using chiral catalysis.[7]

The reaction of ethyl pyruvate **1a** with *trans*-1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene (Danishefsky's diene) **2** [eqn. (1)] has been studied in the presence of various bidentate bisoxazoline and tridentate bisoxazoline–pyridine ligands in combination with copper(II) salts [(*S*)-**4a**, (*R*)- **4b**, (*S*)-**5a**,**b** and (*R*)-**5c**, respectively] in order to investigate the catalytic properties of the different ligands on the HDA reaction. The reaction of **1a** with **2** in the presence of (*S*)-**4a**, (*R*)-**4b**, (*S*)-**5a**,**b** or (*R*)-**5c** (X = OTf) (10 mol%) as the catalyst in CH_2Cl_2 at room temperature gives the HDA product **3a** in various yields and enantiomeric excesses (ees) depending on the catalyst used. By application of (*S*)-**4a** as the catalyst, **3a** is isolated in 85% yield, with an ee of 92% (reaction time, 8 h), while (*R*)-**4b** gave the same yield of **3a**, but with an ee of only 26% (reaction time, 8 h). It should be noted that both catalysts give the same enantiomer of the HDA product **3a**.[5a,c] The catalysts (*S*)-**5a**,**b** and (*R*)-**5c** are less effective and much longer reaction times are required (*ca.* 100 h); with (*S*)-**5a**,**b**, the HDA product **3a** is isolated in 29 and 15% yield, and with an ee of 9 and 27%, respectively, while (*R*)-**5c** gave nearly the same yield (23%), but a slightly higher ee (55%).

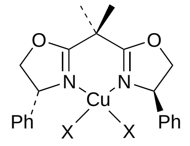


(1)

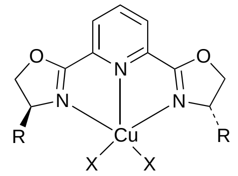
1a **2** **3a**



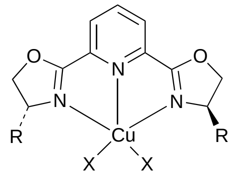
(*S*)-**4a**



(*R*)-**4b**



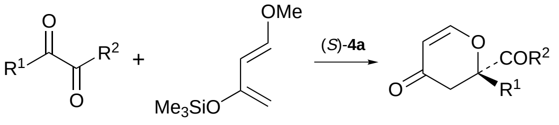
(*S*)-**5a** R = Bu^t
(*S*)-**5b** R = Pr^i



(*R*)-**5c**

X = OTf, SbF_6

It turned out the catalyst (*S*)-**4a** was the most promising chiral catalyst, both in terms of yield and ee of the HDA product formed. This catalyst was therefore applied for the reaction of different α-keto esters and an α-diketone **1a–d** with *trans*-1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene **2** [eqn. (2)] under various reaction conditions to extend the scope of the reaction.†



(2)

1a R^1 = Me, R^2 = OEt
b R^1 = Me, R^2 = OMe
c R^1 = Ph, R^2 = OEt
d R^1 = R^2 = Me

2

3a R^1 = Me, R^2 = OEt
b R^1 = Me, R^2 = OMe
c R^1 = Ph, R^2 = OEt
d R^1 = R^2 = Me

The results for the HDA reaction of the various ketones **1a–d** with *trans*-1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene **2** catalysed by (*S*)-**4a** under various conditions are presented in Table 1.

Table 1 Hetero-Diels–Alder reactions of the ketones **1a–d** with *trans*-1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene **2** catalysed by (*S*)-**4a** [eqn. (2)] under various reaction conditions

						Diels–Alder product	
Entry	Ketone	(*S*)-**4a** X	*T*/°C	*t*/h	Solvent	Yield[a] (%)	Ee (%)
1	**1a**	OTf	room temp.	8	CH_2Cl_2	**3a** 85	92[b]
2	**1a**	OTf	−40	30	CH_2Cl_2	**3a** 78	99[b]
3	**1a**	SbF_6	room temp.	24	CH_2Cl_2	**3a** 22	80[b]
4	**1a**	SbF_6	−40	50	CH_2Cl_2	**3a** 37	89[b]
5	**1b**	OTf	room temp.	23	CH_2Cl_2	**3b** 95	91[b]
6	**1c**	OTf	room temp.	20	THF	**3c** 77	77[c]
7	**1d**	OTf	−40	60	THF	**3d** 90	94[b]

[a] Isolated yield. [b] Ee determined by GC on a Chrompack Chirasil-DEX CB column. [c] Ee determined by HPLC on a Daicel Chiralpak AD column, eluent: hexane–Pr^{i}OH (99 : 1).

Ethyl pyruvate **1a** reacts with *trans*-1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene **2** in the presence of the catalyst (*S*)-**4a** having triflate as the anion at room temperature to give the HDA product in 85% yield with 92% ee (Table 1, entry 1). Performing the reaction at −40 °C leads to an improvement of the ee of **3a** to 99% without affecting the yield significantly (entry 2). Exchange of the anion from triflate to antimonate leads to a decrease in the yield of **3a** to only 22%, and also to a reduction of the ee (80%) (entry 3). Performing the reaction between **1a** and **2** in the presence (*S*)-**4a** (X = SbF_5) at −40 °C slightly increases the ee of the HDA product (entry 4). The ester substituent is of minor importance for the highly enantioselective HDA reaction as methyl pyruvate **1b** reacts with **2** in the presence of (*S*)-**4a** (X = OTf) as the catalyst to give **3b** in high yield (95%) and with high ee (91%) (entry 5). The reaction of the aromatic ketone **1c** with **2** in the presence of (*S*)-**4a** (X = OTf) also proceeds well, giving a 77% yield of the HDA product **3c** with an ee of 77%. The enantiomeric HDA reaction is not only restricted to α-keto esters such as **1a–c**; the α-diketo compound butane-2,3-dione **1d** also reacts with **2** in the presence of (*S*)-**4a** (X = OTf) as the catalyst to give **3d** in high yield (89%) and with very high ee (94%).

The potential of this new enantioselective HDA reaction for the various ketones is obvious from entries 2, 5–7 in Table 1. The HDA products are formed in high yields for both the aliphatic and aromatic ketones and, furthermore, the aliphatic ketones give up to 99% ee in these reactions, whereas 77% ee is found for the aromatic ketone. Work is in progress to develop this HDA reaction further and to understand the mechanistic aspects of the reaction.

Thanks are expressed to The Danish National Science Foundation for financial support.

Footnotes and References

* E-mail: kaj@kemi.aau.dk

† *Typical procedure*: (*S*)-**4a** (X = OTf) was prepared by addition of $Cu(OTf)_2$ (36 mg, 0.1 mmol) to 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (31 mg, 0.105 mmol) dissolved in dry CH_2Cl_2 (2 ml) under an inert atmosphere and stirred for 2 h. The catalyst was cooled to −40 °C, ethyl pyruvate **1a** (110 µl, 1 mmol) and *trans*-1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene **2** (250 µl, 1.2 mmol) were added, and the solution stirred for 30 h at this temperature. Then TFA (0.1 ml) dissolved in CH_2Cl_2 (20 ml) was added at −40 °C and the solution stirred for 1 h at 0 °C. The solution was then neutralised with saturated $NaHCO_3$ and the solution was filtered through a plug of cotton. The organic phase was separated and the water phase was extracted twice with CH_2Cl_2. The combined organic phases were dried, filtered and the solvent evaporated. Purification of the crude product using flash chromatography (EtOAc–light petroleum, 1 : 4) gave **3a** in 78% yield and 99% ee (chiral GC); $[\alpha]_D^{25}$ + 149 (*c* 1.1, $CHCl_3$).

1 R. R. Schmidt, *Acc. Chem. Res.,* 1986, **19**, 250; D. L. Boger and S. M. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press, New York, 1987.

2 M. Bednarski, C. Maring and S. Danishefsky, *Tetrahedron Lett.,* 1983, 3451.

3 K. Narasaka, M. Inoue and N. Okada, *Chem. Lett.,* 1986, 1109; H. Waldmann, *Synthesis*, 1994, 535; K. Narasaka, *Synthesis*, 1991, 1; K. Maruoka and H. Yamamoto, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH, Weinheim, 1993, p. 413; H. B. Kagan and O. Riant, *Chem. Rev.,* 1992, **92**, 1007.

4 G. E. Keck, X.-Y. Li and D. Krishnamurthy, *J. Org. Chem.,* 1995, **60**, 5998; K. Maruoka, T. Itoh, T. Shirasaka and H. Yamamoto, *J. Am. Chem. Soc.,* 1988, **110**, 310; T. Hanamoto, H. Furuno and J. Inanaga, *Synlett*, 1997, 79; Q. Gao, T. Maruyama, M. Mouri and H. Yamamoto, *J. Org. Chem.,* 1992, **57**, 1951; A. Togni, *Organometallics,* 1990, **9**, 3106; Y. Motoyama and K. Mikami, *J. Chem. Soc., Chem. Commun.,* 1994, 1563.

5 (*a*) M. Johannsen and K. A. Jørgensen, *J. Org. Chem.,* 1995, **60**, 5757; (*b*) M. Johannsen and K. A. Jørgensen, *Tetrahedron,* 1996, **52**, 7321; (*c*) S. Yao, M. Johannsen and K. A. Jørgensen, *J. Chem. Soc., Perkin Trans. 1,* 1997, 1234; (*d*) M. Johannsen and K. A. Jørgensen, *J. Chem. Soc., Perkin Trans. 2,* 1997, 1183.

6 A. Graven, M. Johannsen and K. A. Jørgensen, *Chem. Commun.,* 1996, 2373.

7 To the best of our knowledge this is the only other paper on enantioselective HDA reactions with ketones, albeit with modest ee: M. Quimpére and K. Jankowski, *J. Chem. Soc., Chem. Commun.,* 1987, 676. See also P. C. B. Page, P. H. Williams, E. W. Collington and H. Finch, *J. Chem. Soc., Chem. Commun.,* 1987, 756.

Received in Cambridge, UK, 4th September 1997; 7/06463B