Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 7693–7696
Tetrahedron Letters

The enantioselective high-pressure Diels–Alder reaction of 1-methoxybuta-1,3-diene with *tert*-butyldimethylsilyloxyacetaldehyde catalyzed by (salen)Co(II) and (salen)Cr(III)Cl complexes

Małgorzata Malinowska,[a] Piotr Kwiatkowski[b] and Janusz Jurczak[a,b,*]

[a]*Department of Chemistry, Warsaw University, Pasteura 1, 02-093 Warsaw, Poland*
[b]*Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland*

Received 8 June 2004; revised 9 August 2004; accepted 16 August 2004

Abstract—The high-pressure (10–11 kbar) reaction of 1-methoxybuta-1,3-diene (**1**) with *tert*-butyldimethylsilyloxyacetaldehyde (**2**), catalyzed by the chiral (salen)Co(II) **4** or (salen)Cr(III)Cl **5** complexes, has been studied. We found that the reaction afforded, in good yield (up to 90%) and both with very good diastereoselectivity (up to 92%) and enantioselectivity (up to 94% ee), the [4 + 2]cycloadducts **3**, which are compounds of significant synthetic interest.

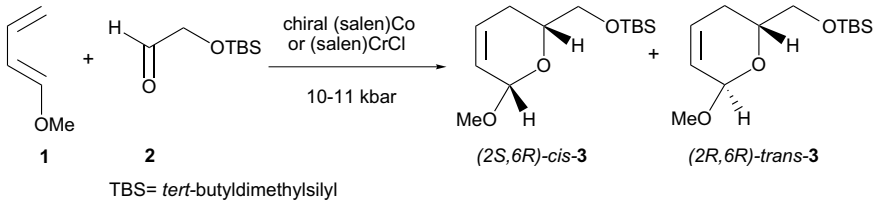
One of the most important tasks of modern organic synthesis is the quest for novel synthetic methods useful for the preparation of chiral compounds with high enantiomeric purity. Until very recently, the main approach for the development of these methods was by diastereoselective reactions.[1] However, requirements for simplification of procedures as well as improvement of the economy of chemical process has led to the development of enantioselective strategies, especially asymmetric catalysis.[2]

The hetero-Diels–Alder (HDA) reaction is one of the most useful processes leading to dihydropyran derivatives, which are compounds of significant synthetic interest.[3] [4 + 2]Cycloadditions of 1,3-dienes possessing electron-donating substituents, such as 1-alkoxybuta-1,3-dienes, to carbonyl compounds having electron-withdrawing substituents, such as alkyl glyoxylates, proceed readily affording 2-alkoxy-5,6-dihydro-2*H*-pyran derivatives,[4] as convenient precursors for the synthesis of modified carbohydrates[5] and other biologically active substances, for example, compactin and mevinolin.[6] Optically active systems of this type can be obtained via diastereoselective synthesis using chiral sultam glyoximides.[6c,7] Mikami and co-workers[8] and Kalesse and co-workers[9] demonstrated that these reactions can be carried out enantioselectively using titanium BINOL complexes. In turn, we have shown, very recently, that commercially available salen chromium(III)[10] and cobalt(II)[11] complexes are useful for the reaction of 1-methoxybuta-1,3-diene (**1**) with *n*-butyl glyoxylate, which afforded enantioselectivities in the range of 70–90% ee. When non-activated heterodienophiles, such as acetaldehyde or benzaldehyde, were used under ambient conditions, the [4 + 2]cycloaddition reaction failed. However, application of the high-pressure technique led to a successful reaction.[12] This methodology has been applied to the diastereoselective synthesis of many natural products using α-hydroxy and α-amino aldehydes as chiral heterodienophiles.[13] Recently, we have published a paper[14] dealing with the high-pressure Diels–Alder reaction of the reactive 1,3-diene **1** with non-activated heterodienophiles of type **2** (Scheme 1). This reaction proceeds in the presence of a catalytic amount of weak Lewis acids, for example, $Eu(fod)_3$. Unfortunately, the use of $Eu(hfc)_3$ as a chiral catalyst was not efficient enough (~15% ee). This finding prompted us to extend the range of catalysts tested to complexes of transition metals with chiral salen ligands.

Preliminary tests on the cationic salen–chromium catalyst with BF_4^- as the counterion, as applied for the first

Keywords: Asymmetric catalysis; Cobalt; Chromium; Diels–Alder reaction; Salen; Stereoselectivity.
* Corresponding author. Tel.: +48 22 6320578; fax: +48 22 6326681; e-mail: jurczak@icho.edu.pl

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.08.081



Scheme 1.

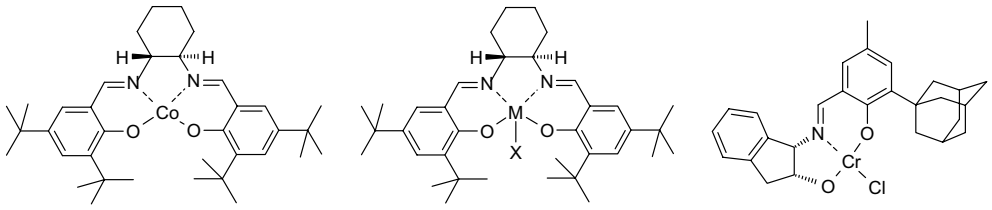


Figure 1. The chiral catalysts used.

time in HDA reaction by Jacobsen and co-workers,[15] displayed enantioselectivity as low as in the case of $Eu(hfc)_3$; however, the use of the neutral cobalt catalyst **4a** (Fig. 1) seemed to be more promising.

Dienophile **2** had already been employed by Jacobsen and co-workers[16] for the Diels–Alder reaction with 1-methoxybuta-1,3-diene in the presence of tridentate chromium(III) complex **7** (Fig. 1). This reaction proceeded without any solvent in the presence of activated 4 Å molecular sieves under atmospheric pressure and gave very high stereoselectivities and yields.

We found that, under the conditions suggested by Jacobsen, with no solvent and in the presence of molecular sieves, the use of (salen)Co(II) **4a** resulted in very low yields of about 5%, with a diastereoselectivity of 95:5 and 80% ee for the *cis* product. The chromium(III) chloride complex **5a** provides much higher yields (up to 45%) and diastereoselectivity of 92:8 and enantioselectivity of 64% ee. Of note is fact that, the complexes **4a** and **5a**, which have the C_2-symmetry, perform much better under the high-pressure conditions (the ee for the *cis* product is 75–94%, Table 1). We have also tested the behaviour of the tridentate complex **7** (2 mol%) under similar conditions (10 kbar, CH_2Cl_2). Despite the good yield (80%) and diastereoselectivity (98:2), the enantioselectivity dropped to nearly 65% ee, as compared to the method of Jacobsen and co-workers.[16] The preliminary studies demonstrated that the salen complexes of cobalt(II) and chromium(III)Cl, having C_2-symmetry, afforded much better results in terms of both yield and selectivity under high-pressure conditions.

We next investigated the influence of the amount of catalyst, solvent and concentration of *tert*-butyldimethylsilyloxyacetaldehyde (**2**)[17] on the course of the reaction catalyzed by complexes **4a** and **5a** (Table 1). We also checked how the cationic cobalt complex **6** (Fig. 1) performed in this reaction.

In the case of (salen)Co **4a**, an increase in concentration of the catalyst influenced slightly, but favourably, the reaction yield, whereas the diastereoselectivity and

Table 1. High-pressure [4 + 2]cycloaddition of diene **1** with *tert*-butyldimethylsilyloxyacetaldehyde (**2**) in the presence of complexes **4a**, **5a** or **6**[a]

Entry	Catalyst	Mol% of the catalyst	Concn of **2** (mol/L)	Solvent	Yield (%)	*cis*/*trans*[b]	ee for *cis*-**3**[b] (%)	ee for *trans*-**3**[b] (%)
1	**4a**	5	1	CH_2Cl_2	61	93:7	93	73
2	**4a**	2	1	CH_2Cl_2	52	93:7	92	70
3	**4a**	0.5	1	CH_2Cl_2	30	90:10	81	43
4	**4a**	2	1	Toluene	33	88:12	75	48
5	**4a**	5	0.5	CH_2Cl_2	52	95:5	94	74
6	**4a**	2	0.5	CH_2Cl_2	47	95:5	93	79
7	**6**	2	0.5	CH_2Cl_2	32	81:19	75	32
8	**5a**	5	0.5	CH_2Cl_2	80	91:9	84	66
9	**5a**	2	0.5	CH_2Cl_2	70	95:5	85	65
10	**5a**	2	0.5	Toluene	84	96:4	87	78
11	**5a**	2	1	CH_2Cl_2	88	93:7	83	69
12	**5a**	0.5	0.5	CH_2Cl_2	60	96:4	85	65

[a] The reactions were carried out using 1 mmol of aldehyde **2** and 1.2 mmol of diene **1** under high pressure (10–11 kbar) at 20 °C for 24 h.
[b] *cis*/*trans* ratio and enantiomeric excess were determined by GC on a capillary chiral β-dex 120 column.

enantioselectivity remained practically unchanged (Table 1, entries 1, 2, 5 and 6). Only a decrease of the catalyst content to 0.5 mol% resulted in a significant reduction in yield and a drop of enantioselectivity from 93% to 81% ee (compare entries 1 and 3). In turn, the change of the solvent from methylene dichloride to toluene decreased the yield of the reaction, diastereoselectivity and enantioselectivity (entry 4). Double dilution of the reaction mixture had practically no influence on the diastereoselectivity and enantioselectivity of this reaction (entries 5 and 6).

Application of the cationic cobalt chloride complex **6** resulted in a decrease of both yield and selectivities, as compared to the neutral complex (entry 7).

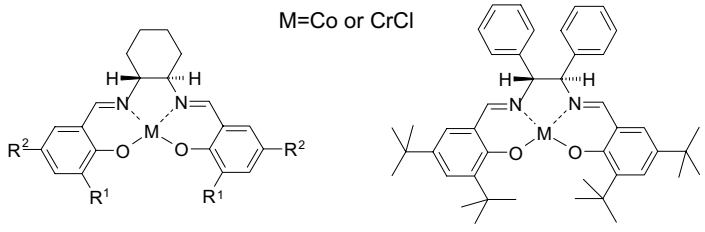
The chromium chloride complex **5a**, in contrast to its BF_4^- analogue, catalyzed the reaction more efficiently—the yields were good, but the enantioselectivities were slightly lower compared to the cobalt complex **4a**. Regardless of the reaction conditions used and the amount of the catalyst **5a**, the enantioselectivity for *cis*-**3** was about 84–87% ee (entries 8–12), and the diastereoselectivities and yields were higher than in the case of cobalt complexes. The reaction catalyzed by chromium complex **5a** proceeded well in toluene (entry 10) and also with a low amount of the catalyst (0.5 mol%, entry 12).

In the next part of this study, we investigated the influence of the structure of the chiral salen ligand of the cobalt(II) and chromium(III) complexes on the stereochemical course of the reaction, in hope of improving the stereochemical outcome (Table 2).

As can be seen from Table 2 (entries 1–9), simple modifications of the salicylidene part of the complexes of cobalt **4** and chromium **5** had a small influence on changes in diastereoselectivity and enantioselectivity of the process. When R^1 and R^2 are alkyl or methoxy, the resulting enantioselectivities were in the range of 85–93%. The presence of electron-withdrawing groups such as NO_2 (entry 10) resulted in a drop in diastereoselectivity and enantioselectivity. A change in the diamine part, from 1,2-diaminocyclohexane to 1,2-diphenylethylenediamine, resulted in a significant loss of both selectivity and yield in the case of the cobalt catalyst **8** (entry 11), while this was not observed in the case of the chromium catalyst **9** (entry 12).

We determined the absolute configuration of the major product by chemical correlation (Scheme 2). Formation of the stereoisomer (2*S*,6*R*)-**3** predominated in the presence of the (1*R*,2*R*)-cobalt **4** and (1*R*,2*R*)-chromium **5** catalysts. The post-reaction mixture containing the cycloadducts **3** was isomerized in the presence of a catalytic amount of pyridinium *p*-toluene sulfonate (PPTS)

Table 2. Influence of the structure of (salen)Co(II) and (salen)Cr(III)Cl complexes on the yield and stereochemical course of the reaction **1** + **2** → **3**[a]



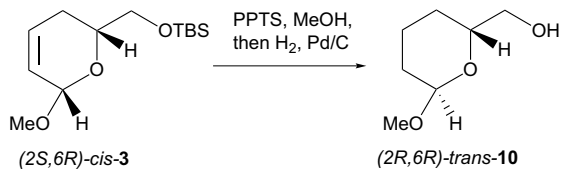
(1R,2R)-**4a-f** M=Co *(1R,2R)*-**5a-d** M=CrCl

(1R,2R)-**8** M= Co
(1R,2R)-**9** M= CrCl

4a R^1=R^2= Bu^t **5a** R^1=R^2= Bu^t
4b R^1=Bu^t, R^2=Me **5b** R^1=Bu^t, R^2=Me
4c R^1=Bu^t, R^2=OMe **5c** R^1=Bu^t, R^2=OMe
4d R^1=Me, R^2=Bu^t **5d** R^1=Me, R^2=Bu^t
4e R^1=Bu^t, R^2=H
4f R^1=Bu^t, R^2=NO_2

Entry	Catalyst	Yield (%)	*cis*/*trans*-**3**	ee for *cis*-**3**	ee for *trans*-**3**
1	**4a**	47	95:5	93	79
2	**5a**	70	95:5	85	65
3	**4b**	27	93:7	86	72
4	**5b**	82	94:6	86	73
5	**4c**	32	93:7	85	69
6	**5c**	70	93:7	86	76
7	**4d**	49	95:5	91	75
8	**5d**	59	89:11	86	66
9	**4e**	38	93:7	85	71
10	**4f**	35	86:14	70	33
11	**8**	15	88:12	58	18
12	**9**	90	96:4	82	46

[a] Reactions were carried out using 1 mmol of aldehyde **2** (0.5 mol/L) and 1.2 mmol of diene **1** in CH_2Cl_2 as a solvent, in the presence of 2 mol% of catalyst at 20 °C under high pressure (10–11 kbar) for 24 h.



Scheme 2.

and methanol, and the resulting mixture of *trans*-**3** was hydrogenated using 10% palladium on charcoal to yield the enantiomeric mixture of alcohols *trans*-**10**.[5a] The optical rotation measurement indicated unequivocal that the major enantiomer was (2*R*,6*R*)-**10** corresponding to the cycloadduct (2*S*,6*R*)-**3** as the main product of the original post-reaction mixture.

To recapitulate, this paper presents a novel high-pressure method of synthesis of 2-alkoxy-5,6-dihydro-2*H*-pyran derivatives **3** starting from non-activated aldehyde **2**, carried out in the presence of 2–5 mol% of the commercially available (salen)Co complex **4a**. The enantioselectivities obtained are up to 94% ee, and the yields are in the range of 30–61%. Also, the commercially available chromium complex **5a** (0.5–2 mol%) catalyzes the reaction effectively under high pressure; the enantioselectivities are somewhat lower (84–87%), but the yields are higher, up to 90%. The present results open up a rational and efficient route to optically active 6-substituted 2-methoxy-5,6-dihydro-2*H*-pyrans, which are widely used in the synthesis of various naturally occurring sugars, biologically active substances and polyhydroxy compounds. Our results indicate that further studies on modification of the catalyst are necessary, which should enable optimization of the stereochemical outcome of this reaction.

References and notes

1. *Stereocontrolled Organic Synthesis*; Trost, B. M., Ed.; Blackwell: London, 1994.
2. (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vols. 1–3; (b) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558–3588.
3. Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15–23.
4. (a) Konowal, A.; Jurczak, J.; Zamojski, A. *Rocz. Chem.* **1968**, *42*, 2045–2059. *Chem. Abstr.* **1969**, *71*, 3209; (b) Jurczak, J.; Zamojski, A. *Tetrahedron* **1972**, *28*, 1505–1516.
5. (a) Konowal, A.; Jurczak, J.; Zamojski, A. *Tetrahedron* **1976**, *32*, 2957–2959; (b) Zamojski, A.; Banaszek, A.; Grynkiewicz, G. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 1; (c) Zamojski, A.; Grynkiewicz, G. In *The Total Synthesis of Natural Products*; ApSimon, J. W., Ed.; J. Wiley: Chichester, 1984; Vol. 6, pp 141–235.
6. (a) Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4909–4951; (b) Bauer, T.; Kozak, J.; Chapuis, C.; Jurczak, J. *J. Chem. Soc., Chem. Commun.* **1990**, 1178–1179; (c) Bauer, T.; Chapuis, C.; Jezewski, A.; Kozak, J.; Jurczak, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1391–1404.
7. Bauer, T.; Chapuis, C.; Kozak, J.; Jurczak, J. *Helv. Chim. Acta* **1989**, *72*, 482–486.
8. (a) Terada, M.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1991**, *32*, 935–938; (b) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812–2820.
9. Quitschalle, M.; Christmann, M.; Bhatt, U.; Kalesse, M. *Tetrahedron Lett.* **2001**, *42*, 1263–1265.
10. Kwiatkowski, P.; Asztemborska, M.; Jurczak, J. *Synlett* **2004**, 1755–1758.
11. Kwiatkowski, P.; Jurczak, J., *Tetrahedron: Asymmetry,* in press. doi:10.1016/j.tetasy.2004.08.002.
12. Jurczak, J.; Chmielewski, M.; Filipek, S. *Synthesis* **1979**, 41–42.
13. (a) Golebiowski, A.; Jurczak, J. *Synlett* **1993**, 235–241; (b) Jurczak, J. In *Total Synthesis of Amino Sugars in Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; pp 595–614.
14. Malinowska, M.; Salanski, P.; Caille, J.-C.; Jurczak, J. *Synthesis* **2002**, 2707–2710.
15. Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403–405.
16. Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398–2400.
17. The synthesis of the aldehyde **2** is described: Enders, D.; Schüßeler, T. *Synthesis* **2002**, 2280–2288, it is important to use DMSO-free **2**, because this solvent slows down the reaction and lowers the stereoselectivity.