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# Stereochemistry of the Diels–Alder reaction at high pressure: diastereo- and enantioselective [4+2]cycloaddition of buta-1,3-diene to glyoxylic acid derivatives catalysed by (salen) chromium(III) complexes

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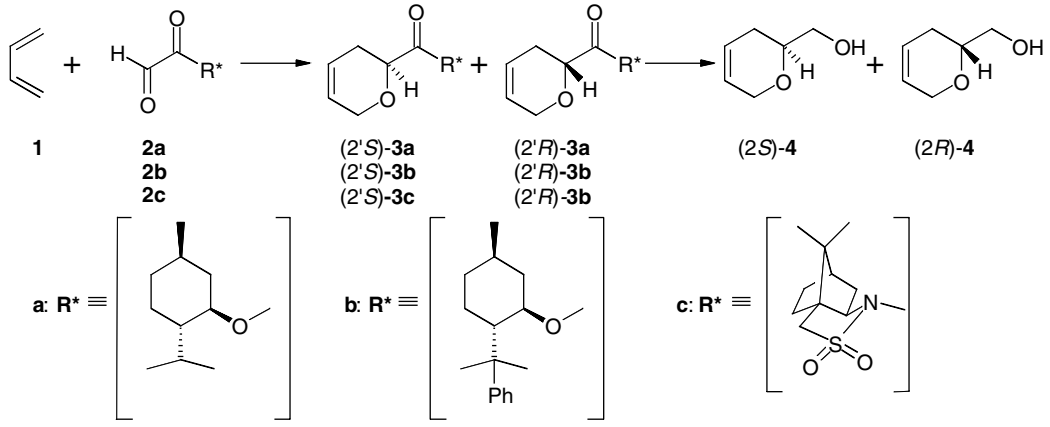
**Abstract**—High-pressure [4+2]cycloadditions of buta-1,3-diene **1** to chiral **2a–c** and achiral **7a–c** glyoxylates, in the presence of (salen) chromium(III) complexes **5** and **6**, were studied. The influence of such chiral Lewis acids on diastereoselectivity or enantioselectivity of the cycloaddition was investigated; a moderate asymmetric induction for both diastereo- and enantioselective variants of the cycloaddition was observed (up to 58% de and up to 71% ee, respectively).


## 1. Introduction

During our synthetic studies[1,2] on bisindolylmaleimides,[3] which are reversible inhibitors of the protein kinase C (PKC) which regulates the vascular function,[4] we found that the Lewis-acid catalysed hetero-Diels–Alder reaction of buta-1,3-diene **1** with (*R*)-8-phenylmenthyl glyoxylate **2b**[2] or with *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **2c**[1,2] presents an effective route to the enantiomerically pure 2-substituted 3,6-dihydro-2*H*-pyrans of type **3** (Scheme 1).




**Scheme 1.**

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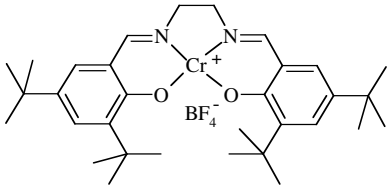
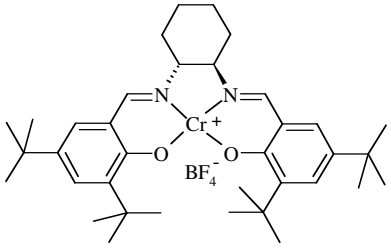
It was worthwhile extending the stereochemical studies to high-pressure diastereo- and enantioselective hetero-Diels–Alder reactions in order to compare these two approaches and to describe more precisely the stereochemical course of both types of cycloaddition. For the diastereoselective reaction study, we have chosen three chiral heterodienophiles **2a**,**b** and **2c**. Compound **2a** is known to react with diene **1** under high-pressure conditions and without any catalyst, affording cycloadducts **3a** both in poor yield and poor diastereomeric excess.[5] Reduction of cycloadduct **3a** with lithium aluminium hydride leads to the dextrorotatory alcohol (2*R*)-**4**. The use of the more efficient heterodienophiles **2b** and **2c**, under high-pressure conditions, could be expected to bring about a better asymmetric induction. On the other hand, we expected that the use of the salen-type catalysts (achiral **5** and chiral **6**) could also improve the stereoselectivity of the high-pressure diastereoselective reactions.




**5**




**(*R*,*R*)-6**

## 2. Results and discussion

It has been known for a long time that the noncatalysed reaction of the inexpensive and readily available (*R*)-menthyl glyoxylate **2a** with buta-1,3-diene **1** under high-pressure conditions affords low diastereomeric excesses (up to 15% de) in favour of (*R*)-**3a**[5] (Table 1, entries 1 and 2). Therefore, we resolved to test other chiral auxiliaries, such as (*R*)-8-phenylmenthol and (2*R*)-bornane-10,2-sultam, considered effective in many diastereoselective reactions. In the case of the reaction of diene **1** with (*R*)-8-phenylmenthyl glyoxylate **2b**, the asymmetric induction was opposite to what was obtained using (*R*)-menthyl glyoxylate **2a** as a dienophile and this was accompanied by an increase in the diastereomeric excess (cf. entries 1 and 3). Under the noncatalysed conditions, the best results were obtained using *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **2c** (entry 7). Cycloadduct **3c** was formed in 50% yield and with 51% diastereomeric excess in favour of the (*S*)-configuration. The results of all the studied noncatalysed reactions were much better in $CH_2Cl_2$ than in toluene as solvent.

We decided to investigate further the effect of salen complexes of chromium(III), being mild Lewis acids, on the stereochemical course of the reaction. Their effectiveness in the enantioselective hetero-Diels–Alder reactions with the Danishefsky dienes was demonstrated by Jacobsen et al.[6,7] Firstly, we used the achiral chromium complex **5** as an achiral catalyst for the reaction of diene **1** with glyoxylate **2a** (Table 1, entry 8). The use of **5** caused no substantial changes in the reaction yield and diastereoselectivity. However, the use of chiral complex **6** for this reaction led to a distinct increase in the stereoselectivity (entries 9–12). It should be mentioned here that the major product obtained using (*R*,*R*)-**6** catalyst had an (*R*)- absolute configuration, whereas the use of the (*S*,*S*)-**6** catalyst caused a reversal of the product configuration along with a clear increase in diastereoselectivity, being the result of the 'matching' effect (entries 9 and 11 vs 10 and 12).

**Table 1.** The results of the reaction of diene **1** with heterodienophiles **2a**,**b** and **2c** under high-pressure conditions (10 kbar)[a]

| Entry | Dienophile | Catalyst | Solvent | Temperature (°C) | Yield (%) | Absolute config. | Diastereomeric excess (% de) |
|---|---|---|---|---|---|---|---|
| 1 | **2a** | — | $CH_2Cl_2$ | 25 | 44 | (*R*) | 12 |
| 2 | **2a** | — | Toluene | 25 | 15 | (*R*) | 15 |
| 3 | **2b** | — | $CH_2Cl_2$ | 25 | 14 | (*S*) | 42 |
| 4 | **2b** | — | $CH_2Cl_2$ | 50 | 53 | (*S*) | 36 |
| 5 | **2b** | — | Toluene | 25 | 0 | — | — |
| 6 | **2b** | — | Toluene | 50 | 21 | (*S*) | 22 |
| 7 | **2c** | — | $CH_2Cl_2$ | 25 | 50 | (*S*) | 51 |
| 8 | **2a** | **5** | $CH_2Cl_2$ | 25 | 48 | (*R*) | 6 |
| 9 | **2a** | (*R*,*R*)-**6** | $CH_2Cl_2$ | 25 | 50 | (*R*) | 34 |
| 10 | **2a** | (*R*,*R*)-**6** | Toluene | 25 | 45 | (*R*) | 36 |
| 11 | **2a** | (*S*,*S*)-**6** | $CH_2Cl_2$ | 25 | 50 | (*S*) | 48 |
| 12 | **2a** | (*S*,*S*)-**6** | Toluene | 25 | 40 | (*S*) | 58 |
| 13 | **2b** | (*R*,*R*)-**6** | $CH_2Cl_2$ | 25 | 50 | (*R*) | 4 |
| 14 | **2b** | (*S*,*S*)-**6** | $CH_2Cl_2$ | 25 | 40 | (*S*) | 24 |
| 15 | **2c** | (*R*,*R*)-**6** | $CH_2Cl_2$ | 25 | 51 | (*S*) | 35 |
| 16 | **2c** | (*S*,*S*)-**6** | $CH_2Cl_2$ | 25 | 48 | (*S*) | 35 |

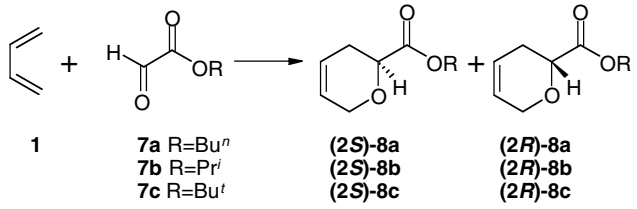
[a] Other reaction conditions: 5 mol % of chromium catalyst was used; 24 h.

In the case of using glyoxylic acid derivatives **2b** (entries 13 and 14) and **2c** (entries 15 and 16), being more sterically demanding than **2a**, the use of the chiral chromium complexes caused a decrease in the asymmetric induction in comparison to the noncatalysed reactions. Moreover, in the case of *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **2c**, the absolute configuration of catalyst **6** has no effect on the stereochemical outcome of the reaction. This is probably because of that the interaction of the sterically demanding catalyst **6** as well as aldehyde **2b** (in particular **2c**) does not allow the formation of a binding optimal for the chiral differentiation. For the catalysed reactions, the type of solvent used had no substantial effect on the reaction yield; whereas somewhat better diastereoselectivities were obtained in toluene.

In order to acquire a better understanding of the effect of the chiral salen catalyst **6** on the investigated Diels–Alder reaction, we resolved to study the enantioselective variant of [4+2]cycloaddition of diene **1** to simple alkyl glyoxylates **7a–c** (Scheme 2).

Uptil now, the literature provided only one example of the enantioselective reaction of diene **1** with isopropyl glyoxylate **7b** in the presence of the chiral bisoxazoline complex with $Cu(OTf)_2$ during 120h.[8] This reaction led to the desired product **8b** in 55% at 87% ee. Our own results obtained for the reactions carried out in the presence of the chiral salen catalyst **6** are shown in Table 2.

The yields of the investigated reactions were not high (up to 46%), always being slightly higher in toluene than in $CH_2Cl_2$ (cf. Table 2, entries 1 vs 3 and 7 vs 9).[9] The analogous dependence on the solvent used was observed for the asymmetric induction; this was also dependent on the glyoxylate used. The best enantioselectivity was noted for *t*-butyl glyoxylate **7c**, a slightly lower one for the isopropyl derivative **7b** and a comparable one for *n*-butyl glyoxylate **7a** (cf. entries 3, 6 and 9). In all the investigated reactions, the use of complex (*R*,*R*)-**6** resulted in formation of the predominating enantiomers **8a–c** with a (2*R*) configuration.




**Scheme 2.**

## 3. Conclusion

In summary, we have found that the high-pressure [4+2]cycloaddition reactions of buta-1,3-diene **1** with chiral derivatives of glyoxylic acid **2a–c** can be carried out under both non-catalytic and catalytic conditions. However, their chemical yields and diastereoselectivities are not very high, probably due to the steric requirements both of the catalyst and the dienophile. Much better results have been obtained for the enantioselective variant of this reaction using achiral glyoxylates. This latter variant deserves further efforts to optimize it, because the reaction products are attractive as chirons for the synthesis of the biologically active compounds.

## 4. Experimental

All the reported NMR spectra were recorded using a Varian Unity plus spectrometer at 200 MHz ($^1$H NMR) and 50 MHz ($^{13}$C NMR). The chemical shifts are reported as $\delta$ values relative to a TMS peak defined at $\delta = 0.00$ ($^1$H NMR) or $\delta = 0.0$ ($^{13}$C NMR). The mass spectra were obtained with a Mariner BioSystem unit using the ESI technique. Analytical TLC was carried out on the commercially prepared plates coated with 0.25 mm of Merck Kieselgel 60. The preparative flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh). The GC experiments were carried out with a Hewlett–Packard 5890 apparatus equipped with a FID detector and a β-dex 120 chiral column (30 m × 0.25 mm ID) for cycloadducts **7a–c** and a β-dex 225 chiral column (30 m × 0.25 mm ID) for alcohol **4**. Chromatography conditions: carrier gas–argon, 100 kPa; injection temperature 200 °C; detector temperature 250 °C.

All commercially available chemicals were used as received, unless stated otherwise. The reagent-grade

**Table 2.** The enantioselective reaction of diene **1** with alkyl glyoxylates **7a–c** in the presence of the catalyst **6** under high-pressure conditions (10 kbar)[a]

| Entry | Dienophile | Catalyst | mol % | Solvent | Yield (%) | Absolute config. | Enantiomeric excess (% ee) |
|---|---|---|---|---|---|---|---|
| 1 | **7a** | (*R*,*R*)-**6** | 5 | $CH_2Cl_2$ | 39 | (*R*) | 44 |
| 2 | **7a** | (*R*,*R*)-**6** | 2 | Toluene | 27 | (*R*) | 44 |
| 3 | **7a** | (*R*,*R*)-**6** | 5 | Toluene | 46 | (*R*) | 54 |
| 4 | **7a** | (*S*,*S*)-**6** | 5 | Toluene | 40 | (*S*) | 52 |
| 5 | **7b** | (*R*,*R*)-**6** | 2 | Toluene | 26 | (*R*) | 51 |
| 6 | **7b** | (*R*,*R*)-**6** | 5 | Toluene | 37 | (*R*) | 56 |
| 7 | **7c** | (*R*,*R*)-**6** | 5 | $CH_2Cl_2$ | 24 | (*R*) | 57 |
| 8 | **7c** | (*R*,*R*)-**6** | 2 | Toluene | 24 | (*R*) | 66 |
| 9 | **7c** | (*R*,*R*)-**6** | 5 | Toluene | 31 | (*R*) | 71 |

[a] Other reaction conditions: concentration of **7a–c** is 0.5 mol/L, ~3 equiv of **1**, 10 kbar, 25 °C, 24 h.

solvents were dried and distilled prior to use. (Salen) chromium complexes **5** and **6**,[6,10] (*R*)-8-phenylmenthyl glyoxylate **2b**,[11] and *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **6a**[12] were prepared according to the literature procedures.

### 4.1. High-pressure reaction—a typical procedure for dienophiles 2a–c[13]

A solution of buta-1,3-diene **1** (2 mmol) and heterodienophile **2** (1 mmol) (previously distilled under reduced pressure) in dry $CH_2Cl_2$ (2 mL) was placed in a Teflon ampoule. In the catalysed experiments, the catalyst (**5** or **6**) was added to the reaction mixture (5 mol %). The ampoule was placed in the high-pressure apparatus and compressed up to 10 kbar for 24 h. Following decompression, the post-reaction mixture was subjected to a chemical correlation to alcohol **4**. The analytical data of compounds **3a–c** are in agreement with those described in the literature.[1,2,5]

### 4.2. Chemical correlation of cycloadducts 3a–c to alcohol 4

To a suspension of $LiAlH_4$ (0.5 mmol) in dry diethyl ether, cooled to 0 °C, a mixture of diastereomers **3** (1 mmol) dissolved in dry diethyl ether (or in dry $CH_2Cl_2$, in the case of **3c**) was added dropwise and a reaction mixture stirred for 2 h at room temperature. After the usual work-up, the post-reaction mixture was filtered, the filtrate then evaporated and the residue analysed by GC to determine the diastereomeric excess. The analytical data of compound **4** is in agreement with the literature.[1,2,5] GC (column β-dex 225): $T = 95$ °C, $t_R$ [(2*S*)-(−)-**4**] = 14.9 min, $t_R$ [(2*R*)-(+)-**4**] = 15.6 min.

### 4.3. High-pressure reaction—a typical procedure for dienophiles 7a–c[13]

To a solution (~0.5 mL) of catalyst **6** (2 or 5 mol %) in dry $CH_2Cl_2$ or toluene, charged in 2 mL Teflon ampoule, freshly distilled glyoxylate **7** (1 mmol) was added. Then the ampoule was filled with a solution of diene **1** (~3 equiv), placed in a high-pressure vessel and pressure was slowly increased to 10 kbar at 25 °C. After stabilisation of pressure, the reaction mixture was kept under these conditions for 24 h. After decompression, the mixture was subjected to column chromatography on a silica gel using hexane–AcOEt 9:1 as an eluent.

**4.3.1. *n*-Butyl 3,6-dihydro-2*H*-pyran-2-carboxylate 8a.** $^1$H NMR (200 MHz, $CDCl_3$): $\delta = 5.90$–$5.69$ (m, 2H, =CH), 4.44–4.20 (m, 3H, OCH, $OCH_2$), 4.19 (t, $J = 6.6$ Hz, 2H, $OCH_2$), 2.42–2.33 (m, 2H, $CH_2$), 1.72–1.58 (m, 2H, $CH_2$), 1.48–1.29 (m, 2H, $CH_2$), 0.93 (t, $J = 7.3$ Hz, 3H, $CH_3$); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta = 171.4$ (C), 126.0 (CH), 122.8 (CH), 72.0 (CH), 65.4 ($CH_2$), 64.8 ($CH_2$), 30.5 ($CH_2$), 27.7 ($CH_2$), 19.0 ($CH_2$), 13.6 ($CH_3$); HRMS calcd for $C_{10}H_{16}O_3Na$ 207.0992, found 207.0998; GC(β-dex 120): $T = 140$ °C, $t_R$ [(2*S*)-**8a**] = 22.1 min, $t_R$ [(2*R*)-**8a**] = 22.5 min; $T = 130$ °C, $t_R$ [(2*S*)-**8a**] = 34.7 min, $t_R$ [(2*R*)-**8a**] = 35.5 min.

**4.3.2. Isopropyl 3,6-dihydro-2*H*-pyran-2-carboxylate 8b.** $^1$H NMR: (200 MHz, $CDCl_3$): $\delta$ (ppm): 5.89–5.68 (m, 2H, =CH), 5.12 (sept, $J = 6.2$ Hz, 1H, OCH), 4.45–4.15 (m, 3H, $OCH_2$, OCH), 2.40–2.31 (m, 2H, $CH_2$), 1.28 (d, $J = 6.2$ Hz, 3H, $CH_3$), 1.27 (d, $J = 6.2$ Hz, 3H, $CH_3$); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta = 171.0$ (C), 126.0 (CH), 122.9 (CH), 72.1 (CH), 68.5 (CH), 65.5 ($CH_2$), 27.7 ($CH_2$), 21.7 ($2 \times CH_3$); HRMS calcd for $C_9H_{14}O_3Na$ 193.0835, found 193.0825; GC(β-DM): $T = 110$ °C, $t_R$ [(2*S*)-**8b**] = 29.7 min, $t_R$ [(2*R*)-**8b**] = 31.9 min, GC(β-dex 120): $T = 110$ °C, $t_R$ [(2*S*)-**8b**] = 29.6 min, $t_R$ [(2*R*)-**8b**] = 30.2 min.

**4.3.3. *t*-Butyl 3,6-dihydro-2*H*-pyran-2-carboxylate 8c.** $^1$H NMR: (200 MHz, $CDCl_3$), $\delta$ (ppm): 5.88–5.68 (m, 2H, =CH), 4.43–4.15 (m, 2H, $OCH_2$), 4.13–4.06 (m, 1H, OCH), 2.38–2.28 (m, 2H, $CH_2$), 1.48 (s, 9H, $3 \times CH_3$); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta = 170.6$ (C), 126.0 (CH), 123.0 (CH), 81.5 (C), 72.3 (CH), 65.4 ($CH_2$), 28.0 ($3 \times CH_3$), 27.8 ($CH_2$); HRMS calcd for $C_{10}H_{16}O_3Na$ 207.0992, found 207.0988; GC(β-dex 120): $T = 120$ °C, $t_R$ [(2*S*)-**8c**] = 23.4 min, $t_R$ [(2*R*)-**8c**] = 23.7 min.

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