Enantioselective [4+2] Cycloaddition of Buta-1,3-dienes to Alkyl Glyoxylates Catalyzed by the Chiral (Salen)Chromium(III) Complex

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Abstract: Thermal and high-pressure [4+2] cycloadditions of buta-1,3-diene (**3**), cyclohexa-1,3-diene (**5**), and 2,3-dimethylbuta-1,3-diene (**6**) to alkyl glyoxylates of type **2** (R=*n*-Bu, *i*-Pr, *t*-Bu), catalyzed by chromium complex *(R,R)*-**1**, leading to the corresponding cycloadducts **4**, **7** and **8** with relatively high enantioselectivity, are described.

Keywords: aldehydes; asymmetric catalysis; Diels–Alder reaction; high-pressure chemistry; (salen)chromium(III) complex

Introduction

Application of chiral catalysis to the Diels–Alder reaction offers a unique possibility of introducing chirality to a practically unlimited number of cycloadducts. This important discovery pioneered by Guseinov et al.,[1] followed by the first successful use of (−)-menthyloxyaluminum dichloride,[2] remained unexplored until the mid-1980's.[3] The past two decades have, however, been characterized by tremendous acceleration of the studies of homo-[4] and hetero-Diels–Alder reactions,[4,5] mediated by chiral catalysts.

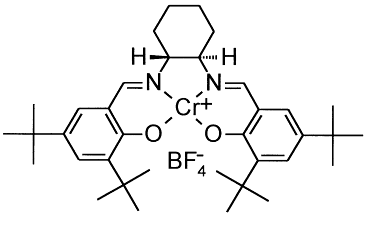
The hetero-Diels–Alder reaction of 1,3-dienes with carbonyl compounds opens a perfect route to dihydropyranone and dihydropyran derivatives, valuable intermediates in the total synthesis of many natural products, e.g., sugars.[6] Attention of synthetic chemists was focused mostly on Danishefsky's cyclocondensation using simple aldehydes, which led to the dihydropyranone system.[7] The [4+2] cycloadditions of simple 1,3-dienes, like buta-1,3-diene or cyclohexa-1,3-diene to highly activated carbonyl compounds, such as alkyl glyoxylates, were not so intensively investigated. There are in the literature only few reports on asymmetric version of this reaction, by Mikami's,[8] Jørgensen's,[9] and Oi's[10] groups, who successfully used chiral catalysts mainly based on a binaphthyl and bisoxazoline ligands.

Jacobsen's recent discoveries in the field of chiral salen-type catalysts and their synthetic applications,[11,12,13] prompted us to study the enantioselective hetero-Diels–Alder reaction, catalyzed by the chiral (salen)chromium(III) complex *(R,R)*-**1**.[11,14]

In this paper we present results of our preliminary studies on the thermal and high-pressure [4+2] cycloadditions of simple 1,3-dienes to alkyl glyoxylates, carried out in the presence of *(R,R)*-**1** as a chiral catalyst. As model heterodienophiles *n*-butyl (**2a**), isopropyl (**2b**), and *tert*-butyl (**2c**) glyoxylates were selected owing to their high reactivity and the well established stereochemical outcomes of reactions with these components, elaborated during earlier investigations of diastereoselective [4+2] cycloadditions of this type.[15]

Results and Discussion

The high-pressure [4+2] cycloaddition of buta-1,3-diene (**3**) to *n*-butyl glyoxylate (**2a**) [10 kbar, 25 °C, 5 mol % of *(R,R)*-**1**], carried out in two different solvents,



(R,R)- **1**

CH_2Cl_2 and toluene, afforded a mixture of the enantiomeric dihydropyrans **4** (Scheme 1) in moderate yields (39 and 46%, respectively) and enantioselectivity (44 and 54% ee, respectively). The enantioselectivity can be improved when higher pressure or glyoxylates of more bulky alcohols than *n*-butanol are used.[16] Thermal [4+2] cycloaddition of buta-1,3-diene (**3**) to glyoxylate **2a**, carried out in the presence of *(R,R)*-**1**, gave only traces of **4**.

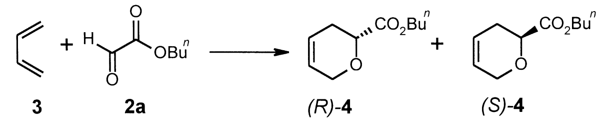
On the other hand, the thermal reaction of cyclohexa-1,3-diene (**5**) with *n*-butyl glyoxylate (**2a**) produces two diastereoisomeric products **7** (Scheme 2, Table 1) with *endo*-selectivity.

Enantioselectivity of the *endo*-**7** formation was 80% ee (Table 1, entry 1). The drop in temperature of the reaction (from 25 to – 15 °C) caused improvement in the *endo/exo* ratio as well as in enantioselectivity of the *endo*-**7** formation (84% ee, entry 2). When the reaction was carried out at lower concentration of dienophile **2a**, a further improvement in enantioselectivity (90% ee) was found (entry 3). The solvents used did not effect substantially the enantioselectivity, however, their influence on the *endo/exo* ratio is noteworthy (entries 4–6). When the high pressure (10 kbar) was applied for this reaction carried out in toluene, *exo*-selectivity accompanied by moderate enantioselectivity (31% ee) was observed (entry 7).

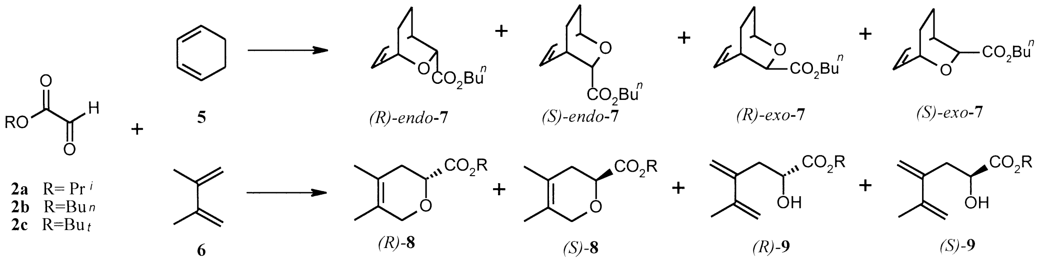
Finally, we resolved to study the reaction of 2,3-dimethyl-1,3-butadiene (**6**) with heterodienophiles **2a–c** (Scheme 2, Table 2).

In the above-mentioned reaction, apart from the enantiomeric [4+2] cycloadducts **8**, the enantiomeric products **9** *via* the ene reaction were formed in good overall yield and with a ratio of **8**:**9** in a range of 1:1 to 7:3. In all instances studied the asymmetric induction for [4+2] cycloaddition was in the range of 40–74% ee, leading to predomination of *(R)*-enantiomer. Enantioselectivity for the ene reaction was substantially lower (around 20% ee) and at this stage of our studies we are unable to establish the absolute configuration of products. When the reaction was carried out at – 15 °C, instead of 25 °C, the enantioselectivity was slightly improved, e.g., from 62% ee to 74% ee (Table 2, entries 7 and 9). The use of high pressure (10 kbar, entry 3) caused a rise in a content of ene product **9** but the enantioselectivity remained at the same level. In this reaction salen complexes with other metals and counterions, e.g., CrCl, $CrClO_4$, $CrSbF_6$, CoCl, $CoBF_4$, MnCl, $MnBF_4$, $TiCl_2$ were tested. Complexes containing Co, Mn and Ti catalyzed the reaction but it proceeded with very low enantioselectivity. Chromium complexes with ClO_4^- and SbF_6^- as counterions gave comparable results as *(R,R)*-**1**.

The absolute configurations of cycloadducts **4**, *endo*-**7** and **8** were determined by chemical correlations. Com-



Scheme 1.



Scheme 2.

Table 1. The reaction of **5** with **2a** catalyzed by *(R,R)*-**1**.[a]

Entry	Solvent	Conc. of **2a** [mol/L]	Pressure [bar]	Temp. [°C]	Yield [%]	Ratio *endo:exo*	Enantiomeric excess [%]	
							endo-**7**	*exo*-**7**
1	toluene	0.5	1	25	84	70:30	80	10
2	toluene	0.5	1	– 15	53	75:25	84	12
3	toluene	0.2	1	– 15	47	80:20	90	10
4	CH_2Cl_2	0.5	1	25	90	45:55	52	5
5	anisole	0.5	1	25	65	62:38	69	13
6	*t*-BuOMe	0.5	1	25	68	60:40	65	14[b]
7	toluene	0.5	10000	25	83	45:55	58	31

[a] 5 mol % of chiral catalyst was used.

[b] Product with opposite configuration was formed.

Table 2. The reaction of **6** with **2a–c** catalyzed by *(R,R)*-**1**.[a]

Entry	Dienophile	Solvent	Pressure [bar]	Temp. [°C]	Yield [%]	**8:9**	**8** [% ee]
1	**2a**	CH_2Cl_2	1	25	79	54:46	40
2	**2a**	toluene	1	25	71	62:38	60
3	**2a**	toluene	10000	25	72	47:53	60
4	**2b**	CH_2Cl_2	1	25	76	53:47	42
5	**2b**	toluene	1	25	68	60:40	46
6	**2c**	CH_2Cl_2	1	25	62	59:41	56
7	**2c**	toluene	1	25	56	70:30	62
8	**2c**	CH_2Cl_2	1	-15	66	62:38	66
9	**2c**	toluene	1	-15	37	70:30	74

[a] 5 mol % of chiral catalyst was used.

pounds **4** and **8** were reduced to the appropriate alcohols,[17] and *endo*-**7** was subjected to alkaline hydrolysis, followed by acidification, to afford the known bicyclic lactone.[9,18] In all cases when *(R,R)*-**1** was used, formation of cycloadducts with the *(R)* configuration was observed.

Conclusion

The present results open an efficient and economic route to optically active [4 + 2] cycloadducts which may be used in the synthesis of various natural products. Further extension of this interesting field is under way and will be reported soon.

Experimental Section

General Information

All chemicals were used as received unless otherwise noted. Reagent grade solvents (CH_2Cl_2, toluene, *t*-BuOMe, hexane, AcOEt) were distilled prior use. All reported NMR spectra were recorded with a Varian Gemini spectrometer at 200 (^{1}H NMR) and 50 (^{13}C NMR) MHz. Chemical shifts are reported as δ values relative to TMS peak defined at $\delta = 0.00$ (^{1}H NMR) or at $\delta = 0.0$ (^{13}C NMR). Chromatography was performed on silica (Kieselgel 60, 200–400 mesh). Optical rotations were recorded using a JASCO DIP-360 polarimeter.

Enantiomeric excess of products was determined by gas chromatography performed using a Hewlett-Packard GC unit equipped with a capillary chiral column β-dex 120 (permethyl-β-cyclodextrin, 30 m × 0.25 mm I.D. Supelco, Bellefonte, USA). Chromatography conditions: carrier gas argon, 100 kPa; injection temp. 200 °C; detector temp. 250 °C. Chromatographic parameters of enantioseparation of investigated compounds are given in Table 3.

n-Butyl (**2a**) and isopropyl (**2b**) glyoxylates were prepared by oxidative cleavage of the appropriate tartrate esters, using $NaIO_4$ in water,[19] and *tert*-butyl glyoxylate (**2c**) by ozonolysis of di-*tert*-butyl fumarate[20]. Glyoxylates **2a–c** were distilled in the presence of P_2O_5 prior the use.

Table 3. Chromatographic parameters of enantioseparation of investigated compounds.

Compound	Temp. [°C]	t_{R1} [min]	t_{R2} [min]	α (t_{R2}/t_{R1})
4	140	22.1	22.5	1.018
endo-**7**	150	43.4	44.4	1.023
exo-**7**	150	38.8	39.8	1.026
8a	140	46.7	47.3	1.013
8b	130	29.7	30.2	1.017
8c	130	33.4	34.1	1.021
9a	140	33.2	34.5	1.039
9b	130	22.6	23.0	1.018
9c	130	26.6	26.6	1.000

General Procedure for the [4 + 2] Cycloaddition under Atmospheric Pressure

To a solution of *(R,R)*-**1** (35 mg, 0.05 mmol) in toluene or CH_2Cl_2 (2 mL), freshly distilled alkyl glyoxylate (**2a–c**) (1 mmol) was added. After 10 min at 25 °C, 1,3-diene **5** or **6** (1.5 mmol) was added in one portion to the solution and stirred at −15 °C or +25 °C. After 24 h, the reaction mixture was chromatographed on a silica gel column using hexane/AcOEt (9:1) as eluent.

General Procedure for the High-Pressure [4 + 2] Cycloaddition

To a toluene solution (1–2 mL) of catalyst *(R,R)*-**1** (86 mg), charged in a Teflon ampoule (5 mL), freshly distilled *n*-butyl glyoxylate (**2a**) (326 mg, 2.5 mmol) was added. Then the ampoule was filled with a solution of diene **3** (~5 equiv.), **5** or **6** (1.5 equiv.), placed in a high-pressure vessel, and the pressure was slowly increased to 10 kbar at 25 °C. After stabilization of the pressure, the reaction mixture was kept under these conditions for 24 h. After decompression, the mixture was subjected to column chromatography as in the previous procedure.

***n*-Butyl 3,6-Dihydro-2*H*-pyran-2-carboxylate (4):** ^{1}H NMR: $\delta = 5.91-5.69$ (m, 2H, =CH), 4.44–4.25 (m, 3H, OCH, OCH_2), 4.19 (t, $J = 6.6$ Hz, 2H, OCH_2), 2.43–2.33 (m, 2H, CH_2), 1.73–

1.58 (m, 2H, CH_2), 1.48 – 1.29 (m, 2H, CH_2), 0,94 (t, $J = 7.3$ Hz, 3H, CH_3); ^{13}C NMR: $\delta = 171.4$ (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).

***n*-Butyl *endo*-2-Oxabicyclo[2.2.2]oct-5-ene-3-carboxylate (*endo*-7):** ^{1}H NMR: $\delta = 6.57 - 6.49$ (m, 1H, =CH), 6.31 – 6.22 (m, 1H, =CH), 4.62 – 4.55 (m, 1H, OCH), 4.31 (d, $J = 1.9$ Hz, 1H, OCH), 4.10 (t, $J = 6.6$ Hz, 2H, OCH_2), 3.13 – 3.05 (m, 1H, CH), 2.14 – 2.00 (m, 1H, CH), 1.82 – 1.69 (m, 1H, CH), 1.68 – 1.53 (m, 2H, CH_2), 1.48 – 1.25 (m, 4H, CH_2, 2 CH), 0.92 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR: $\delta = 172.2$ (C), 134.7 (CH), 130.4 (CH), 74.1 (CH), 66.4 (CH), 64.5 (CH_2), 33.2 (CH), 30.6 (CH_2), 25.7 (CH_2), 20.8 (CH_2), 19.0 (CH_2), 13.6 (CH_3).

***n*-Butyl *exo*-2-Oxabicyclo[2.2.2]oct-5-ene-3-carboxylate (*exo*-7):** ^{1}H NMR: $\delta = 6.60 - 6.45$ (m, 2H, =CH), 4.59 – 4.52 (m, 1H, OCH), 4.19 (t, $J = 6.6$ Hz, 2H, OCH_2), 3.89 (t, $J = 2.0$ Hz, 1H, OCH), 2.98 – 2.90 (m, 1H, CH), 2.30 – 2.15 (m, 1H, CH), 1.74 – 1.52 (m, 3H), 1.49 – 1.11 (m, 5H), 0.95 (t, $J = 7.3$ Hz, 3H, CH_3); ^{13}C NMR: $\delta = 172.6$ (C), 133.8 (CH), 133.4 (CH), 74.1 (CH), 66.5 (CH), 64.7 (CH_2), 32.8 (CH), 30.6 (CH_2), 25.6 (CH_2), 19.1 (CH_2), 17.3 (CH_2), 13.6 (CH_3).

***tert*-Butyl 4,5-Dimethyl-3,6-dihydro-2*H*-pyran-2-carboxylate (8c):** ^{1}H NMR: $\delta = 4.18 - 3.96$ (m, 3H, OCH_2, OCH), 2.36 – 2.02 (m, 2H, CH_2),1.69 – 1.64(m, 3H, CH_3), 1.56 – 1.51 (m, 3H, CH_3), 1.49 (s, 9H, 3 CH_3); ^{13}C NMR: $\delta = 170.8$ (C), 124.2 (C), 122.5 (C), 81.3 (C), 73.1 (CH), 69.1 (CH_2), 33.1 (CH_2), 28.0 (3 CH_3), 18.2 (CH_3), 13.7 (CH_3).

***tert*-Butyl 2-Hydroxy-5-methyl-4-methylene-5-hexanoate (9c):** ^{1}H NMR: $\delta = 5.23$ (s, 1H, =CH), 5.13 (s, 1H, =CH), 5.10 (s, 1H, =CH), 5.03 (s, 1H, =CH), 4.21 (ddd, $J = 8.2$, 6.3, 4.2 Hz, 1H, OCH), 2.82 (dd, 1H, $J = 14.4$, 4.2 Hz, CH), 2.73 (d, 1H, $J = 6.3$ Hz, OH), 2.48 (dd, 1H, $J = 14.4$, 8.2 Hz, CH), 1.94 (s, 3H, CH_3), 1.48 (s, 9H, 3 CH_3); ^{13}C NMR: $\delta = 174.0$ (C), 143.1 (C), 142.2 (C), 115.4 (CH_2), 113.3 (CH_2), 82.4 (C), 69.7 (CH), 39.4 (CH_2), 28.0 (3 CH_3), 21.1 (CH_3).

The NMR data of compounds **8a, 8b, 9a, 9b** are in agreement with those described in the literature.[10]

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