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Asymmetric Friedel–Crafts reaction of furans with alkyl glyoxylates catalyzed by (salen)Co(II) complexes

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Abstract

An asymmetric high-pressure (ca. 10 kbar) reaction of various 2-alkylfurans and atmospheric-pressure reaction of 2-methoxyfuran with alkyl glyoxylates, catalyzed by the chiral (salen)Co complexes, has been studied. The reaction afforded chiral furfuryl alcohols, compounds of significant synthetic interest, with moderate to good enantioselectivity (up to 76% ee).

Keywords: Asymmetric catalysis; Glyoxylates; High-pressure technique; Friedel–Crafts reaction; Furans; (Salen)Co complexes

1. Introduction

The application of chiral catalysts to the Friedel–Crafts reaction of furans with carbonyl compounds opens a useful route to optically active furfuryl alcohols (Scheme 1), the valuable intermediates in organic synthesis, e.g., for preparation of dihydropyrones under oxidative conditions [1]. Up to now, there are few published examples of the enantioselective version of the reaction of aromatic derivatives with carbonyl compounds in the literature [2]. In these papers, the catalysts used were mainly the complexes of type bisoxazoline/Cu(II) [3] and BINOL/Ti(IV) [4]. One can find there only scarce examples of enantioselective reactions of aldehydes and furans, although the results being worse than for the benzene derivatives [3a].

We have recently shown that the commercially available catalyst (salen)cobalt(II) (**3a**, Fig. 1), being a well-known catalyst for kinetic resolution of epoxides [5], was also a catalyst for the reaction of alkyl glyoxylates with 2-methylfuran under high-pressure conditions [6]. In this paper, we report an extension of our study. We decided to use, as substrates, variously 2-substituted furans **1** and glyoxylates **2** (Fig. 1). We have also tested the modified cobalt complexes **3b**–**h** (Fig. 1).

2. Results and discussion

The investigated model reaction was the Friedel–Crafts reaction between silvan (2-methylfuran, **1a**) and *n*-butyl glyoxylate (**2a**) (Scheme 2). In this reaction, the salen complexes of various metals, e.g., Cr(III), Mn(III), Co(III), and Al(III), have been tested. However, despite the often satisfactory yields, the enantioselectivities were very low, did not exceed 20% ee. With respect to the enantioselectivity of this reaction, the best catalysts appeared to be the neutral cobalt complexes of type **3**, which, because of low Lewis acidity, did not allow good yields. An improvement in the yield of the reaction was achieved by using the high-pressure technique [7]. It was known from our earlier studies, that this reaction was accelerated by pressure in the absence of Lewis acids [8]. Table 1 shows an effect of pressure on both the yield and the enantioselectivity of this reaction. Increase of pressure not only rises the yield, but also significantly influences the asymmetric induction, nearly doubling the enantioselectivity (from 44 to 72% ee) when pressure is increased to 10 kbar (Table 1).

In turn, we have successively investigated the effects of the solvents, the reactant concentrations, and the catalyst amounts, on the model reaction (Table 2). Toluene appeared to be the best one of the investigated solvents and, surprisingly, the asymmetric induction in CH_2Cl_2 was low; because of that, only toluene was used in the further investigations.

The reactant concentrations have an evident influence on the enantioselectivity, which is higher for the lower substrate concentrations. Unfortunately, the lower substrate concentrations

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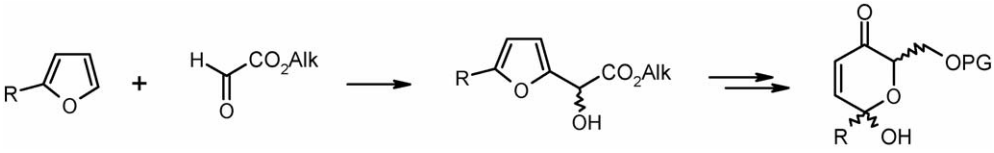


Scheme 1.

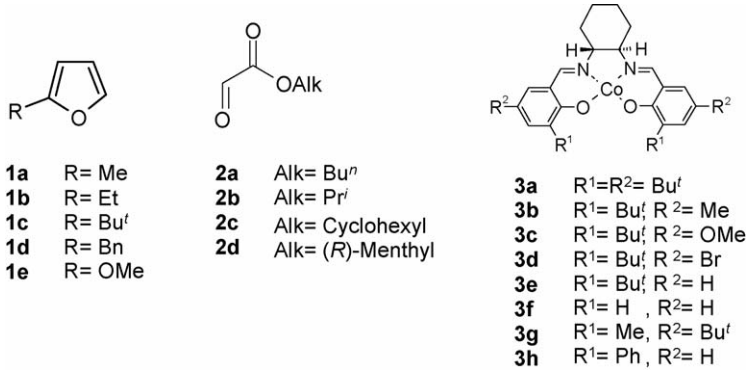


Fig. 1. The reactants used for the Friedel–Crafts reaction and the catalysts therefore.

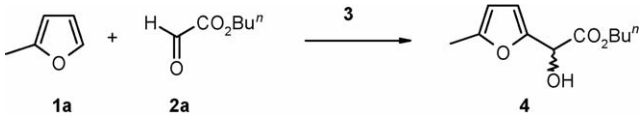
Table 1
Influence of pressure on the reaction of 2-methylfuran (**1a**) with *n*-butyl glyoxylate (**2a**) catalyzed by **3a**[a]

Entry	Pressure (bar)	Yield (%)	ee (%)[b]
1	1	15	44
2	6000	68	48
3	8000	70	52
4	10000	70	72

[a] The reactions were carried out using 0.5 mmol of *n*-butyl glyoxylate, 0.75 mmol of silvan, 5 mol% of **3a** in toluene in a Teflon® vessel (2 ml) under 10 kbar at 25 °C for 20 h.
[b] The enantiomeric excess was determined by GC.

result in a drop of the chemical yield (Table 2, Entries 1–3). The amount of the catalyst is also important for the reaction course. Several trials were carried out using from 0.1 to 10 mol% of the catalyst, what gave the enantioselectivities rising from 38 to 64% ee (Entries 3–8), whereas the yields ranged from 28% (for the lowest catalyst concentration) to 70%. We could not obtain a yield above 70%; usually, the yields were about 50–60%. Low ee with 0.1–0.5 mol% of catalyst can be explained because of competing uncatalyzed reaction leading to the racemic product.

The discussed reaction, when catalyzed by the cobalt complexes, has some limitations pertaining to the furan reactant. The simplest representative of the furan type, i.e., furan itself, is too less reactive, and affords only traces of a product. The 2-alkoxymethyl derivatives of furan behave similarly. 2-Alkylfurans (**1a**–**c**, Fig. 1, Table 3) are more reactive than unsubstituted furan, and they can be used for the high-pressure reaction with glyoxylates in the presence of the cobalt catalyst **3a**. Silvan (**1a**, Entry 1), 2-ethylfuran (**1b**, Entry 2) and 2-benzylfuran (**1d**, Entry 4) gave similar results. Unfortunately, the furans substituted with bulky alkyls in the position 2 (e.g., *t*-Bu, **1c**, Entry 3) gave much lower yields and much lower asymmetric inductions compared to silvan.



Scheme 2. The model reaction of **1a** with **2a**.

Use of the much more reactive 2-methoxyfuran (**1e**) requires no high pressure. Its reaction with glyoxylates proceeds readily under atmospheric pressure even without a catalyst. In the case of the catalyzed reaction, cooling of the reaction mixture is recommended. This improves the enantioselectivity from 32 to 46% ee (Entries 5 and 6).

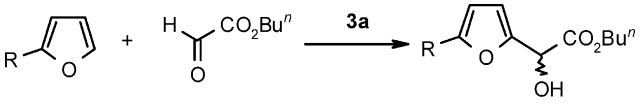
Silvan (**1a**) was also reacted with glyoxylates other than *n*-butyl glyoxylate (**2a**), viz., with isopropyl (**2b**), cyclohexyl (**2c**), as well as (*R*)-menthyl glyoxylate (**2d**) (Table 4). We found that isopropyl glyoxylate gave somewhat lower enantioselectivities and lower yields (Entry 2) than **2a**. It is noteworthy that the resulting adduct **9** is crystalline, but since it crystallizes as a racemate, the mother liquors become enantiomerically enriched.

Table 2
High-pressure reaction of **1a** with **2a** catalyzed by **3a**[a]

Entry	**2a** (mol/L)	Catalyst **3a** (mol%)	Yield (%)	ee (%)[b]
1	0.25	5	70	72
2	0.1	5	47	76
3	0.5	5	69	66
4	0.5	10	68	64
5	0.5	2	70	62
6	0.5	1	33	56
7	0.5	0.5	31	42
8	0.5	0.1	28	38

[a] The reactions were carried out using 1.5 equivalent of silvan in toluene under 10 kbar at 25 °C for 20 h.
[b] The enantiomeric excess was determined by GC.

Table 3
Reactions of 2-substituted furans **1a–e** with *n*-butyl glyoxylate **2a** catalyzed by **3a**[a]

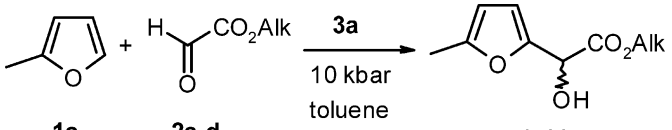


1a-e **2a** **4-8**

Entry	Furan		Pressure (bar)	*T* (°C)	Product		
	No.	R			No.	Yield (%)	ee (%)[c]
1	**1a**	Me	10000	25	**4**	70	64
2	**1b**	Et	10000	25	**5**	57	55
3	**1c**	Bu^t	10000	25	**6**	28	26
4	**1d**	Bn	10000	25	**7**	54	58
5[b]	**1e**	OMe	1	25	**8**	85	32
6[b]	**1e**	OMe	1	−78 → 25	**8**	59	46

[a] The reactions were carried out using 1 mmol of *n*-butyl glyoxylate, ∼1.5 mmol of **1a–d**, and 2 mol% of complex **3a** in toluene in a Teflon® vessel (2 ml) under 10 kbar for 20 h.
[b] The reactions were carried out using 1 mmol of *n*-butyl glyoxylate, 1.1 mmol of **1e**, and 2 mol% of complex **3a** in toluene (2 ml) for 4 h.
[c] The enantiomeric excess was determined by GC or HPLC.

Table 4
The high-pressure reactions of glyoxylates **2a–d** with **1a** in the presence of **3a**[a]



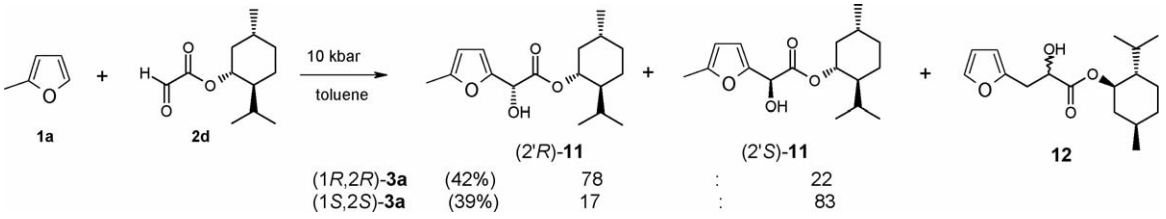
1a **2a-d** **4, 9-11**

Entry	Glyoxylate		Catalyst **3a**	Product		
	No.	Alk		No.	Yield	(*R*):(*S*)[b]
1	**2a**	Bu^n	*R,R*	**4**	69	83:17
2	**2b**	Pr^i	*R,R*	**9**	50	80:20
3	**2c**	Cyclohexyl	*R,R*	**10**	48	81:19
4	**2d**	(*R*)-Menthyl	*R,R*	**11**	42	78:22
5	**2d**	(*R*)-Menthyl	*S,S*	**11**	39	17:83

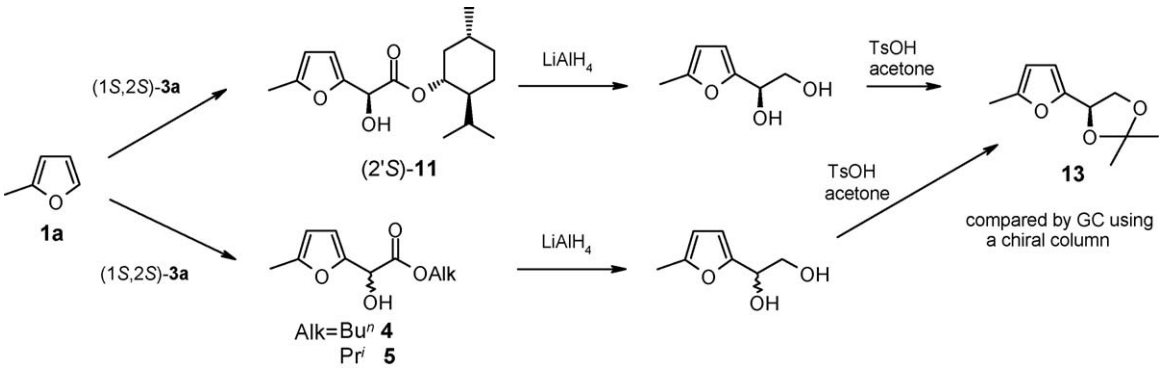
[a] The reactions were carried out using 1 mmol of glyoxylate **2a–d**, ∼1.5 mmol of silvane, and 5 mol% of complex **3a** in toluene in a Teflon® vessel (2 ml) under 10 kbar at 25 °C for 20 h.
[b] The enantiomeric excess was determined by GC or HPLC.

Another crystalline product, **11**, was obtained from the reaction of (2*R*)-menthyl glyoxylate (**2d**) using the catalyst (1*S*,2*S*)-**3a** (Entry 5). Without a catalyst, this glyoxylate gave a very low asymmetric induction (below 10% d.e.). The non-catalyzed reaction carried out in toluene under the pressure of 10 kbar gives a significant proportion of the byproduct **12** (**11**:**12** ≈ 3:7) (Scheme 3) [8], whereas the addition of the cobalt catalyst **3a** favors formation of the Friedel–Crafts product **11**. A slightly higher diastereomeric excess of **11** was achieved using the catalyst **3a** having (1*S*,2*S*) configuration (Scheme 3). We succeeded to crystallize the product (2′*S*)-**11** in a diastereomerically pure form. The resulting monocrystals were suitable for diffractometric measurements. The results of X-ray crystallographic analysis (Fig. 2) proved that the product of (*S*) configuration was obtained using the catalyst **3a** of (1*S*,2*S*) configuration.

In order to confirm that the achiral glyoxylates gave the same direction of induction, the compound (2′*S*)-**11** as well as the products of the reaction of silvan with glyoxylates **2a** and **2b**, prepared in the presence of the same catalyst (1*S*,2*S*)-**3a**, were separately transformed into the isopropylidene derivatives of



Scheme 3.



Scheme 4. Assigning the absolute configuration of the products of addition of silvan to achiral glyoxylates.

Table 5
Effect of the ligand structure in the (1*R*,2*R*)-cobalt complexes on the reaction of 2–methylfuran (**1a**) with *n*-butyl glyoxylate (**2a**)[a]

Entry	Catalyst			Product		
	No.	R^1	R^2	Yield (%)	Configuration	EE (%)
1	**3a**	Bu^t	Bu^t	70	(*R*)	64
2	**3b**	Bu^t	Me	60	(*R*)	72
3	**3c**	Bu^t	OMe	38	(*R*)	66
4	**3d**	Bu^t	Br	28	(*R*)	62
5	**3e**	Bu^t	H	49	(*R*)	64
6[b]	**3f**	H	H	23	(*S*)	52
7	**3g**	Me	Bu^t	30	(*S*)	52
8[b]	**3h**	Ph	H	38	(*S*)	62

[a] The reactions were carried out using 1 mmol of *n*-butyl glyoxylate, 1.5 mmol of silvan, in the presence of 2 mol% of the cobalt complexes in toluene in a Teflon® vessel (2 ml) under the pressure of 10 kbar at 25 °C for 20 h.
[b] Incomplete dissolution of the catalyst.

1,2-diol (**13**), and then compared by GC on a chiral column (Scheme 4). As expected, in each case, the (*S*) isomer of the product predominated.

The model reaction of silvan with *n*-butyl glyoxylate was also used for testing the cobalt complexes other than **3a** (Fig. 1, Table 5). It is clearly seen that if the *tert*-butyl substituent is at 3-position, then the enantiomeric ratios are very similar, independently of the catalyst used (Entries 1–5). In practice, the 5-substituent has no effect on the asymmetric induction, it affects only the reaction yield. Surprising results were obtained for the cobalt complex having the same configuration but, instead of *tert*-butyl, a hydrogen atom, methyl or phenyl group at 3- and 3′-positions (Entries 6–8). In such cases, a reversal of the asymmetric induction occurred (52–62% ee). Among these complexes, the highest induction was caused by the catalyst **3h** having phenyl groups at 3- and 3′-positions. These results are not easily rationalized, especially taken together with the observation, that in the HDA [9] and allylation [10] reactions there is no change of the asymmetric induction direction in the presence of catalysts having such substituents at 3-positions. However, for these particular examples, it seems that the steric requirements due to the *tert*-butyl groups modify strongly the structure of a transition state of the investigated Friedel–Crafts reaction.

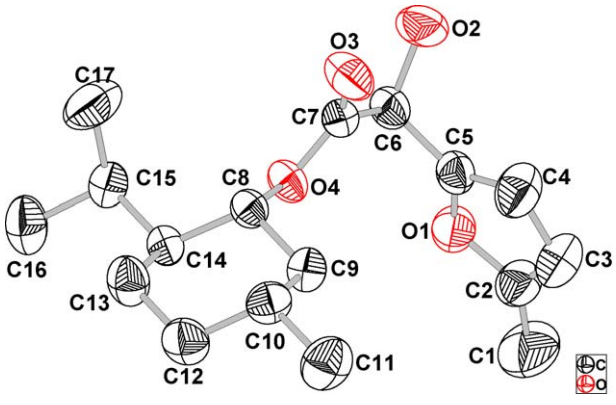


Fig. 2. The ORTEP drawing of the compound (2′*S*)-**11**.

3. Conclusions

In summary, we have found that the asymmetric catalytic Friedel–Crafts reactions of 2-alkylfurans with alkyl glyoxylates can be carried out under high-pressure conditions in the presence of (salen)cobalt catalysts to afford chiral furfuryl alcohols, compounds of substantial interest with moderate to good chemical yields and enantioselectivities. For the more reactive 2-methoxyfuran, the reaction proceeds under atmospheric pressure in good yield and with enantioselectivity up to 46% ee.

4. Experimental

4.1. General remarks

All reported NMR spectra were recorded in $CDCl_3$ using a Varian Gemini spectrometer at 200 MHz (^{1}H NMR) and 50 MHz (^{13}C NMR). Chemical shifts of ^{1}H NMR are reported as δ values relative to TMS peak defined at $\delta = 0.00$. Chemical shifts of ^{13}C NMR are reported as δ values relative to $CDCl_3$ peak defined at $\delta = 77.0$. High-resolution mass spectra (HRMS) were recorded on a Mariner PE Biosystems unit using the ESI technique. Optical rotations were measured using a JASCO P-1020 polarimeter. Analytical TLC was carried out on commercial plates coated with 0.25 mm of Merck Kieselgel 60. Preparative flash chromatography over silica gel was performed using Merck Kieselgel 60 (230–400 mesh). Enantiomeric excesses of the products were determined using GC and HPLC techniques. GC analyses were carried out on Trace 2000 GC (Thermo Finnigan) apparatus equipped with a flame-ionization detector (FID) and a chiral capillary β-dex 120 column (permethyl-β-cyclodextrin, 30 m × 0.25 mm I.D. Supelco, Bellefonte, USA) employing nitrogen as a carrier gas. Data were collected under the following conditions: pressure of nitrogen, 100 kPa; injector temperature, 200 °C; detector temperature, 250 °C. The oven temperature varied according to types of products (vide infra). HPLC analyses were performed on a chromatograph fitted with the diode-array detector (DAD) and Chiracel OD-H (250 mm × 4.6 mm, 5 μm) column eluted with 5% *i*-propanol in hexane.

4.2. Materials

All commercially available chemicals were used as received unless otherwise noted. Reagent-grade solvents were dried and distilled prior to use. (*R*,*R*)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (**3a**) was purchased from Aldrich.[6] Remaining cobalt(II) complexes (**3b**–**h**) were prepared according to the known procedures, starting from appropriate salen ligand and cobalt(II) acetate tetrahydrate in MeOH with 2 equivalents of NaOH (Table 6) [11].

Table 6
HRMS for (salen)cobalt(II) complexes

Cobalt(II) complex	Yield (%)	Molecular formula	Calcd	Found
3a	80	$C_{36}H_{52}N_2O_2Co$	603.3355	603.3347
3b	71	$C_{30}H_{40}N_2O_2Co$	519.2422	519.2423
3c	91	$C_{30}H_{40}N_2O_4Co$	551.2320	551.2322
3d	75	$C_{28}H_{34}N_2O_2Br_2Co$	647.0319	647.0287
3e	75	$C_{28}H_{36}N_2O_2Co$	491.2109	491.2133
3f	57	$C_{20}H_{20}N_2O_2Co$	379.0857	379.0835
3g	83	$C_{30}H_{40}N_2O_2Co$	519.2422	519.2424
3h	52	$C_{32}H_{28}N_2O_2Co$	531.1483	531.1459

The salen ligands were synthesized according to the method described by Jacobsen et al. [12]. Ligands used for preparation of complexes **3d**, **3g** and **3h** were not characterized before.

4.2.1. (1R,2R)-N,N′-Bis(5-bromo-3-tert-butylsalicylidene)-1,2-cyclohexanediamine

Yield 82%; yellow powder; $[\alpha]_D^{22} = -262$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 13.85 (bs, 2H), 8.17 (s, 2H), 7.31 (d, $J = 2.4$ Hz, 2H), 7.08 (d, $J = 2.4$ Hz, 2H), 3.38–3.25 (m, 2H), 2.05–1.45 (m, 8H), 1.39 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 164.4 (2 × CH = N), 159.3 (2 × C), 139.9 (2 × C), 132.3 (2 × CH), 131.6 (2 × CH), 119.7 (2 × C), 109.7 (2 × C), 72.3 (2 × CH), 35.0 (2 × C), 32.8 (2 × CH_2), 29.1 (6 × CH_3), 24.2 (2 × CH_2); IR (film) 2936, 2860, 1630, 1430, 1271, 1173, 868, 706 cm^{-1}; HRMS calculated for $C_{28}H_{36}N_2O_2Br_2Na$ $[M + Na]^+$: 613.1041, found: 613.1043.

4.2.2. (1R,2R)-N,N′-Bis(5-tert-butyl-3-methylsalicylidene)-1,2-cyclohexanediamine

Yield 82%; yellow crystals, mp 163–164 °C; $[\alpha]_D^{22} = -257$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 13.44 (bs, 2H), 8.28 (s, 2H), 7.18–7.15 (m, 2H), 7.00 (d, $J = 2.4$ Hz, 2H), 3.37–3.23 (m, 2H), 2.24 (s, 6H), 1.97–1.39 (m, 8H), 1.25 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 165.0 (2 × CH = N), 156.9 (2 × C), 140.6 (2 × C), 130.6 (2 × CH), 125.5 (2 × CH), 124.9 (2 × C), 117.2 (2 × C), 72.8 (2 × CH), 33.8 (2 × C), 33.3 (2 × CH_2), 31.4 (6 × CH_3), 24.2 (2 × CH_2), 15.7 (2 × CH_3); IR (film) 2956, 2860, 1631, 1481, 1272, 1225, 1040, 824 cm^{-1}; HRMS calculated for $C_{30}H_{42}N_2O_2Na$ $[M + Na]^+$: 485.3144, found: 485.3138.

4.2.3. (1R,2R)-N,N′-Bis(3-phenylsalicylidene)-1,2-cyclohexanediamine

Yield 72%; yellow oil; $[\alpha]_D^{22} = -561$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 14.00 (bs, 2H), 8.31 (s, 2H), 7.64–7.55 (m, 4H), 7.50–7.33 (m, 6H), 7.34 (dd, $J = 7.6$, 1.7 Hz, 2H), 7.16 (dd, $J = 7.6$, 1.7 Hz, 2H), 6.89 (t, $J = 7.6$ Hz, 2H), 3.39–3.34 (m, 2H), 1.98–1.36 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 164.9 (2 × CH = N), 158.4 (2 × C), 137.8 (2 × C), 133.1 (2 × CH), 130.9 (2 × CH), 129.6 (2 × C), 129.3 (4 × CH), 128.1 (4 × CH), 127.0 (2 × CH), 118.7 (2 × C), 118.5 (2 × CH), 72.6 (2 × CH), 33.1 (2 × CH_2), 24.1 (2 × CH_2); IR (film) 2931, 2857, 1627, 1432, 1289, 1280, 1100, 757, 696 cm^{-1}; HRMS calculated for $C_{32}H_{30}N_2O_2Na$ $[M + Na]^+$: 497.2205, found: 497.2209.

n-Butyl (**2a**), *iso*-propyl (**2b**), and cyclohexyl (**2c**) glyoxylates were prepared by oxidative cleavage of appropriate tartrate esters using $NaIO_4$ in water, and (*R*)-menthyl glyoxylate (**2d**) was prepared by ozonolysis of dimenthyl fumarate. The glyoxylates **2a**–**d** were distilled in the presence of P_2O_5 prior to use. Furans **1a**–**c**,**e** were purchased from Aldrich. The benzylfuran **1d** was prepared from furan via treatment with butyllithium followed by addition of benzyl bromide.

4.3. General procedure for the high-pressure Friedel–Crafts reaction

The 2-ml Teflon ampoule was charged with (salen)Co **3a** (usually 12.1 mg, 2 mol%), ca. 1 ml of toluene, followed by the freshly distilled glyoxylate (usually 1 mmol) and furan (∼1.5

equivalent). Finally, the ampoule was made up with toluene, closed and placed in a high-pressure chamber, 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 20 h. After decompression, the reaction mixture was purified by chromatography on a silica gel column using hexane/AcOEt 9:1 as an eluent.

4.4. Procedure for the reaction of 2-methoxyfuran with n-butyl glyoxylate

To a solution of complex **3a** (12.1 mg, 2 mol%) in toluene (2 mL), freshly distilled *n*-butyl glyoxylate (**2a**) (1 mmol) was added. After 10 min, 2-methoxyfuran (**1e**) (1.1 mmol) was added dropwise at appropriate temperature. After 4 h, the reaction mixture was purified by chromatography on a silica gel column using hexane/AcOEt 9:1 → 8:2 as an eluent.

4.4.1. Hydroxy-(5-methyl-furan-2-yl)-acetic acid n-butyl ester (*4*)

(*R*)-**4**:62% ee, $[\alpha]_D^{25} = -30.0$ (*c* 1.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 6.24 (d, $J = 3.2$ Hz, 1H), 5.93 (dq, $J = 3.2$, 1.0 Hz, 1H), 5.11 (s, 1H), 4.33–4.13 (m, 2H), 3.4 (bs, 1H), 2.27 (d, $J = 1.0$ Hz, 3H), 1.68–1.54 (m, 2H), 1.39–1.22 (m, 2H), 0.89 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 171.8 (C), 152.8 (C), 149.0 (C), 109.6 (CH), 106.4 (CH), 66.9 (CH), 66.1 (CH_2), 30.4 (CH_2), 18.8 (CH_2), 13.5 ($2 \times CH_3$); HRMS calculated for $C_{11}H_{16}O_4Na$ $[M + Na]^+$: 235.0941, found: 235.0952; GC (β-dex 120): $T = 160$ °C, t_R[(2*S*)-**4**] = 19.7 min, t_R[(2*R*)-**4**] = 20.1 min; HPLC (Chiracel OD-H column, hexane:*i*-PrOH, 95:5, flow rate 1.0 mL/min, $\lambda = 205$ nm): t_R[(2*S*)-**4**] = 7.7 min, t_R[(2*R*)-**4**] = 9.8 min.

4.4.2. (5-Ethyl-furan-2-yl)-hydroxyacetic acid n-butyl ester (*5*)

^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 6.25 (d, $J = 3.2$ Hz, 1H), 5.96–5.91 (m, 1H), 5.12 (d, $J = 6.5$ Hz, 1H), 4.33–4.13 (m, 2H), 3.3 (d, $J = 6.5$ Hz, 1H), 2.62 (q, $J = 7.6$ Hz), 1.69–1.53 (m, 2H), 1.44–1.17 (m, 2H), 1.21 (t, $J = 7.6$ Hz), 0.89 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 171.8 (C), 158.5 (C), 148.9 (C), 109.3 (CH), 104.8 (CH), 66.9 (CH), 66.1 (CH_2), 30.4 (CH_2), 21.3 (CH_2), 18.8 (CH_2), 13.5 (CH_3), 12.0 (CH_3); GC (β-dex 120): $T = 150$ °C, $t_{R1} = 36.2$ min, $t_{R2} = 36.9$ min.

4.4.3. (5-tert-Butyl-furan-2-yl)-hydroxyacetic acid n-butyl ester (*6*)

^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 6.23 (d, $J = 3.2$ Hz, 1H), 5.91 (d, $J = 3.2$ Hz, 1H), 5.13 (d, $J = 6.7$ Hz, 1H), 4.35–4.11 (m, 2H), 3.3 (d, $J = 6.7$ Hz, 1H), 1.67–1.53 (m, 2H), 1.39–1.14 (m, 2H), 1.25 (s, 9H), 0.88 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 171.9 (C), 164.8 (C), 148.8 (C), 108.9 (CH), 102.8 (CH), 67.0 (CH), 66.1 (CH_2) 32.7(C), 30.5 (CH_2), 28.9 ($3 \times CH_3$), 18.8(CH_2), 13.5(CH_3); HRMS calculated for $C_{14}H_{22}O_4Na$ $[M + Na]^+$: 277.1410, found: 277.1429; HPLC (Chiracel OD-H column, hexane:*i*-PrOH, 95:5, flow rate 1.0 mL/min, $\lambda = 205$ nm): $t_{R1} = 5.6$ min, $t_{R2} = 6.8$ min.

4.4.4. (5-Benzyl-furan-2-yl)-hydroxyacetic acid n-butyl ester (*7*)

^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 7.34–7.17 (m, 5H), 6.26 (d, $J = 3.2$ Hz, 1H), 5.93 (d, $J = 3.2$ Hz, 1H), 5.12 (d, $J = 6.6$ Hz, 1H), 4.29–4.10 (m, 2H), 3.94 (s, 2H), 3.3 (d, $J = 6.6$ Hz), 1.64–1.49 (m, 2H), 1.37–1.18 (m, 2H), 0.87 (t, $J = 7.3$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 171.7 (C), 155.3 (C), 149.8 (C), 137.7 (C), 128.7 ($2 \times$ CH), 128.4 ($2 \times$ CH), 126.5 (CH), 109.4 (CH), 107.2 (CH), 66.9 (CH), 66.2 (CH_2), 34.5 (CH_2), 30.4 (CH_2), 18.8 (CH_2), 13.5 (CH_3); HRMS calculated for $C_{16}H_{20}O_4Na$ $[M + Na]^+$: 311.1254, found: 311.1249; HPLC (Chiracel OD-H column, hexane:*i*-PrOH, 95:5, flow rate 1.0 mL/min, $\lambda = 205$ nm): $t_{R1} = 10.9$ min, $t_{R2} = 14.7$ min.

4.4.5. Hydroxy-(5-methoxy-furan-2-yl)-acetic acid n-butyl ester (*8*)

^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 6.25 (d, $J = 3.3$ Hz, 1H), 5.11 (d, $J = 3.3$ Hz, 1H), 5.04 (d, $J = 6.5$ Hz, 1H), 4.22 (t, $J = 6.5$ Hz, 2H), 3.82 (s, 3H), 3.3 (d, $J = 6.5$ Hz), 1.69–1.55 (m, 2H), 1.41–1.22 (m, 2H), 0.90 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 171.5 (C), 161.7 (C), 140.8 (C), 110.4 (CH), 80.4 (CH), 66.9 (CH_3), 66.2 (CH_2), 57.7 (CH), 30.4 (CH_2), 18.8 (CH_2), 13.5 (CH_3); GC (β-dex 120): $T = 160$ °C, $t_{R1} = 39.9$ min, $t_{R2} = 41.0$ min; HPLC (Chiracel OD-H column, hexane:*i*-PrOH, 95:5, flow rate 1.0 mL/min, $\lambda = 205$ nm): $t_{R1} = 11.7$ min, $t_{R2} = 16.3$ min.

4.4.6. Hydroxy-(5-methyl-furan-2-yl)-acetic acid isopropyl ester (*9*)

^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 6.22 (d, $J = 3.2$ Hz, 1H), 5.93 (dq, $J = 3.2$, 1.0 Hz, 1H), 5.15 (septet, $J = 6.3$ Hz, 1H), 5.08 (s, 1H), 3.4 (bs, 1H), 2.27 (d, $J = 1.0$ Hz, 3H), 1.29 (d, $J = 6.3$ Hz, 3H), 1.22 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 171.2 (C), 152.8 (C), 149.2 (C), 109.4 (CH), 106.4 (CH), 70.3 (CH), 66.9 (CH), 21.6 (CH_3), 21.4 (CH_3), 13.5 (CH_3); HRMS calculated for $C_{10}H_{14}O_4Na$ $[M + Na]^+$: 221.0784, found: 221.0800; GC (β-dex 120): $T = 150$ °C, t_R[(2*S*)-**9**] = 11.9 min, t_R[(2*R*)-**9**] = 12.5 min.

4.4.7. Hydroxy-(5-methyl-furan-2-yl)-acetic acid cyclohexyl ester (*10*)

^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 6.22 (d, $J = 3.2$ Hz, 1H), 5.94–5.91 (m, 1H), 5.10 (d, $J = 6.7$ Hz, 1H), 4.92 (septet, $J = 4.0$ Hz, 1H), 3.4 (d, $J = 6.7$ Hz, 1H), 2.27 (d, $J = 0.9$ Hz, 3H), 1.92–1.21 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 171.1 (C), 152.6 (C), 149.3 (C), 109.3 (CH), 106.3 (CH), 74.9 (CH), 66.9 (CH), 31.2 (CH_2), 31.0 (CH_2), 25.2 (CH_2), 23.3 (CH_2), 23.2 (CH_2), 13.5 (CH_3); HPLC (Chiracel OD-H column, hexane:*i*-PrOH, 95:5, flow rate 1.0 mL/min, $\lambda = 205$ nm): $t_{R1} = 7.1$ min, $t_{R2} = 8.7$ min.

4.4.8. (2′*S*)-Hydroxy-(5-methyl-furan-2-yl)-acetic acid (*R*)-menthyl ester ((2′*S*)-*11*)

mp 83–85 °C (crystallized from Et_2O/hexane); $[\alpha]_D^{20} = -32.5$ (*c* = 1.15, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 6.22 (d, $J = 3.2$ Hz, 1H), 5.96–5.91 (m, 1H), 5.10 (d, $J = 7.0$ Hz,

1H), 4.83 (dt, $J = 10.9$, 4.4 Hz, 1H), 3.30 (d, $J = 7.0$ Hz), 2.27 (d, $J = 0.8$ Hz, 3H), 2.01–1.78 (m, 2H), 1.74–1.31 (m, 5H), 1.15–0.93 (m, 2H), 0.89 (d, $J = 6.8$ Hz, 6H), 0.77 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 171.3 (C), 152.7 (C), 149.4(C), 109.4 (CH), 106.4 (CH), 76.8 (CH), 66.9 (CH), 46.7 (CH), 40.2 (CH_2), 34.0 (CH_2), 31.3 (CH), 26.2 (CH), 23.3 (CH_2), 21.9 (CH_3), 20.7 (CH_3), 16.2 (CH_3), 13.5 (CH_3); HRMS calculated for $C_{17}H_{26}O_4Na$ $[M + Na]^+$: 317.1723, found: 317.1737; HPLC (Chiracel OD-H column, hexane:*i*-PrOH, 95:5, flow rate 1.0 mL/min, $\lambda = 205$ nm): $t_R[(2'S)$-**11**$] = 5.0$ min.

4.4.9. (2′R)-Hydroxy-(5-methyl-furan-2-yl)-acetic acid (R)-menthyl ester ((2′R)-*11*)

^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 6.25 (d, $J = 3.2$ Hz, 1H), 5.94–5.89 (m, 1H), 5.06 (d, $J = 6.2$ Hz, 1H), 4.75 (dt, $J = 10.9$, 4.4 Hz, 1H), 3.45 (d, $J = 6.2$ Hz), 2.25 (d, $J = 0.8$ Hz, 3H), 2.12–1.82 (m, 2H), 1.73–1.20 (m, 5H), 1.13–0.90 (m, 2H), 0.91 (d, $J = 6.5$ Hz, 3H), 0.75 (d, $J = 7.0$ Hz, 3H), 0.62 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 171.5 (C), 152.5 (C), 149.2 (C), 109.8 (CH), 106.3 (CH), 76.9 (CH), 66.8 (CH), 46.8 (CH), 40.6 (CH_2), 34.1 (CH_2), 31.4 (CH), 25.6 (CH), 23.1 (CH_2), 21.9 (CH_3), 20.5 (CH_3), 15.9 (CH_3), 13.4 (CH_3); HPLC (Chiracel OD-H column, hexane:*i*-PrOH, 95:5, flow rate 1.0 mL/min, $\lambda = 205$ nm): $t_R[(2'R)$-**11**$]$ = 6.9 min.

Table 7
Crystal data and structure refinement for (2′*S*)-**11**

Chemical formula	$C_{17}H_{26}O_4$
Molecular weight	294.38
T (K)	293 (2)
λ (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	
a (Å)	8.1005
b (Å)	6.0724(6)
c (Å)	17.2398(17)
α (°)	90
β (°)	97.111(8)
γ (°)	90
V (Å^3)	841.49(14)
Z	2
Calculated density (Mg m^{-3})	1.162
Absorption coefficient (mm^{-1})	0.081
F(0 0 0)	320
Crystal size (mm)	0.53 × 0.18 × 0.14
θ Range for data collection (°)	3.26–25.00
Limiting indices	$-9 \le h \le 9$, $-7 \le k \le 7$, $-20 \le l \le 20$
Reflections collected	12733
Independent reflections (R_{int})	2954 (0.0461)
Completeness to θ	25.00° (99.7%)
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	0.879
Final R indices [$I > 2\sigma$ (I)]	$R_1 = 0.0346$, $wR_2 = 0.0588$
R indices (all data)	$R_1 = 0.0509$, $wR_2 = 0.0632$
Largest diff. peak and hole (e Å^{-3})	0.093 and −0.102

4.4.10. 2,2-Dimethyl-4-(5-methyl-furan-2-yl)-[1,3] dioxolane (*13*)

Each one of the esters (*S*)-**11**, **4**, and **5** was separately reduced with $LiAlH_4$ in THF at reflux. The resulting 1,2-diol was transformed into the isopropylidene derivative **13**, which was then analyzed by gas chromatography.

^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 6.24 (d, $J = 3.0$ Hz, 1H), 5.94–5.90 (m, 1H), 5.04 (dd, $J = 7.9$, 6.5 Hz, 1H), 4.24–4.04 (m, 2H), 2.28 (d, $J = 0.8$ Hz, 3H), 1.50 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 152.8 (C), 149.4 (C), 109.7 (C), 109.4 (CH), 106.2 (CH), 71.4 (CH), 67.7 (CH_2), 26.4 (CH_3), 26.0 (CH_3), 13.6 (CH_3); GC (β-dex 120): $T = 140$ °C, $t_R[(2S)$-**13**$] = 8.5$ min, $t_R[(2R)$-**13**$] = 8.9$ min.

The product of reduction of (*S*)-**11** and subsequent isopropylidenation gave a peak having retention time of 8.9 min.

The X-ray structure investigations for compound (2′*S*)-**11**: The intensity data were collected using Kuma KM4CCD κ-axis diffractometer, using the omega scan mode. The structure was solved by direct methods and refined using SHELXL. Crystal data and details of the crystal structure determinations are presented in Table 7.

Crystallographic data (excluding structure factors) has been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 607097 for compound (2′*S*)-**11**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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The X-ray measurements were undertaken in the Crystallographic Unit of the Physical Chemistry Laboratory at the Chemistry Department of the University of Warsaw.

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