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Asymmetric hetero-Diels–Alder reaction of 1-alkyl-3-silyloxy-1,3-dienes with ethyl glyoxylate catalyzed by a chiral (salen)cobalt(II) complex

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Abstract

The hetero-Diels–Alder reactions of 1-alkyl-3-(*tert*-butyldimethylsilyl)oxy-1,3-butadienes with ethyl glyoxylate catalyzed by chiral salen–metal complexes have been studied. With a cobalt(II) complex as the catalyst, the reaction of 1-(2-benzyloxyethyl)-3-(*tert*-butyldimethylsilyl)oxy-1,3-butadiene with ethyl glyoxylate gave the Diels–Alder product in 75% isolated yield with the *endo*:*exo* ratio >99:1 and the enantiomeric excess ≥52%. The effects of temperature, catalyst and solvent are also discussed.

1. Introduction

The asymmetric hetero-Diels–Alder (HDA) reaction is one of the most efficient synthetic methodologies for the regio- and stereoselective construction of six-membered heterocycles. The last two decades have witnessed many successful cases of employing asymmetric Diels–Alder reactions[1–3] as the key step in the synthesis of natural products. The selectivities of the HDA reactions, however, are not always high. It is therefore not surprising that much attention[4–10] has been paid to developing new catalysts for different reaction systems.

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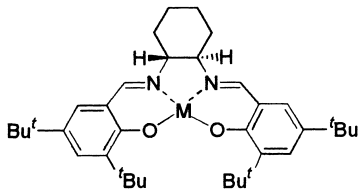
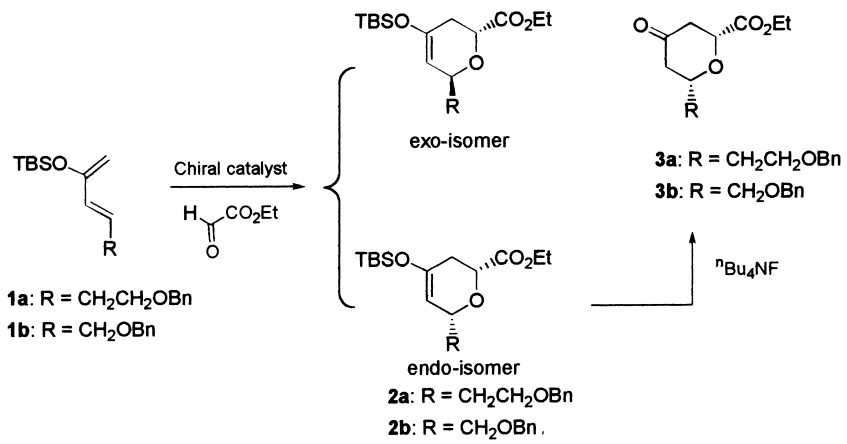


M = Co(II), Co(III)OAc, Co(III)Br, Mn(III)Cl, Ni(II), V(IV)=O.

We recently reported a (salen)Co(II) complex-catalysed formal total synthesis[11] of KDO (3-deoxy-D-manno-2-octulosonic acid), where high selectivities were achieved (*endo*:*exo*=93:7, d.e.=70) when a chiral diene was used. As an extension of that work, we next examined some achiral dienes and other salen-derived catalysts. Disclosed herein are some of the results.

2. Results and discussion

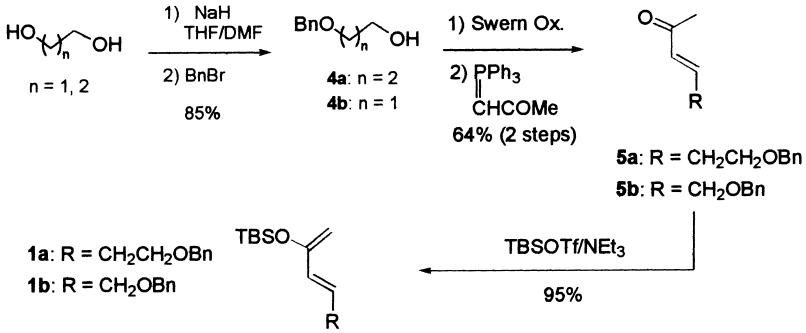
The model system chosen for our study is shown in Scheme 1, with ethyl glyoxylate as the dienophile and **1a** as well as **1b** (prepared from propane-1,3-diol or ethylene glycol, respectively, Scheme 2) as the diene. Several salen–transition metal complexes were then tested under different conditions for catalytic activity. The main results are summarized in Table 1. Due to the instability and the low polarity of the silyl enol ethers (which led to difficulties in purification), the ee values for the main isomers **2a,b** were determined (by HPLC on a chiral column) after hydrolysis to the corresponding ketones **3a,b**.



Scheme 1.

We first ran the reaction at 0°C in CH_2Cl_2 using 2 mol% of (salen)Co(II) as the catalyst (entry 1, Table 1). Under these conditions, the HDA products were obtained in 68% yield with the *endo*:*exo* ratio=90:10. The enantioselectivity, however, was rather poor (13% e.e.). Using larger amounts of the catalyst (entries 2 and 3) led to moderately improved e.e. values. Lowering the reaction temperature from 0°C to −78°C further raised the e.e. value to 52%, the best result so far obtained. The presence of 4 Å molecular sieves did not cause any changes in the outcome of the reaction.

Recently both Jacobsen[12] and Katsuki[13] reported in a different context (not related to Diels–Alder reactions) that Co(III) species showed better enantioselectivity than the corresponding Co(II). This persuaded us to examine (salen)Co(III)OAc and (salen)Co(III)Br complexes. The results were rather disappointing (entries 4 and 5), so we extended the catalyst further to some other salen–M complexes



Scheme 2.

Table 1
The results of the HDA reaction of **1a** with ethyl glyoxylate (1.5 equiv.) in CH_2Cl_2

Entry	Catalyst (mol%)	°C	Yield[a] (%)	*endo:exo*[b]	e.e.[c] (%) of **3a**
1	Salen Co(II) (2)	0	68	90:10	13
2	Salen Co(II) (10)	0	70	>99:1	46
3	Salen Co(II) (20)	0	71	>99:1	45
4	Salen Co(III) OAc (10)	0	70	95:5	18
5	Salen Co(III) Br (10)	0	no reactions *		
6	Salen Co(II) (10)	-78	75	>99:1	52
7	Salen Mn(III) Cl (10)	-78	65	76:24	0
8	Salen Ni(II) (10)	-78	60	85:15	8
9	Salen V(IV)=O (10)	0	35	60:40	3

[a] Isolated yield. [b] Based on the isolated yields. [c] Determined by HPLC on a chiral column (Chiralpak AD), eluting with 8:2 hexane-^{i}PrOH (monitored at 254 nm). The relative configuration was determined by ^{1}H NMR spectroscopy. The absolute configuration was assigned to be (*2R*, *6R*) based on the positive Cotton effect (λ = 292 nm, $\Delta\varepsilon$ = + 0.52) in the CD spectrum.

* Only starting materials were recovered.

(M=Mn(III)Cl, Ni(II), V(IV)=O); all prepared by known methods.[14,15] We found that with the nickel(II) complex as the catalyst the e.e. was only 8%, whereas with the manganese(III) and the vanadium(IV) complexes almost no enantioselectivity was observed, even at low temperature (entries 7, 8, and 9).

We have also explored the solvent effects on the stereochemical outcome (Table 2) in the (salen)Co(II)-catalyzed reaction of **1a** with ethyl glyoxylate. CH_2Cl_2 seems to be the most suitable solvent for this reaction. When using ether solvents (diethyl ether or THF) to replace CH_2Cl_2, not only the e.e. value

Table 2
HDA reaction[a] of **1a** with ethyl glyoxylate catalyzed by (salen)Co(II) complex (10 mol%) in different solvents at 0°C

Entry	Solvent	Yield (%)	*endo: exo*	e.e.[b] (%) of **3a**
1	CH_2Cl_2	70	>99:1	46
2	ether	60	80: 20	24
3	THF	62	90:10	25
4	hexane	74	>99:1	38

[a] For general conditions see Table 1. [b]Determined by HPLC, see Table 1.

decreases, but also the *endo*:*exo* ratio. In hexanes the *endo*:*exo* selectivity is the same as in CH_2Cl_2 but the enantioselectivity is significantly reduced.

Considering the tendency of ethyl glyoxylate to polymerize or hydrate, we normally used an excess of ethyl glyoxylate (1.5 equiv. with respect to the diene) in the reaction. Reducing the amount of ethyl glyoxylate to 1 equiv. lowered the yield to 62% (compared with entry 6 in Table 1) but did not lead to any improvement in the selectivities (*endo*:*exo*>99:1, 41% e.e. for the *endo* isomer).

The diene **1a** used in the present work does not bear any oxygen atom at the carbon α to the C–C double bond. This might be a reason for the relatively lower enantioselectivity in comparison with our earlier work.[11] To look into this, we synthesized **1b** and tested it in place of **1a**. It turned out that no changes (*endo*:*exo*>99:1, 45% e.e. for the *endo* isomer) could be detected, except that the yield was lowered to 45% (presumably due to the increased steric hindrance associated with the bulky benzyl group). In other words, the better selectivities[11] recorded with the chiral diene do stem from the matched interactions between the substrate and the chiral catalyst as suggested earlier.

3. Experimental

IR spectra were recorded on a Shimadzu IR-440 spectrometer. ^1H and ^{13}C NMR were recorded on an EM-360A, an FX 90q, or an AMX-300 spectrometer with TMS as the internal standard. Mass spectra were taken on a VG Quattro MS/MS or an HP 5989A instrument. The HRMS (EI) spectrum was obtained on a Finnigan Mat 8430 mass spectrometer. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter. The CD spectrum was recorded on a J-715 spectropolarimeter. Flash column chromatography was performed on silica gel H (10–40 μm) with a petroleum ether–ethyl acetate system as eluant. Microanalyses were carried out in the Microanalytical Laboratory at Shanghai Institute of Organic Chemistry.

3.1. 3-Benzyloxypropanol[16] ***4a***

To a solution of NaH (5.0 g, 125 mmol) in a 10:7 mixture of THF:DMF (85 mL) stirred at 0°C was added dropwise a solution of propane-1,3-diol (8.5 g, 112 mmol) in THF (25 mL). After stirring at room temperature for 3 h, benzyl bromide (13.3 mL, 112 mmol) was introduced dropwise. The stirring was continued at room temperature for another 12 h before the reaction was quenched with water. The reaction mixture was extracted three times with ether. The combined organic layers were dried over

$MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 5:1 petroleum ether:ethyl acetate) to afford **4a** (12.0 g, 65% yield). ^{1}H NMR (90 MHz, CCl_4): δ 7.32 (s, 5H), 4.49 (s, 2H), 3.45–3.72 (m, 4H), 1.73 (m, 2H); IR (film): 3385, 2929, 2866, 1603, 1495, 1451, 748 cm^{-1}; EI MS (m/z): 167 (M^++1), 107 (90.08), 91 (100), 79 (30.38).

3.2. 2-Benzyloxyethanol[17] *4b*

This compound was obtained using the procedure for **4a** (except for utilizing ethylene glycol instead of 1,3-propanediol). ^{1}H NMR (90 MHz, $CDCl_3$): δ 7.38 (s, 5H), 4.51 (s, 2H), 3.72–3.45 (m, 4H), 2.65 (s, 1H); IR (film): 3389, 3029, 2942, 1635, 1495, 1452, 742 cm^{-1}; EI MS (m/z): 152 (M^+, 42.95), 107 (67.07), 91 (100, $PhCH_2$).

3.3. (3E)-6-Benzyloxyhex-3-en-2-one[18] E-*5a*

To a solution of oxalyl chloride (3.32 mL, 33.2 mmol) in CH_2Cl_2 (75 ml) stirred at −78°C was added DMSO (5.10 mL, 73 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred at −78°C for 30 min. A solution of compound **4a** (5.4 g, 33.2 mmol) in CH_2Cl_2 (15 mL) was added, and the stirring was continued at −78°C for 30 min before NEt_3 (23.4 mL, 166 mmol) was added at the same temperature. After stirring at 0°C for 30 min and then at room temperature for 1 h, water (80 mL) was added. The organic layer was washed with 2 M aq. HCl, saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$. Removal of the drying agent and the solvent *in vacuo* gave the crude product, which was dissolved in dry benzene (80 mL) and treated with $Ph_3P{=}CHCOCH_3$ (10.8 g, 34.1 mmol). The mixture was heated at reflux for 5 h, then was cooled and concentrated. The residue was extracted with hexane several times. The organic layers were combined and concentrated to give the crude mixture of the *Z/E* isomers, which were separated by flash chromatography (10:1 petroleum ether:ethyl acetate) to afford *Z*-**5a** (500 mg) and *E*-**5a** (4.1 g) in a total yield of 64% (over two steps). Data for *E*-**5a**: ^{1}H NMR (90 MHz, $CDCl_3$): δ 7.20 (m, 5H), 6.75 (m, 1H), 5.96 (d, 1H, *J*=15.5 Hz), 4.43 (s, 2H), 3.46 (t, 2H, *J*=6 Hz), 2.42 (m, 2H), 2.10 (s, 3H); IR (film): 3040, 2870, 1680, 1500, 1460, 1100, 740, 700 cm^{-1}; EI MS (m/z): 204 (M^+), 91 (100, $PhCH_2$).

3.4. (3E)-5-Benzyloxypent-3-en-2-one[19] E-*5b*

This compound was obtained using the procedure for **5a** (except for utilizing **4b** instead of **4a**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 5H), 6.80 (dt, 1H, *J*=16.1, 4.5 Hz), 6.35 (dt, 1H, *J*=16.1, 3.9 Hz), 4.57 (s, 2H), 4.20 (dd, 2H, *J*=4.5, 2.0 Hz), 2.26 (s, 3H); IR (film): 3032, 2857, 1677, 1635, 1497, 1454, 1121, 740, 699 cm^{-1}; EI MS (m/z): 189 (M^+−1), 91 (100, $PhCH_2$).

3.5. (3E)-2-(tert-Butyldimethylsilyl)oxy-6-benzyloxy-hexa-1,3-diene E-*1a*

To a cooled ether solution (0°C) of enone **5a** (1.02 g, 5 mmol in 30 mL of dry ether) was added dropwise *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.26 mL, 5.5 mmol) followed by triethylamine (0.83 mL, 6 mmol). The mixture was stirred for 10 min before the cooling bath was removed. The stirring was continued at room temperature for another 30 min, when TLC showed the consumption of the starting material. The solvent was removed *in vacuo* and the residue was chromatographed on neutral alumina (eluting with petroleum ether) to afford **1a** (1.84 g, 99% yield) as a colorless oil. ^{1}H NMR (300 MHz, CD_3COCD_3): δ 7.33 (m, 5H), 6.04 (m, 2H), 4.49 (s, 2H), 4.24 (d, 2H, *J*=3.1 Hz), 3.52 (t, 2H,

J=6.5 Hz), 2.39 (m, 2H), 0.96 (s, 9H), 0.17 (s, 6H); IR (film): 3020, 2940, 1600, 1500, 1460, 1030, 700 cm^{-1}; EIMS (m/z): 319 (M^++1, 4.11), 91 (100, $PhCH_2$).

*3.6. (3*E*)-2-(*tert-*Butyldimethylsilyl)oxy-5-benzyloxy-penta-1,3-diene* E-***1b***

This compound was obtained using the procedure for **1a** (except for utilizing *E*-**5b** instead of *E*-**5a**). ^{1}H NMR (300 MHz, CD_3COCD_3): δ 7.33 (m, 5H), 6.18 (dt, 1H, *J*=15.08, 1.25 Hz), 6.07 (dt, 1H, *J*=15.08, 5.6 Hz), 4.51 (s, 2H), 4.36 (d, 2H, *J*=7.54 Hz), 4.10 (d, 2H, *J*=4.79 Hz), 0.97 (s, 9H), 0.19 (s, 6H); IR (film): 3032, 2958, 2859, 1661, 1595, 1497, 1455, 1318, 1255, 1025, 697 cm^{-1}; EI MS (m/z): 305 (M^++1, 2.01), 91 (100, $PhCH_2$).

*3.7. (2*R,*6*R*)-2-(2-Benzyloxyethyl)-3-(*tert-*butyldimethylsilyl)oxy-6-ethoxycarbonyl-5,6-dihydro-2*H-*pyran* ***2a***

To a solution of ethyl glyoxylate (78.5 mg, 0.75 mmol) in anhydrous CH_2Cl_2 (5 mL) stirred at −78°C (or 0°C) under nitrogen, was added the catalyst (salen–M, M=Co(II), Co(III), Mn(III), Ni(II), V(IV)=O) (10 mol%) in dry CH_2Cl_2 (5 ml). The mixture was stirred for 30 min then the diene *E*-**1a** (159 mg, 0.5 mmol) was added. The stirring was continued at the same temperature until TLC (4:1 petroleum ether:ethyl acetate) showed the disappearance of the starting material. After removal of the solvent, the residue was chromatographed on silica gel (20:1 petroleum ether:ethyl acetate) to afford **2a**. ^{1}H NMR (300 MHz, CD_3COCD_3): δ 7.34 (m, 5H), 4.91 (s, 1H), 4.49 (s, 2H), 4.34 (m, 1H), 4.21 (dd, 1H, *J*=10.7, 4.0 Hz), 4.17 (q, 2H, *J*=7.0 Hz), 3.61 (m, 2H), 2.29 (m, 1H), 2.15 (m, 1H), 1.82 (m, 2H), 1.24 (t, 3H, *J*=7.0 Hz), 0.92 (s, 9H), 0.16 (s, 6H); IR (film): 2931, 2859, 1747, 1676, 1497, 1455, 1207, 1184, 840, 698 cm^{-1}; EI MS (m/z): 419 (M^+ −1, 1.84), 329 (45.64), 285 (61.77), 91 (100), 73 (84.37).

*3.8. (2*S,*6*R*)-2-(2-Benzyloxymethyl)-3-(*tert-*butyldimethylsilyl)oxy-6-ethoxycarbonyl-5,6-dihydro-2*H-*pyran* ***2b***

This compound was obtained using the procedure for **2a** (except for utilizing *E*-**1b** instead of *E*-**1a**). ^{1}H NMR (300 MHz, CD_3COCD_3): δ 7.40–7.32 (m, 5H), 4.92 (m, 1H), 4.56 (m, 2H), 4.40 (m, 1H), 4.26 (dd, 1H, *J*=10.9, 4.0 Hz), 4.18 (q, 2H, *J*=7.0 Hz), 3.58–3.44 (m, 2H), 2.40–2.32 (m, 2H), 1.24 (t, 3H, *J*=7.0 Hz), 0.92 (s, 9H), 0.16 (s, 6H); IR (film): 2932, 2860, 1739, 1674, 1497, 1455, 1203, 1184, 840, 698 cm^{-1}; EI MS (m/z): 405 (M^+ −1), 285 (100), 91 (62.35), 73 (50.08).

*3.9. (2*R,*6*R*)-2-Ethoxycarbonyl-6-(2-benzyloxyethyl)-tetrahydro-1,4-pyrone* ***3a***

To a solution of compound **2a** (120 mg, 0.3 mmol) in dry THF (4 mL) stirred at room temperature under nitrogen, was added tetrabutylammonium fluoride (1 N, 0.4 mL). The mixture was stirred for 15 min when TLC (4:1 petroleum ether:ethyl acetate) showed the completion of the reaction. The mixture was then diluted with ether (10 mL), washed with water and brine. The organic layer was dried over $MgSO_4$. After removal of the drying agent and the solvent, the residue was chromatographed on silica gel (4:1 petroleum ether:ethyl acetate) to afford product **3a** as a clear oil (75 mg, 87% yield). $[\alpha]_D^{18}$=+20.5 (c 1.53, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48–7.35 (m, 5H), 4.50 (s, 2H), 4.25 (q, 2H, *J*=7.08 Hz), 4.21 (dd, 1H, *J*=11.66, 3.28 Hz), 3.92–3.83 (m, 1H), 3.73–3.65 (m, 1H), 3.63–3.58 (m, 1H), 2.61 (m, 2H), 2.40 (m, 2H), 2.10–2.01 (m, 1H), 1.93–1.84 (m, 1H), 1.30 (t, 3H, *J*=7.0 Hz); IR (film): 2982,

2868, 1756, 1725, 1496, 1455, 1098, 740, 699 cm^{-1}; EI MS (m/z): 307 (M^++1), 171 (26.42), 91 (100, $PhCH_2$); anal. calcd for $C_{17}H_{22}O_5$: C, 66.67. H, 7.19. Found: C, 66.57. H, 7.19.

*3.10. (2*R*,6*S*)-2-Ethoxycarbonyl-6-benzyloxymethyl-tetrahydro-1,4-pyrone **3b***

This compound was obtained using the procedure for **3a** (except for utilizing **2b** instead of **2a**). $[\alpha]_D^{20}$=+14.4 (c 1.50, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 5H), 4.60 (m, 2H), 4.25 (q, 2H, *J*=7.1 Hz), 4.24 (dd, 1H, *J*=15.1 and 4.2 Hz), 3.90 (m, 1H), 3.68 (dd, 1H, *J*=10.5, 5.3 Hz), 3.60 (dd, 1H, *J*=10.5, 4.3 Hz), 2.72–2.59 (m, 2H), 2.56–2.42 (m, 2H), 1.29 (t, 3H, *J*=7.1 Hz); IR (film): 2983, 2869, 1726, 1497, 1454, 1107, 740, 700 cm^{-1}; EI MS (m/z): 293 (M^++1, 54.52), 185 (65.11), 91 (100, $PhCH_2$). HRMS (EI): calcd for $C_{16}H_{20}O_5$: 292.1305. Found: 292.1308.

Acknowledgements

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