

Other transition metal reagents: chiral transition-metal Lewis acid catalysis for asymmetric organic synthesis

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1. Introduction

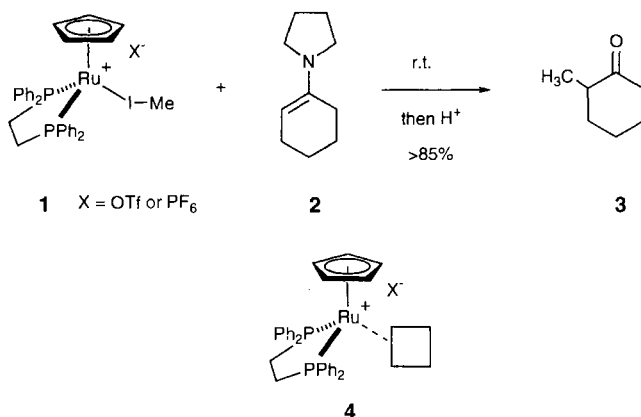
Transition-metal Lewis acid catalysts can supply one or occasionally two vacant sites as Lewis acids for substrates possibly to meet the 18-electron rule for transition metals, and moreover they need not change their valency during the reactions. The unique vacant sites prepared by releasing one or two ligands from the characteristic configurations ML_n ($n = 4-6$, M = metal, L = ligand) consists of different kinds of steric circumstances. Therefore, design of their ligands with consideration not only of stereochemistry but also of valency of metals has been a remarkably attractive subject to develop new Lewis acid catalysts especially for asymmetric synthesis.

The complexes of the early transition metals such as the family of Sc, Ti, V, Cr, or Mn (where d^n , $n \leq 6$), being electron-poor, can easily supply vacant sites as Lewis acids as mentioned in the early chapters. In contrast, those of the late transition metals such as Fe, Co, Ni, or Cu etc., being electron-rich, should be converted into their cationic species to act as acids, such as $[ML_{n-1}]^+$ ($n = 4-6$), accompanied by certain conjugate bases as counter anions.

2. Activation of haloalkanes and carbonyl compounds

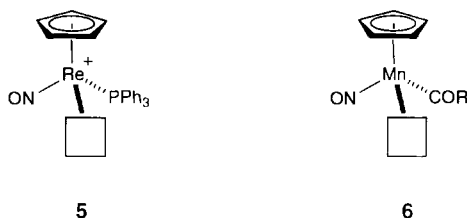
Simple haloalkanes have been found to bind to transition-metal complexes via the halogen lone pair. The co-ordinating iodomethane can act as a methylating reagent which methylated several nucleophiles faster than free iodomethane. For example, Crabtree *et al.* reported that the reaction of the iodomethane complex of Cp-Ru **1** exhibited methylation of the cyclohexanone

enamine **2** to selectively give a 2-methylcyclohexanone **3** in high yield by C-alkylation (Scheme 13.1),^{1,2} although free enamines accompany *N*-alkylation products. Upon co-ordination to the cationic ruthenium(II), the methyl carbon atom of MeI increases electrophilicity attributed to activation by the cationic ruthenium Lewis acid as **4**.



Scheme 13.1

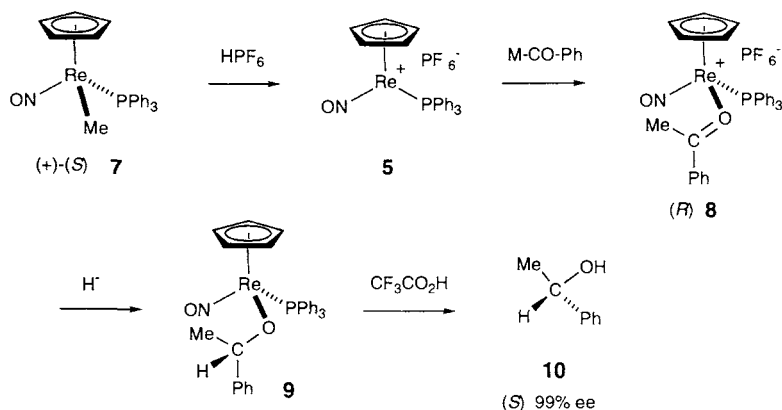
Similar haloalkane complexes of Cp-rhenium have also been reported.^{3,4} The cationic complex $[\text{CpRe}(\text{NO})(\text{PPh}_3)(\text{IME})]^+ \text{BF}_4^-$ can methylate triphenylphosphine at room temperature to produce a phosphonium salt in *c.* 90% yield.⁵ The $\text{CpRe}(\text{NO})(\text{PPh}_3)(\text{vacant})^+$ species **5** (Scheme 13.2) can act as a Lewis acid and activate the carbon-halogen bonds. Moreover, the Cp-Re species **5** maintain the chirality-at-metal during several reactions.⁵ In the sense of chirality-at-metal, a similar observation was disclosed by Brunner in 1974 that the manganese complex $\text{CpMn}(\text{NO})(\text{COR})(\text{PAR}_3)$ exhibits a dissociative substitution by PAR'_3 with retention of the configuration via the intermediate **6**.⁶⁻⁸



Scheme 13.2

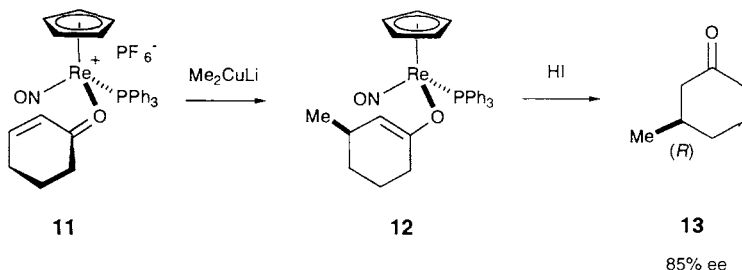
The σ -complex of acetophenone-rhenium was prepared from the methyl complex **7** by treatment with HPF_6 followed by addition of acetophenone via

the unsaturated species **5** (Scheme 13.3).⁹ The acetophenone complex **8** when analysed by X-ray showed that the rhenium atom preferentially binds *syn* to the smaller methyl substituent. The methyl is also directed towards the smallest NO ligand, where the *re*-face of the ketone is opened. Therefore, hydride reduction of the complex (+)-(*R*)-**8** was converted into the corresponding alkoxide complex **9** followed by acidification to produce the optically active 1-phenylethanol **10** in 99% ee (*S*) (Scheme 13.3).



Scheme 13.3

Similarly, the α,β -unsaturated ketone moiety of the chiral rhenium–enone complex (+)-(*R*)-**11** was attacked by dimethyl cuprate followed by acidification to give β -methyl cyclohexanone **13** in 85% ee via the adduct **12** (Scheme 13.4).¹⁰



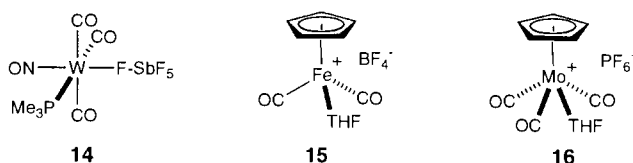
Scheme 13.4

Thus, stoichiometric modes of activation of haloalkanes and carbonyl compounds have been realized in both non-asymmetric and asymmetric reactions by use of the transition-metal complexes as Lewis acids. Many other examples are referred to in the literatures.^{5–10}

3. Catalytic asymmetric Diels–Alder reactions

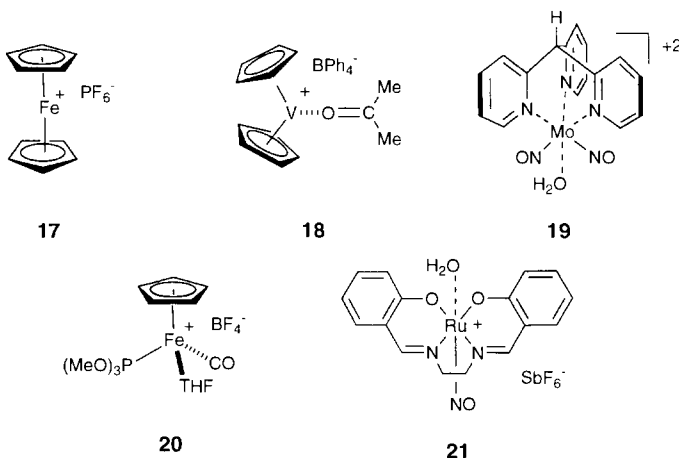
3.1 Achiral transition-metal catalysts

Low oxidation state transition-metal Lewis acids were first reported as catalysts of the Diels–Alder reactions by Hersh *et al.*^{11,12} They originally found the tungsten nitrosyl complex $[\text{W}(\text{PMe}_3)(\text{CO})_3(\text{NO})]^+(\mu\text{-F-SbF}_5)^-$ **14** (Scheme 13.5) as a catalyst of butadiene or cyclopentadiene and α,β -unsaturated enones at 0°C . They suggested that the mode of catalysis is likely due to activation of the α,β -unsaturated enone by simple $\eta^1(\sigma)$ -carbonyl co-ordination on the basis of X-ray analysis of the tungsten–acrolein adduct. They also compared the related cationic fragments of the corresponding η^1 -carbonyl complexes, such as $\text{Cp}(\text{CO})_2\text{Fe}^+$ **15** and $\text{Cp}(\text{CO})_3\text{Mo}^+$ **16**, to well-known transition-metal Lewis acids.¹² The catalytic activity of these reagents for the Diels–Alder reactions was compared; **14** > **15** > **16**. Furthermore, the order of Lewis acidity was measured on the basis of ^1H NMR chemical shifts of crotonaldehyde on co-ordination; Lewis acids (relative power), BBr_3 (1.00) > AlCl_3 (0.82) > BF_3 (0.77) > TiCl_4 (0.66) > **14** (0.62) > **16** (0.47) > AlEt_3 (0.44) > **15** (0.36).



Scheme 13.5

Kelly *et al.*¹³ reported ferrocenium ion, **17** (Scheme 13.6) acting as a catalyst for the Diels–Alder reactions of cyclopentadiene and α,β -unsaturated enones



Scheme 13.6

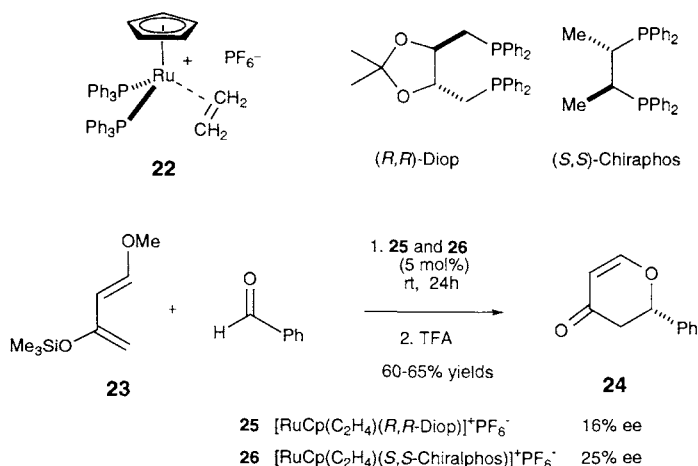
in good yields at 0–20°C. The possibility that metallocenes may serve as Lewis acids can be inferred from the vanadocenium complex of acetone $(\text{Cp})_2\text{V}(\eta^1\text{-O}=\text{CMe}_2)^+$, **18**. However, other metallocenes, such as zirconocene dichloride, titanocene dichloride, cobaltocenium ion, and ferrocene, did not exhibit the catalytic activity of the Diels–Alder reaction as Lewis acids.

Other transition-metal Lewis acids for the Diels–Alder reactions have been reported: the doubly charged complex $[\text{HC}(\text{py})_3\text{Mo}(\text{NO})_2(\text{solvent})]^{+2}(\text{SbF}_6)_2$, **19**,¹⁴ $(\text{Cp})(\text{CO})[\text{P}(\text{OMe})_3]\text{Fe}^+$, **20**,¹⁵ and $[\text{Ru}(\text{salen})(\text{NO})(\text{H}_2\text{O})]\text{SbF}_6$, **21**.^{16,17}

3.2 Chiral transition-metal catalysts

Many of transition-metal complexes, as described above, can sufficiently activate dienophiles by co-ordination of the carbonyl groups. The reactions proceed smoothly under mild conditions to provide high diastereoselectivities and enantioselectivities. Therefore, much effort has been devoted to creating a new asymmetric Diels–Alder reaction with the combination of transition-metals and chiral auxiliaries. Many original chiral auxiliaries have been developed for this purpose.^{18,19}

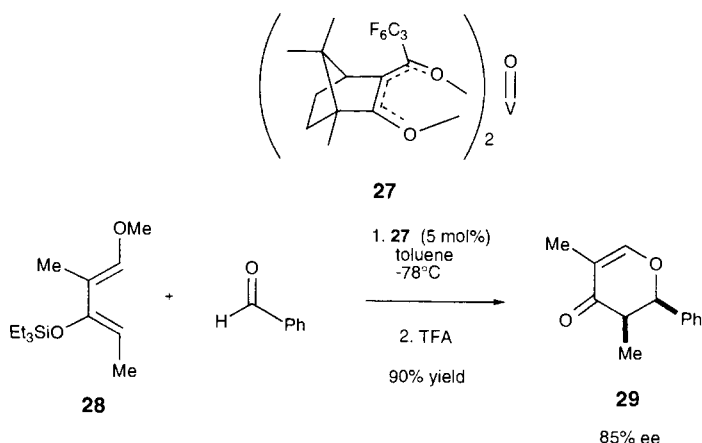
Faller *et al.*²⁰ found that the Cp–Ru cationic complex $[\text{CpRu}(\text{PPh}_3)_2(\text{C}_2\text{H}_4)]\text{PF}_6$, **22** (5 mol%) catalysed the hetero-Diels–Alder reaction of Danishefsky's diene **23** and benzaldehyde at room temperature to give the adduct **24** in 78% yield (Scheme 13.7). The catalytically active species generated by dissociation of ethylene from **22**, activate benzaldehyde reacting easily with the diene **23**. The optically active bidentate phosphines, Diop and Chiralphos, also entered to this reaction. However, the enantioselectivities were not high as expected, 16% ee with the Ru–Diop catalyst, **25**, and 25% ee with the Ru–Chiralphos catalyst, **26**. More recently, Ghosh *et al.*²¹ improved



Scheme 13.7

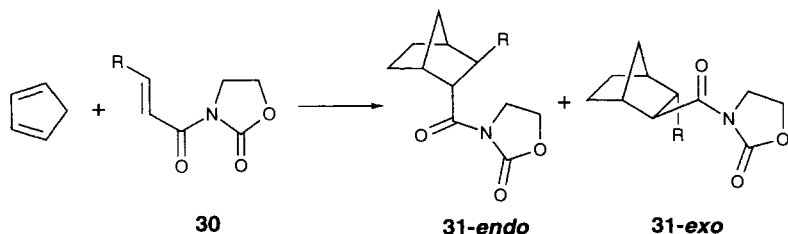
the hetero-Diels–Alder reaction of diene **23** with glyoxylates in the presence of chiral copper–bisoxazoline catalysts to attain 70% ee.

Optically active oxovanadium(IV) complexes with camphor-derived diketono ligands have been investigated for the asymmetric hetero-Diels–Alder reaction.²² The oxovanadium complex, **27**, (5 mol%) effectively catalysed the reaction of the diene **28** and benzaldehyde at -78°C for *c.* 1 day to give the adduct **29** in 90% yield and in 85% ee (Scheme 13.8).



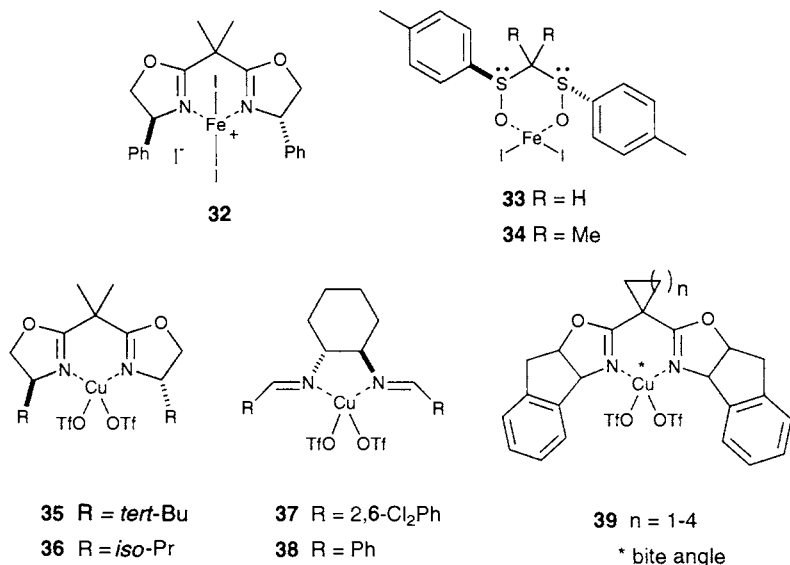
Scheme 13.8

As a bidentate dienophile, the acylimide **30** was introduced to the Diels–Alder reaction by Narasaka in 1986 (Scheme 13.9).²³ To capture this component, the reaction may preferentially need an acid catalyst providing two vacant sites. The octahedral structure of transition-metal complexes can supply this demand, as shown in the chiral iron–bisoxazoline complex, **32**, developed by Corey *et al.*²⁴ (Protocol 1) and the iron–bissulfoxide complexes, **33** and **34** (Scheme 13.10) reported by Khair *et al.*²⁵ (Table 13.1). The iron–bisoxazoline, **32** (10 mol%) catalysed the reaction of the acylimide **30** and



Scheme 13.9

13: Other transition metal reagents



Scheme 13.10

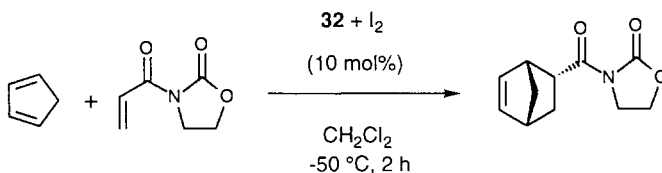
Table 13.1. Asymmetric Diels–Alder reaction with the acylimide **30** and cyclopentadiene with the catalysts **32–39**

Catalyst	mol%	R=	°C, h	yield(%)	ratio of <i>endo:exo</i>	% ee of <i>endo</i>
32	10	H	−50, 15	—	99:1	86
33	10	H	−50, 5	74	68:32	36
34	10	H	−50, 5	78	78:22	56
35	10	H	−78, 18	86	98:2	98
36	10	H	−78–50, 4	93	96:4	58
35	10	Me	−15, 30	85	96:4	97
37	9	H	−78, 36	87	80:20	92
38	9	H	−78, 36	—	80:20	85
37	9	Me	−10, 30	90	65:35	83
38 n=1	10	H	−70, —	90	96:1	98
39 n=4	10	H	−50, —	90	26:1	83

cyclopentadiene at −50°C to give an *endo:exo* ratio of 99:1 and 86% ee for the *endo* isomer of **31**. It was postulated for both reactions that the iron catalysts **32–34** may supply two vacant sites of the equatorial–equatorial or the equatorial–axial.

Protocol 1.**Asymmetric Diels–Alder reaction of 3-acryloyl-1,3-oxazolin-2-one with cyclopentadiene catalysed by chiral bis(oxazoline)-Fe(III) complex²⁴ (Scheme 13.11)**

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

**Scheme 13.11****Equipment**

- Magnetic stirrer
- Syringes
- Oil bath
- Schlenk flask (10 mL)
- Vacuum/inert gas source (argon)
- Cooling bath with dry ice–acetone

Materials

- | | |
|--|-------------------------------------|
| • Cyclopentadiene, 0.68 mL, 8.19 mmol | flammable, toxic |
| • 3-Acryloyl-1,3-oxazolin-2-one, 385 mg, 2.73 mmol | flammable, toxic |
| • 2,2-Bis[2-[4(S)-phenyl-1,3-oxazolinyl]]propane, 109 mg, 0.326 mmol | |
| • Powdered iron, 15.2 mg, 0.272 mmol | moisture-sensitive |
| • Iodine, 173.1 mg, 0.680 mmol | toxic, corrosive |
| • Acetonitrile, 4 mL | flammable, lachrymator |
| • Dichloromethane, 7 mL | harmful by inhalation |
| • Triethylamine, 0.1 mL | flammable, corrosive |
| • Ether | flammable, irritant |
| • Pentane | flammable, irritant |
| • Sodium sulfite | moisture-sensitive, irritant |
| • Copper acetate | irritant, hygroscopic |

1. Prepare a catalyst solution of powdered iron (15.2 mg, 0.272 mmol) and iodine (104 mg, 0.408 mmol) in acetonitrile (2 mL) under argon atmosphere. After stirring for 1 h at 40°C, add a solution of 2,2-bis[2-[4(S)-phenyl-1,3-oxazolinyl]]propane (109 mg, 0.326 mmol) in acetonitrile (2 mL) at 23°C and stir for 1 h at 40°C. Evaporated under reduced pressure to afford a dark viscous oil, and add dichloromethane (7 mL).
2. After cooling the catalyst solution to $-78^{\circ}C$, add iodine (69.1 mg, 0.282 mmol), 3-acryloyl-1,3-oxazolin-2-one (385 mg, 2.73 mmol) and cyclopentadiene (0.68 mL, 8.19 mmol).
3. After stirring for 2 h at $-50^{\circ}C$, add triethylamine (0.1 mL) and dilute with ether–pentane to the reaction mixture.

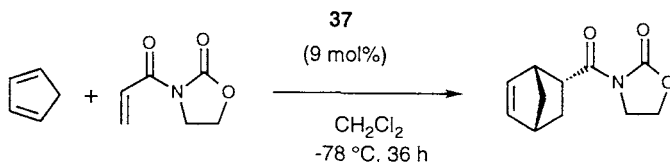
4. Wash the dichloromethane solution with aqueous sodium sulfite and copper acetate. Dry the organic layer and then remove the organic solvent using a rotary evaporator.
5. Apply the crude product to a flash silica gel column with 1:1 mixture of *n*-hexane and ethyl acetate to obtain pure product in 95% yield (539 mg, 96% *endo*, 82.2% ee).
6. Determine the enantiomeric excess by HPLC analysis (Daicel CHIRALCEL OD, 10% *i*-PrOH in hexane, flow rate 1 mL/min), $t_R = 21.4$ min (2*S*), 23.5 min (2*R*).

The most remarkable progress came from the use of the catalysts, **35** and **36** derived from copper(II) triflate and chiral bisoxazoline.²⁶ The reaction of the acylimide **30** and cyclopentadiene in the presence of the catalyst **35** (10 mol%) proceeds at -78°C for 5 h to give the adduct **31** in 86% with 98:2 ratio of the *endo:exo* isomers and 98% ee for the *endo* isomer. Similarly, the copper(II)-bisimine catalyst, **37** and **38**, exhibited high activity at -78°C to give 92% ee (Protocol 2). The sense of asymmetric induction with these copper catalysts can be interpreted by assuming the reaction via a square-planar Cu(II)(chiral ligand)(acylimide) complex, rather than a tetragonal one, which is attacked on the least hindered side by the diene. In a similar system to the copper catalysts, the copper catalysts of new bisoxazolines, **39**, were synthesized to show that the larger the bite angle of the bisoxazolines, the higher the enantioselectivity up to 98 from 82.²⁸

Protocol 2.

Asymmetric Diels–Alder reaction of 3-acryloyl-1,3-oxazolin-2-one with cyclopentadiene catalysed by chiral bis(imine)-Cu(II) complex²⁷ (Scheme 13.12)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 13.12

Equipment

- Magnetic stirrer
- Syringes
- Cooling bath with dry ice–acetone
- Schlenk flask (10 mL)
- Vacuum/inert gas source (argon)

Protocol 2. Continued**Materials**

- Cyclopentadiene, 0.68 mL, 8.19 mmol flammable, toxic
- 3-Acryloyl-1,3-oxazolin-2-one, 385 mg, 2.73 mmol flammable, toxic
- Bis(imine), 43 mg, 0.1 mmol
- Copper(II) triflate, 32.5 mg, 0.09 mmol corrosive, moisture-sensitive
- Dichloromethane, 2 mL harmful by inhalation
- Ether flammable, irritant

1. Prepare a catalyst solution of bis(imine) (43 mg, 0.1 mmol) and copper(II) triflate (32.5 mg, 0.09 mmol) in dichloromethane (2 mL) at room temperature under nitrogen atmosphere and stir for 5 h.
2. After cooling of the catalyst solution to -78°C , add 3-acryloyl-1,3-oxazolin-2-one (141 mg, 1 mmol) and cyclopentadiene (0.83, 10 mmol).
3. After stirring for 36 h at -78°C , dilute the reaction mixture with ether and filter through a small plug (1 cm \times 2 cm) of silica gel. Wash the plug three times with ether (totally 30 mL) : 87% yield, 80% *endo*, 92% ee.

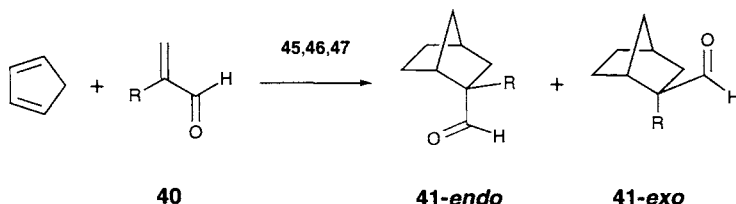
The non-asymmetric Diels–Alder reaction of α,β -unsaturated aldehydes have also been intensively examined with the transition-metal Lewis acids **14–21** as described above (Scheme 13.13). The first asymmetric reaction with chiral transition-metal Lewis acids was realized by Kündig *et al.* in 1994.²⁹ They demonstrated that the chiral iron–bisphosphite catalyst, **42**, (5 mol%), which itself has one acrolein molecule, exhibits catalytic activity for the reaction of acrolein derivatives and cyclopentadiene at -30°C giving in 84–99% ee (Table 13.2). The reaction of methacrolein with **42** as a catalysts is described in Protocol 3 (Scheme 13.14).²⁹

Table 13.2. Asymmetric Diels–Alder reaction with acrolein derivatives and cyclopentadiene with the catalysts **42–44**

Catalyst	R=	$^{\circ}\text{C}$, h	yield(%)	ratio of <i>endo:exo</i>	% ee of major
42	H	-30 , 16	46	62:38	84
42	Me	-20 , 20	62	3:97	90
42	Et	-20 , 20	55	2:98	94
42	Br	-40 , 16	87	5:95	95
43a ^a	H	-20 , 120	>95 ^b	96:4	85
43b ^a	H	-20 , 18	>95 ^b	94:6	85
43a ^a	Me	-20 , 120	>95 ^b	4:96	85
43b ^a	Me	-40 , 8	>95 ^b	3:97	92
43a ^a	Br	-40 , 60	>95 ^b	3:97	87
43b ^a	Br	-78 , 12	>95 ^b	2:98	96
44	Me	-78 , 24	60	2:98	60
44	Br	-78 , 24	93	2:98	68

^a **43** (5 mol%).

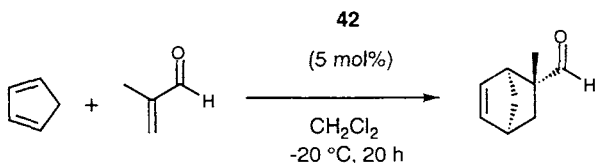
^b Conversion.



Scheme 13.13

Protocol 3.**Asymmetric Diels–Alder reaction of methacrolein with cyclopentadiene catalysed by chiral phosphite-Fe(II) complex²⁹ (Scheme 3.14)**

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 13.14

Equipment

- Magnetic stirrer
- Syringes
- Cooling bath with dry ice–acetone
- Schlenk flask (10 mL)
- Vacuum/inert gas source (argon)

Materials

- | | |
|--|------------------------------|
| • Phosphite-Fe-acrolein complex, 110 mg, 0.10 mmol | flammable, toxic |
| • Cyclopentadiene, 170 μL , 2.0 mmol | flammable, toxic |
| • Methacrolein, 170 μL , 2.0 mmol | flammable, toxic |
| • 2,6-Di- <i>tert</i> -butylpyridine, 12 μL , 0.05 mmol | irritant |
| • Dichloromethane, 2 mL | harmful by inhalation |
| • <i>n</i> -Hexane | flammable, irritant |
| • Ether | flammable, irritant |

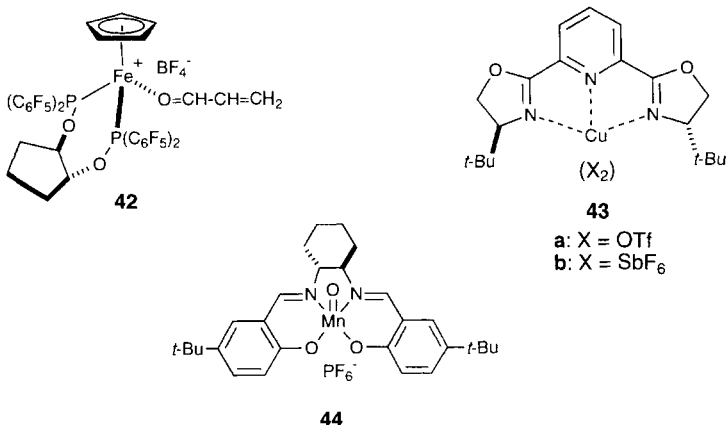
1. Prepare a catalyst solution of phosphite-Fe-acrolein complex (110 mg, 0.10 mmol) and 2,6-di-*tert*-butylpyridine (12 μL , 0.05 mmol) in dichloromethane (2 mL) at -40°C under argon atmosphere.
2. Add methacrolein (170 μL , 2.0 mmol) and stir for 15 min, then add cyclopentadiene (170 mL, 2.0 mmol) slowly.
3. After stirring for 20 h at -20°C , add hexane to precipitate the catalyst and wash three times with the same solvent.
4. Expose the combined organic phases to air for removing traces of residual

Protocol 3. Continued

- catalyst by oxidation. Filter through a pad of Celite and then remove the organic solvent with a rotary evaporator.
5. Apply the crude product to a flash silica gel column with *n*-hexane–ether (10:1) to obtain pure product in 62% yield (174 mg, 97% *exo*, 90% ee).
 6. Determine the *exo/endo* ratio by ^1H NMR; δ 9.40 (*endo*), 9.70 (*exo*).^a
 7. Determine the enantiomeric excess by capillary GC using PEG-25M, column temperature 80 °C; t_R = 36.4 (*exo-2R*), 38.1 min (*exo-2S*), 25.5, 33.1 min (*endo*), after converting the adduct to the corresponding (*R,R*)-2,4-dimethyl-1,3-dioxane. A mixture of the Diels–Alder adduct (10–20 mg), (*R,R*)-2,4-pentanediol (1.5 equiv), triethyl orthoformate (1.1 equiv), and *p*-toluene-sulfonic acid (1–2 mg) in dry benzene (1 mL) was stirred at room temperature for several hours (TLC check).^a

^aFuruta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481–1483. Determine the *exo/endo* ratio by capillary GC using PEG-20M, column temperature 100 °C; t_R = 8.7 min (*exo*), 10.3 min (*endo*).

Evans *et al.*³⁰ introduced the copper(II)-bis(oxazolinyl)pyridine (pybox) catalysts, **43**, (Scheme 13.15) for the same purpose, especially to find the importance of the counterion effect. They anticipated that the Cu–pybox has only one accessible co-ordination site for the carbonyl dienophiles, such as acrolein derivatives, because pybox is a tridentate ligand.^{31,32} The addition of methacrolein and cyclopentadiene with the Cu–pybox-*tb*, **43a**, (X = OTf) (5 mol%) at –20 °C for 120 h gave the adducts in the ratio of the *exo:endo*, 96:4 and 85% ee for the *exo* isomer (Table 13.2). However, the reaction with the Cu–pybox-*tb*, **43b** (X = SbF₆) proceeds only for 8 h to give 95% yield of



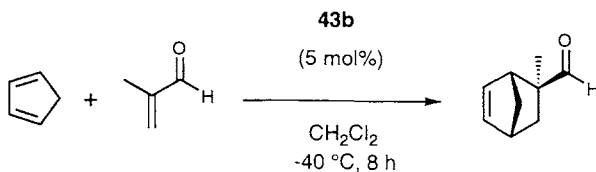
Scheme 13.15

the *exo*-isomer with 92% ee (Protocol 4) (Scheme 13.16). The same tendency was observed for bromoacrolein. The same counterion acceleration effect for the Diels–Alder reaction of the acylimide **30** with the Cu–bisoxazoline **35** ($X = \text{OTf} \Rightarrow \text{SbF}_6$) as also been shown.³⁰ The SbF_6 complex of **35** gave high yields of 96% for the less reactive β -substituted acylimides **30** ($R = \text{Ph}$ and Cl) with 95–96% ees.

Protocol 4.

Asymmetric Diels–Alder reaction of methacrolein with cyclopentadiene catalysed by chiral bis(oxazolinyl)pyridine–Cu(II) complex³⁰ (Scheme 13.16)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 13.16

Equipment

- Magnetic stirrer
- Syringes
- Cooling bath with dry ice–acetone
- Schlenk flask (10 mL)
- Vacuum/inert gas source (argon)

Materials

- | | |
|---|---|
| <ul style="list-style-type: none"> • Cyclopentadiene, 158 mg, 2.4 mmol • Methacrolein, 140 mg, 2.0 mmol • <i>tert</i>-Butyl[pyridine-bis(oxazoline)], 33 mg, 0.10 mmol • Copper bromide, 22 mg, 0.10 mmol • Silver hexafluoroantimonate, 69 mg, 0.20 mmol • Dichloromethane, 4 mL | <p>flammable, toxic</p> <p>flammable, corrosive</p>
<p>irritant, hygroscopic</p> <p>corrosive, hygroscopic</p> <p>harmful by inhalation</p> |
|---|---|

1. Prepare a catalyst solution of powdered copper bromide (22 mg, 0.10 mmol), silver hexafluoroantimonate (69 mg, 0.20 mmol) and *tert*-butyl[pyridine-bis(oxazoline)] (33 mg, 0.10 mmol) in dichloromethane (4 mL). After stirring for 6 h, filter through a plug of cotton to give a clear blue–green solution.
2. After cooling of the catalyst solution to -78°C , add methacrolein (140 mg, 2.0 mmol) and cyclopentadiene (158 mg, 2.4 mmol): >95% yield, 97% *exo*, 92% ee.

Protocol 4. Continued

3. Determine the *exo/endo* ratio by capillary GC (DB-1701, 110°C, 5 psi), t_R = 5.40 (*exo*), 6.01 min (*endo*). Determine the enantiomeric excess by capillary GC (DB-1701, 110°C, 5 psi) after the adduct was converted into the corresponding (*R,R*)-2,4-dimethyl-1,3-dioxane, t_R = 29.89 (2*S*), 30.05 min (2*R*).

Very interestingly, optically active oxo(salen)manganese(V) complex **44** serves as a Lewis acid to catalyse the Diels–Alder reaction of bromoacrolein and cyclopentadiene in 93% yield (98:2 = *exo:endo*) with 68% ee for the *exo* isomer.³³

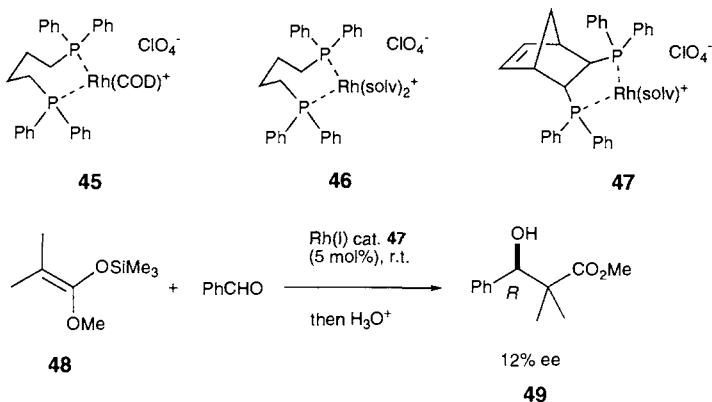
4. Asymmetric aldol condensations

A crossed aldol reaction of trimethylsilyl enol ethers and certain aldehydes catalysed by achiral cationic rhodium–diphosphine catalyst was first reported by Sato *et al.*³⁴ The reaction needs a relatively high temperature, 100°C for 15 h, but 2 mol% of $[(\text{COD})\text{Rh}(\text{DPPB})]^+\text{ClO}_4^-$ **45** (COD = 1,5-cyclooctadiene and DPPB = diphenylphosphinobutane) (Scheme 13.17) catalyses the reaction of $\text{Me}_3\text{SiOC}(\text{CH}_3)=\text{CH}_2$ and *n*-hexanal resulting in 74% yield of the corresponding adduct. They showed no catalytic activity of $\text{HRh}(\text{PPh}_3)_n$ ($n = 3$ and 4), $\text{HClRu}(\text{PPh}_3)_3$, and $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ for that purpose, and they proposed a rhodium enolate as an intermediary.

Reetz *et al.*³⁵ reported similar results of the aldol reaction with more active cationic rhodium–diphosphine complex, $[(\text{solvent})_n\text{Rh}(\text{DPPB})]^+$, **46**, which was generated by treating the corresponding $[(\text{COD})\text{Rh}(\text{DPPB})]^+$ complex under a hydrogen atmosphere. The catalysed reaction of a ketene silylacetal, $\text{Me}_3\text{SiOC}(\text{OMe})=\text{CMe}_2$, **48**, and benzaldehyde with the rhodium catalysts (5 mol%) resulted in 81% yield of the adduct **49** for only 2 h at 22°C. It was pointed out that the mechanism of the aldol reaction may involve co-ordination of aldehyde molecules at the metal leading to activation of the aldehydes, but they did not deny the metal–enolate intermediate. They also applied the aldol reaction to an asymmetric version. The chiral Rh–Norphos cationic complex **47** (5 mol%) catalyses the aldol condensation of the ketene silylacetal **48** and benzaldehyde in good yields (>75%) but in a low enantioselectivity (Scheme 13.17).

Bosnich and colleagues has developed the achiral cationic ruthenium-based complex, $[\text{Ru}(\text{salen})(\text{NO})(\text{H}_2\text{O})]^+\text{SbF}_6^-$, **21** as a powerful transition-metal Lewis acid catalyst for the crossed-aldol reaction at 25°C in nitromethane solution, as well as the Diels–Alder reaction with the same catalyst described in the preceding section.^{17,36} The reaction of the ketene silylacetal **48** and benzaldehyde with **21** (1 mol%) for only 3 min resulted in over 90% reaction (Protocol 5) (Scheme 13.18).

13: Other transition metal reagents

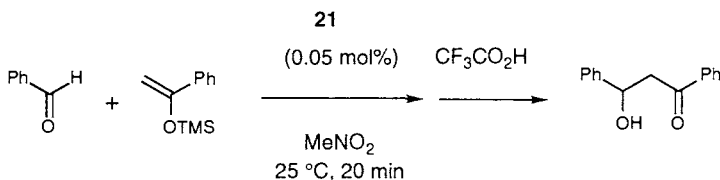


Scheme 13.17

Protocol 5.

Mukaiyama crossed-aldol reaction of 1-phenyl-1-[(trimethylsilyl)oxy]ethylene with benzaldehyde catalysed by [Ru(salen)(NO)H₂O]SbF₆ Complex³⁶ (Scheme 13.18)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 13.18

Equipment

- Magnetic stirrer
- Syringes
- Cooling bath with dry ice-acetone
- Schlenk flask (10 mL)
- Vacuum/inert gas source (argon)

Materials

- [Ru(salen)(NO)H₂O]SbF₆, 0.31 mg, 0.48 μmol
- Benzaldehyde, 104 mL, 1 mmol
- 1-Phenyl-1-[(trimethylsilyl)oxy]ethylene, 204 μL , 1 mmol
- Trifluoroacetic acid, 100 μL , 0.59 mmol
- Nitromethane, 700 μL , 2 mL
- Water, 3 mL
- Dichloromethane

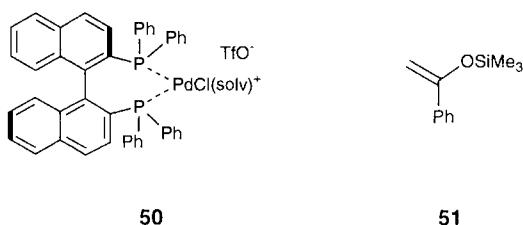
toxic, cancer-suspect agent
moisture-sensitive, irritant
corrosive, toxic
flammable

toxic, irritant

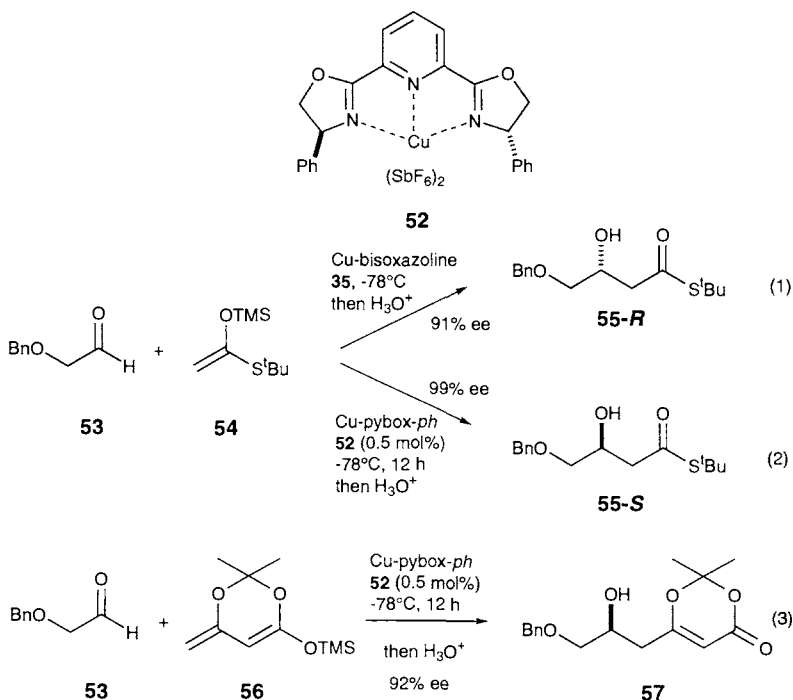
Protocol 5. Continued

1. Prepare a catalyst solution of $[\text{Ru}(\text{salen})(\text{NO})\text{H}_2\text{O}]\text{SbF}_6$,¹⁶ (0.31 mg, 0.48 μmol) in nitromethane (700 μL).
2. Add benzaldehyde (104 μL , 1 mmol) and 1-phenyl-1-[(trimethylsilyl)oxy]ethylene (204 μL , 1 mmol).
3. After stirring for 20 min at 25°C, dilute with nitromethane (2 mL) and stir with trifluoroacetic acid (100 μL) for 15 min.
4. Add water (3 mL) and stir vigorously for 15 min, then dilute with dichloromethane.
5. Extract the organic layer with dichloromethane and concentrate under reduced pressure.
6. Take up in dichloromethane and pass through a short column of Florisil, and remove the eluent solvent under reduced pressure to give the product, $\text{PhCOCH}_2\text{CH}(\text{OH})\text{Ph}$, (0.21 g, 92% yield) as an oil, pure by ^1H NMR.

The catalytic asymmetric aldol reaction with chiral palladium catalysts was reported by Shibasaki.^{37,38} The cationic complex $\text{PdCl}[(R)\text{-Binap}]^+$, **50** (Scheme 13.19) in DMF- H_2O catalysed the condensation of the acetophenone silyl enol ether **51** and benzaldehyde at 23°C to give 96% yield of the adduct with 71–73% ee. However, they concluded that the reaction does not involve a palladium Lewis acid catalyst, and that the reaction is the first example of the asymmetric aldol reaction via $\text{Pd}(\text{II})$ enolate species.

**Scheme 13.19**

A remarkable system was discovered using copper(II) complexes as Lewis acid catalysts, which activates α -alkoxy aldehydes through bidentate coordination.^{39,40} Evans *et al.* applied the cationic complexes of the copper(II)-bisoxazoline, **35** (OTf and SbF_6) and the copper(II)-pybox-*ph*, **52**, as catalysts (Scheme 13.20). The α -(benzyloxy)acetaldehyde, **53**, and the silylketene acetal, **54**, reacted in the presence of $\text{Cu}(\text{II})(\text{OTf})_2$ -bisoxazoline-*tb*-(*S,S*), **35** (5 mol%) at -78°C to give the (*R*)-adduct **55-R** in 91% ee (Scheme 13.20(1)). In contrast, the combination catalyst **53** of $\text{Cu}(\text{II})(\text{SbF}_6)_2$ (5 mol%) and pybox-*ph*-(*S,S*) gave the (*S*)-adduct **55-S** in 99% ee (Protocol 6) (Scheme



Scheme 13.20

13.20(2). Upon optimization, 0.5 mol% of the catalyst **53** catalysed the reaction for 12 h giving more than 94% yield and 92–98% ees for the several silyl enoethers, for example, from **56** to **57** in 92% ee (Scheme 13.20(3)).

Protocol 6.

Asymmetric mukaiyama-aldol reaction of (benzyloxy)acetaldehyde with 1-*tert*-butylthio-[(trimethylsilyl)oxy]ethene catalysed by chiral bis(oxazolinyl)pyridine-Cu(II) complex (Scheme 13.20^{39,40})

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

Equipment

- Magnetic stirrer
- Syringes
- Cooling bath with dry ice–acetone
- Schlenk flask (10 mL)
- Vacuum/inert gas source (argon)

Materials

- Phenyl[pyridine-bis(oxazoline)], 9.2 mg, 0.025 mmol
- Copper chloride, 3.4 mg, 0.025 mmol
- Silver hexafluoroantimonate, 17.2 mg, 0.05 mmol

**irritant, hygroscopic
corrosive, hygroscopic**

Protocol 6. Continued

- Dichloromethane, 4 mL harmful by inhalation
- (Benzyloxy)acetaldehyde, 82.1 mg, 0.50 mmol
- 1-*tert*-Butylthio-[(trimethylsilyl)oxy]ethene, 122.7 mg, 0.60 mmol
- 1 M HCl toxic
- Tetrahydrofuran flammable, irritant

1. Prepare a catalyst solution of powdered copper chloride (3.4 mg, 0.025 mmol), silver hexafluoroantimonate (17.2 mg, 0.05 mmol) and phenyl[pyridine-bis(oxazoline)] (9.2 mg, 0.025 mmol) in dichloromethane (4 mL). After stirring for 4 h at room temperature, filter through a plug of cotton.
2. Add (benzyloxy)acetaldehyde (82.1 mg, 0.50 mmol) and 1-*tert*-butylthio-[(trimethylsilyl)oxy]ethene (122.7 mg, 0.60 mmol) at -78°C .
3. After stirring for 12 h at -78°C , filter the reaction mixture through silica, then hydrolyse silyl ether with 1 M HCl in tetrahydrofuran to give pure product in 100% yield (99% ee).
4. Determine the enantiomeric excess by HPLC analysis (Daicel CHIRALCEL OD-H).

Absolute configuration was assigned by comparison of optical rotation, see; Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 2363–2364.

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