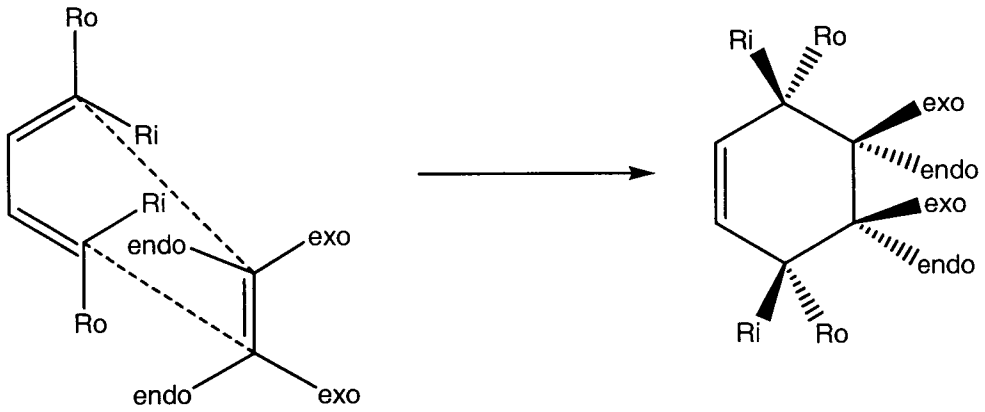
# Catalysis of 1,3-Dipolar Cycloadditions of Nitrones

SED Group Meeting
April 6, 2004
Monica Jo Patten

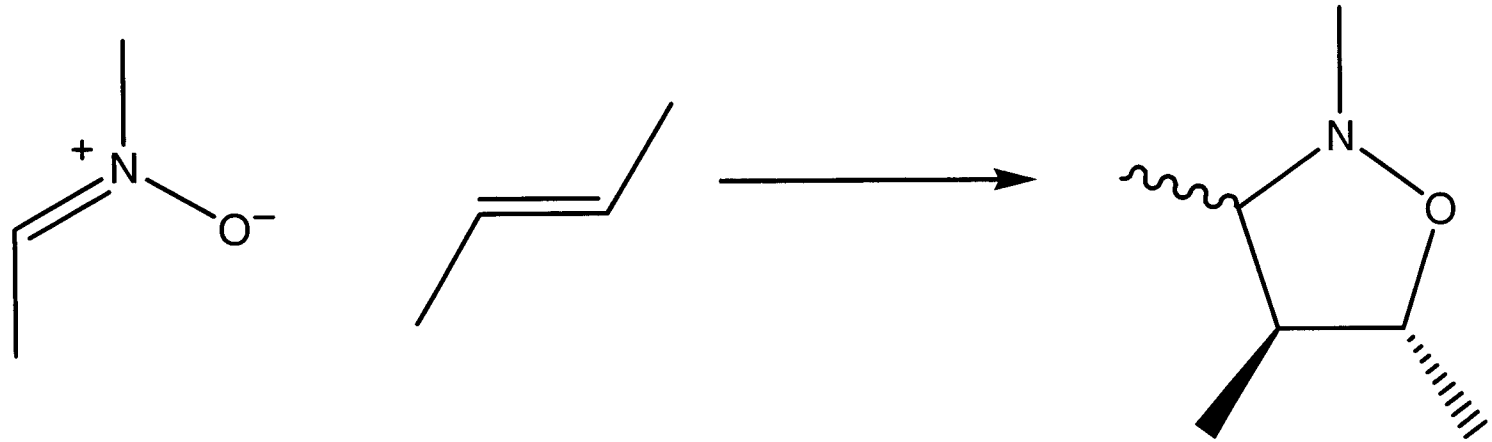
# Cycloadditions:

- Multiple stereocenters
- Multiple bond formation
- Functionality

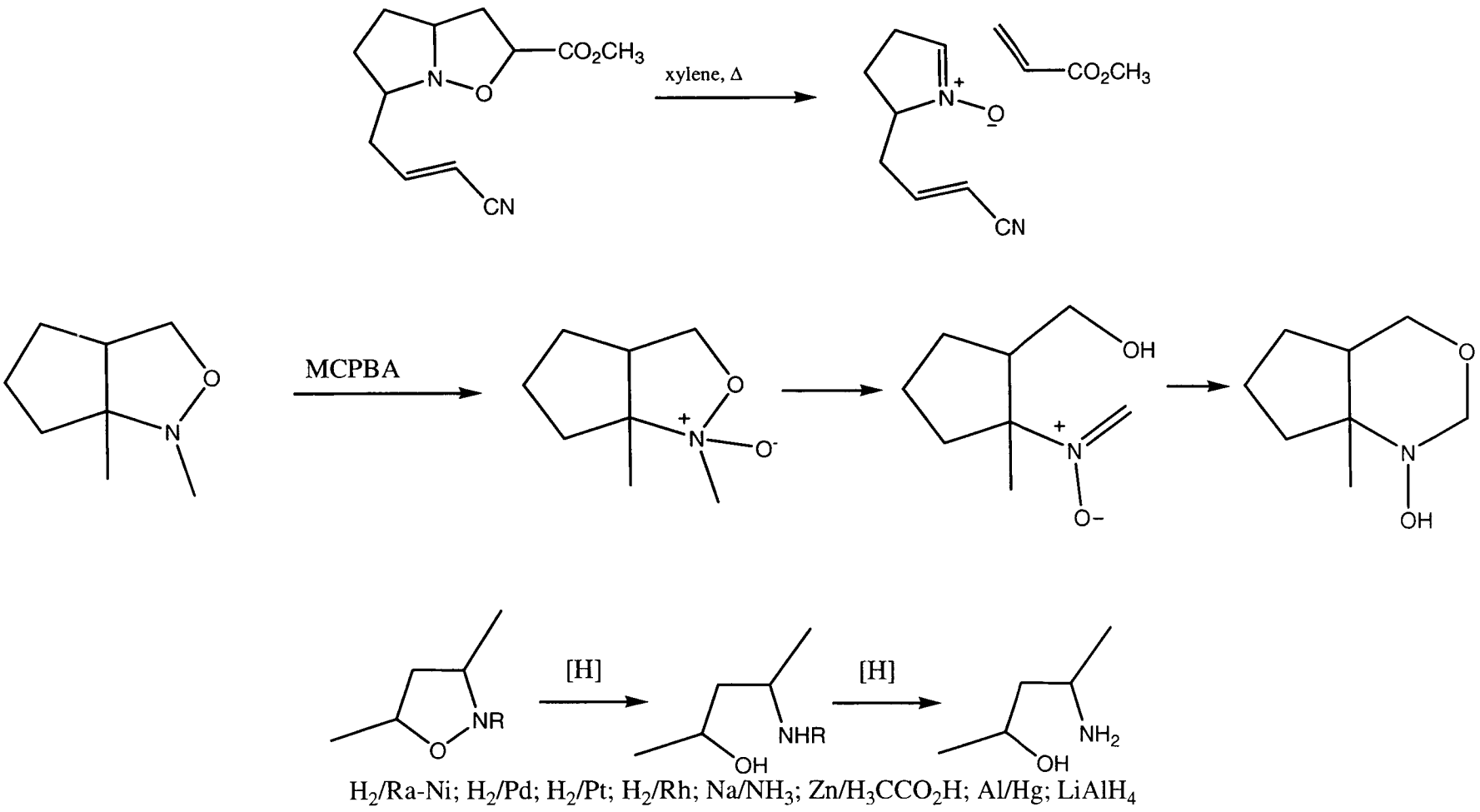


# Applications of Nitrone 1,3 dipolar additions

Isoxazolidine:

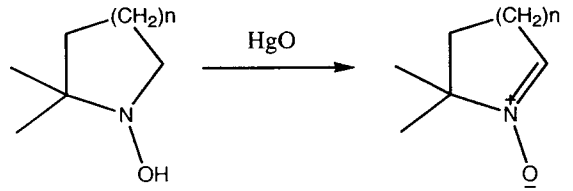


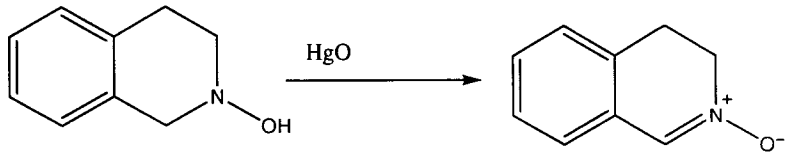
# Masked functionality of isoxazolidines



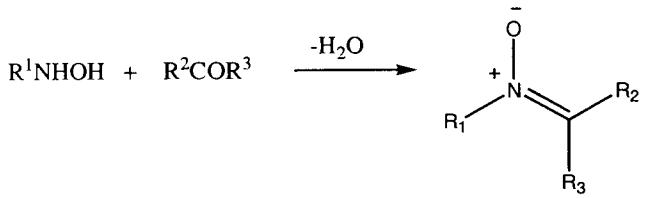

Torssell, K.B.G. Nitrile Oxides, Nitrones, and Nitronates: Novel Strategies in Synthesis. VCH: Weinheim, 1988.

# Preparation of Nitrones

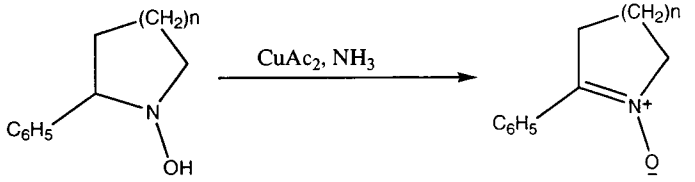


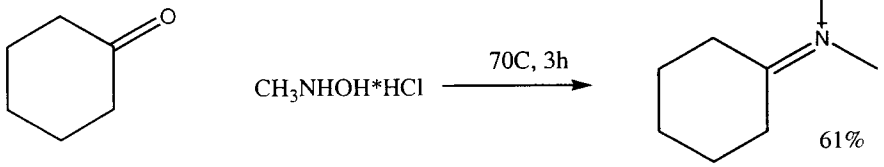




Wide generality

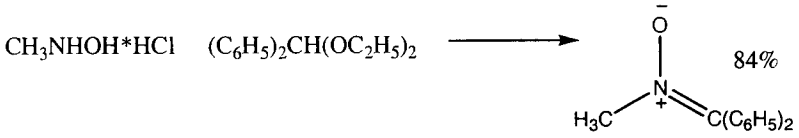



$R_1$=phenyl
$R_2$=n-$C_3H_7$
$R_3$=H
80% yield

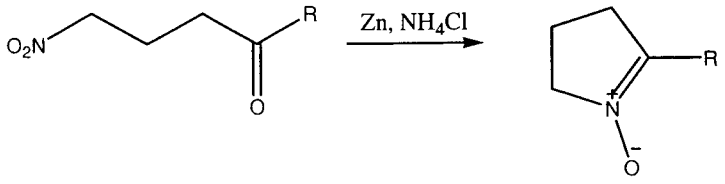



61%



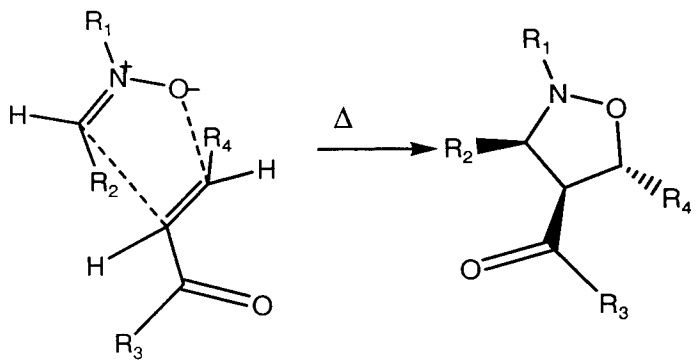

84%

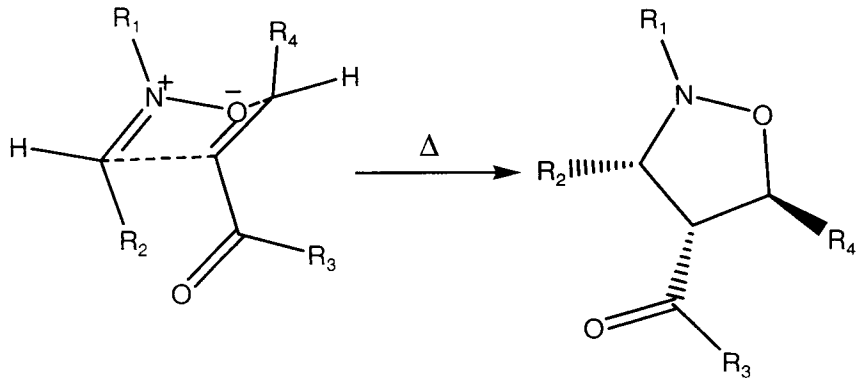



Confalone, P.; Huie, E. "The [3+2] Nitrone Olefin Cycloaddition Reaction. " Org. Reactions. Vol 36.

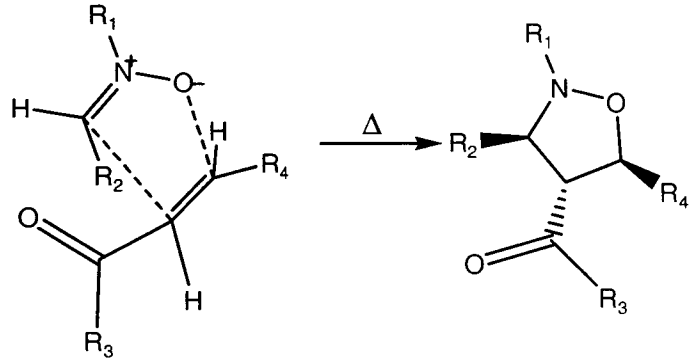
# 1,3-Dipolar Cycloaddition Stereochemistry

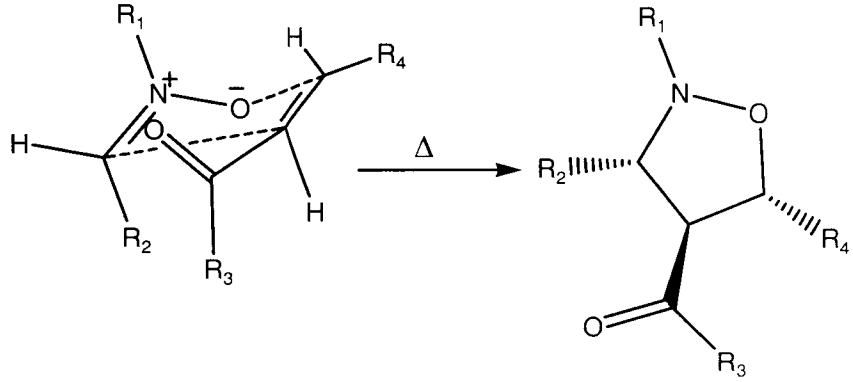
Exo TS:



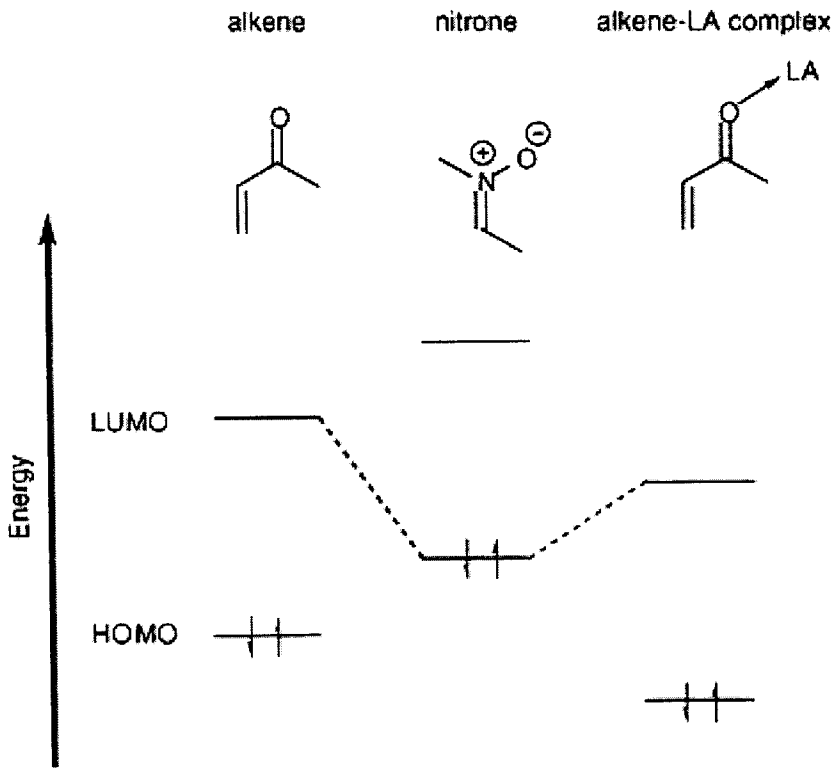

Endo TS:

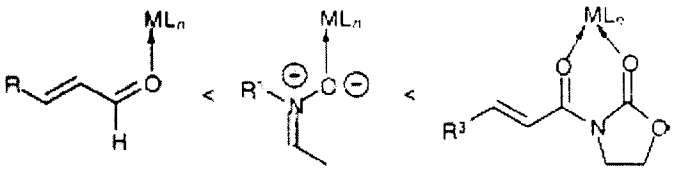


# 1,3-Dipolar Nitrone Cycloaddition Reaction: Electronics

## Normal electron-demand reactions:




Gothelkf, K.; Jorgensen, K. Chem. Commun., 2000, 1449-1458.; Gothelf, K.; Jorgensen, K. J. Org. Chem, 1994, 59, 5687-5691.

# Early usage of chiral catalysts for nitrone/alkene cycloadditions

**Table 1. Catalytic Effects of Ti(*i*-OPr)$_2$Cl$_2$ and Dichlorotitanium Alkoxides 5a-i on the 1,3-Dipolar Cycloaddition Reaction of 1a with 2a[a]**

| entry | catalyst (mol %) | solvent | *T* (°C) | convn (%) | *exo*/*endo* ratio | ee (%) *exo*-**3a** (*endo*-**3a**) |
|---|---|---|---|---|---|---|
| 1 | | $CHCl_3$ | 50 | 39 | 91:9 | |
| 2 | Ti(*i*-OPr)$_2$Cl$_2$ (100) | $CH_2Cl_2$ | rt | 68 | 87:13 | |
| 3 | **5a** (100) | toluene | rt | 73 | 81:19 | 4 |
| 4 | **5b** (100) | toluene | rt | 83 | 90:10 | 8 |
| 5 | **5c** (100) | toluene | rt | 91 | 94:6 | 19 |
| 6 | **5d** (100) | toluene | rt | 85 | 95:5 | 29 |
| 7 | **5e** (100) | $CH_2Cl_2$ | rt | 90 | 89:11 | 47 |
| 8 | **5e** (100) | $CH_2Cl_2$ | 0 | 85 | 89:11 | 56 |
| 9 | **5e** (100) | $CH_2Cl_2$ | −10 | <10 | | |
| 10 | **5e** (10) | $CH_2Cl_2$ | 0 | 83 | 89:11 | 51 |
| 11 | **5e** (10) | toluene | 0 | 94 | 90:10 | 58 |
| 12 | **5f** (100) | $CH_2Cl_2$ | rt | 81 | 77:23 | 20 |
| 13 | **5g** (100) | $CH_2Cl_2$ | rt | 78 | 57:43 | 27 (45) |
| 14 | **5h** (100) | $CH_2Cl_2$ | rt | 72 | 87:13 | 34 |
| 15 | **5i** (100) | toluene | rt | 93 | 88:12 | 22 |
| 16 | **5e** (10)–$ZnCl_2$ (100) | toluene | rt | 71 | 37:63 | (43) |

[a] Reaction conditions: alkene **1a** (0.1 mmol) and nitrone **2a** (0.11 mmol) were dissolved (1 mL solvent). The dissolved catalyst (0.5 mL solvent) was added, and the reaction was stirred for 20 h.

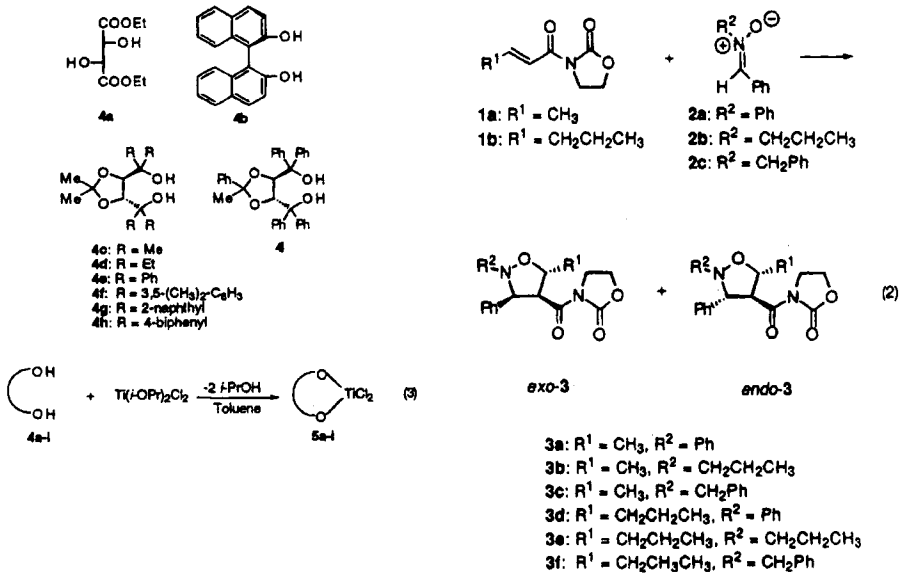


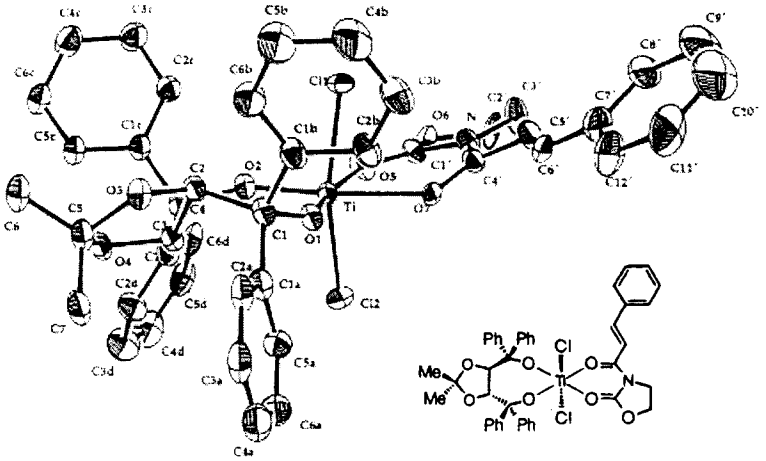

**Table 2. Enantioselective 1,3-Dipolar Cycloaddition Reaction for Alkenes 1a,b with Nitrones 2a-c Catalyzed by 5e[a]**

| entry | alkene | nitrone | *T* (°C) | product | yield (*exo*/*endo*)[b] (%) | ee[c] *exo*-**3**/*endo*-**3** (%) |
|---|---|---|---|---|---|---|
| 1 | **1a** | **2a** | 0 | **3a** | 94 (85:9) | 60/62 |
| 2 | **1a** | **2b** | rt | **3b** | 84 (51:33) | 15/62 |
| 3 | **1a** | **2c** | rt | **3c** | 71 (38:33) | 27/59 |
| 4 | **1b** | **2a** | rt | **3d** | 71 (62:9) | 39/48 |
| 5 | **1b** | **2b** | rt | **3e** | 80 (40:40) | 10/35[d] |
| 6 | **1b** | **2c** | rt | **3f** | 85 (44:41) | 24/53 |

[a] Reaction conditions: see Experimental Section. [b] Isolated yields. [c] The ee was determined by $^1$H NMR using Eu(hfc)$_3$ as chiral shift reagent. [d] Ee determined with some uncertainty.

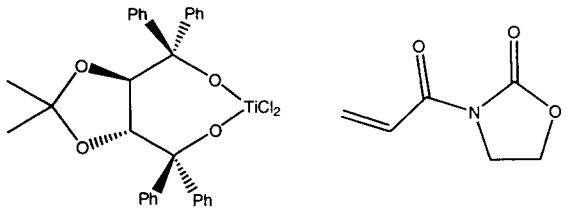
Gothelf, K., Jorgensen, K. J. Org. Chem., 1994, 59(19), 5687-5691.

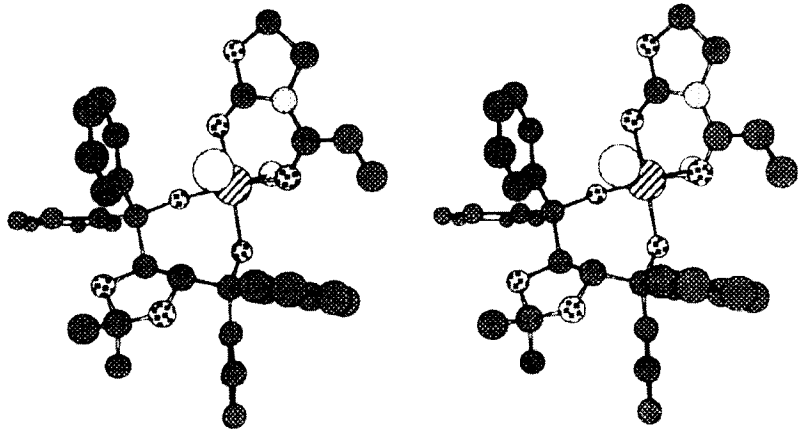
# Ti-X2 Catalysis: Catalyst Dipolarophile Complex



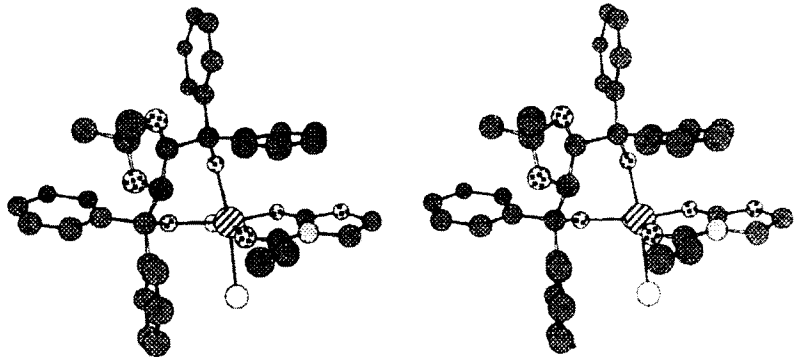
Jorgensen 1995

DiMare 1995





Symmetrical adduct



Asymmetrical adduct

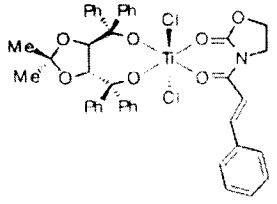
Gothelf, K., Hazell, R. Jorgensen, K. JACS, 1995, 117, 4435-4436.; Haase, C., Sarko, C., DiMare, M. J. Org Chem, 1995, 60, 1777-1787

# Ti-$X_2$ Catalysis: Diels Alder

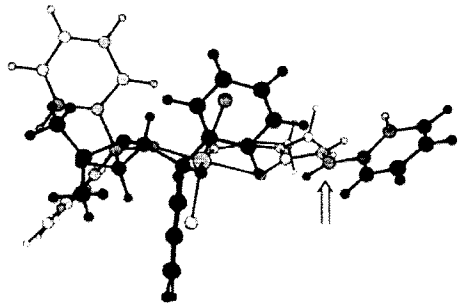
**Table 1. Asymmetric Ti–TADDOLate-Catalyzed Diels–Alder Reactions of Cyclopentadiene (2) with *N*-Acyloxazolidinones 3a,b[a]**

| entry | alkene | catalyst/ amount (%) | product (*endo*:*exo*)[b] | ee (%) (*endo*)[c] | reaction temp (°C) | *endo*:*exo*[d] | ee (%) (*endo*)[d] |
|---|---|---|---|---|---|---|---|
| 1 | | **6** (100) | **4a** (79:21) | 45 | 0 | | |
| 2 | **3a** | **6** (10) | **4a** (79:21) | 54 | −20 | | |
| 3 | **3a** | **7a** (10) | **4a** (78:22) | 49 | 0 | | |
| 4 | **3a** | **7b** (50) | **4a** (42:58) | 37 | −20 | | |
| 5 | **3a** | **7c** (10) | **4a** (83:17) | 60 | −20 | 88:12[3g] | 64[3g] |
| 6 | **3a** | **7d** (50) | **4a** (53:47) | 31 | −20 | | |
| 7 | **3b** | **6** (10) | **4b** (86:14) | 51 | −20 | | |
| 8 | **3b** | **7a** (10) | **4b** (85:15) | 42 | −20 | 93:7[e]<br>83:17[8] | 55[e]<br>44[8] |
| 9 | **3b** | **7b** (50) | **4b** (76:34) | 43 | −20 | | |
| 10 | **3b** | **7c** (10) | **4b** (89:11) | 86 | −20 | 92:8[3g]<br>87:13[8] | 91[3g]<br>86[8] |
| 11 | **3b** | **7d** (50) | **4b** (67:33) | 21 | −20 | | |

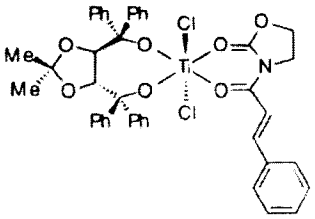
[a] The reactions were run on a 0.1 mmol scale in toluene for 48–72 h. For further details, see the Experimental Section. [b] The *endo*:*exo* ratio was determined by $^1$H NMR spectroscopy on the crude product. [c] The ee was determined by HPLC on a Diacel Chiralpak AD column. [d] Results obtained by others for identical reactions. [e] The catalyst was applied in 100 mol %, see ref 3g.



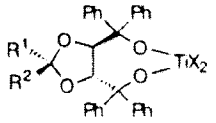
a



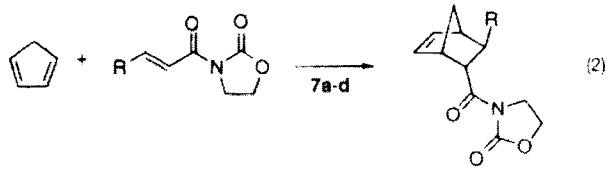
b



6



**7a**: $R^1 = R^2$ = Me, X = Cl
**7b**: $R^1 = R^2$ = Me, X = OTs
**7c**: $R^1$ = Me, $R^2$ = Ph, X = Cl
**7d**: $R^1$ = Me, $R^2$ = Ph, X = OTs



(2)

2

**3a**: R = Ph
**3b**: R = Me

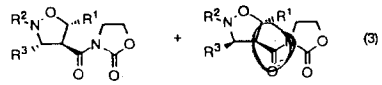
**4a**: R = Ph
**4b**: R = Me

Gothelf, K, Jorgensen, K. J. Org. Chem. 1995, 60, 6847-6851.

# Ti-$X_2$ catalysis-1,3 Dipolar addition to nitrones

**1a**: $R^1 = CH_3$
**1b**: $R^1 = CH_2CH_2CH_3$

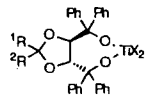
**2a**: $R^2 = R^3 = Ph$
**2b**: $R^2 = CH_2CH_2CH_3$, $R^3 = Ph$
**2c**: $R^2 = CH_2Ph$, $R^3 = Ph$
**2d**: $R^2 = Ph$, $R^3 = p$-tolyl



(3)

*endo*-3 *exo*-3

**3a**: $R^1 = CH_3$, $R^2 = Ph$, $R^3 = Ph$
**3b**: $R^1 = CH_3$, $R^2 = CH_2CH_2CH_3$, $R^3 = Ph$
**3c**: $R^1 = CH_3$, $R^2 = CH_2Ph$, $R^3 = Ph$
**3d**: $R^1 = CH_3$, $R^2 = Ph$, $R^3 = p$-tolyl
**3e**: $R^1 = CH_2CH_2CH_3$, $R^2 = Ph$, $R^3 = Ph$
**3f**: $R^1 = CH_2CH_2CH_3$, $R^2 = CH_2CH_2CH_3$ $R^3 = Ph$
**3g**: $R^1 = CH_2CH_3CH_3$, $R^2 = CH_2Ph$, $R^3 = Ph$
**3h**: $R^1 = CH_2CH_3CH_3$, $R^2 = Ph$, $R^3 = p$-tolyl



**5a**: $R^1 = R^2 = Me$, X = Cl
**5b**: $R^1 = Me$, $R^2 = Ph$, X = Cl
**5c**: $R^1 = R^2 = Me$, X = O*i*-Pr
**5d**: $R^1 = R^2 = Me$, X = Br
**5e**: $R^1 = R^2 = Me$, X = OTf
**5f**: $R^1 = R^2 = Me$, X = OTos
**5g**: $R^1 = Me$, $R^2 = Ph$, X = OTos

**Table 1.** Catalytic Effects of $TiX_2$–TADDOLate Complexes on the 1,3-Dipolar Cycloaddition Reaction of Alkene **1a** with Nitrone **2a**

| entry | catalyst | amount (%) | conv[a] (time (h)) | *endo*:*exo*[a] | ee (%), *endo*[b] (*exo*)[c] |
|---|---|---|---|---|---|
| 1 | **5a** | 10 | 98 (48) | 10:90 | 62 (60) |
| 2 | **5b** | 100 | 93 (20) | 12:88 | – (22) |
| 3 | **5c** | 100 | 0 | – | – |
| 4 | **5d** | 10 | 98 (20) | 64:36 | 76 (64) |
| 5 | **5e** | 10 | 73 (20) | 79:21 | 0 |
| 6 | **5f** | 10 | <10 (20) | – | – |
| 7 | **5f** | 25 | 55 (48) | 82:18 | 90 |
| 8 | **5f** | 50 | 99 (48) | >95:<5 | 93 |
| 9 | **5g** | 50 | 86 (48) | 85:15 | 85 |

[a] Conversions and *endo*:*exo* ratios were determined by $^1$H NMR spectroscopy of the crude product. [b] The enantiomeric excess of *endo*-**3a** was determined by HPLC (Daicel Chiralcel OD using hexane/*i*-PrOH, 90:10). [c] The ee was determined by $^1$H NMR spectroscopy using $Eu(hfc)_3$ as the chiral shift reagent.

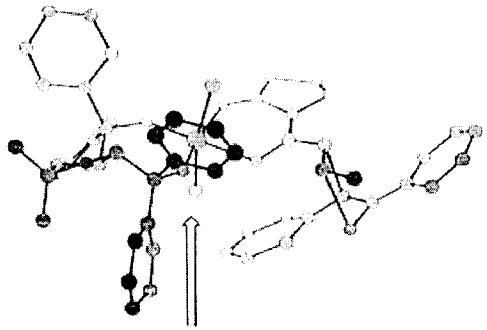


**Figure 1.** Proposed approach of nitrone **2a** to alkene **1a** coordinated to the $TiCl_2$–TADDOLate catalyst **5a**, leading to *exo*-**3a**. The arrow shows the axial chloride ligand which is exchanged with bulkier ligands.

**Table 2.** $Ti(OTos)_2$–TADDOLate-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition Reactions of Alkenes **1a,b** with Nitrones **2a–d** in the Presence of 50 mol % Catalyst

| entry[a] | alkene | nitrone | product | yield[b] (%) | *endo*:*exo*[c] | ee (%), *endo*[d] |
|---|---|---|---|---|---|---|
| 1 | **1a** | **2a** | **3a** | 61 | >95:<5 | 93 |
| 2 | **1a** | **2b** | **3b** | 56 | >95:<5 | 40 |
| 3 | **1a** | **2c** | **3c** | 54 | >95:<5 | 51 |
| 4 | **1a** | **2d** | **3d** | 71 | >95:<5 | 91 |
| 5 | **1b** | **2a** | **3e** | 63 | >95:<5 | 93 |
| 6 | **1b** | **2b** | **3f** | 66 | >95:<5 | 53 |
| 7 | **1b** | **2c** | **3g** | 58 | >95:<5 | 56 |
| 8 | **1b** | **2d** | **3h** | 55 | >95:<5 | 92 |

[a] The reactions were performed on a 0.5 mmol scale in toluene at 0 °C, employing 50 mol% catalyst. For further details see the Experimental Section. [b] Isolated yields. [c] The *endo*:*exo* ratio was determined by $^1$H NMR spectroscopy. [d] The ee of the *endo*-isomer was determined by HPLC using a Daicel Chiralcel OD column.

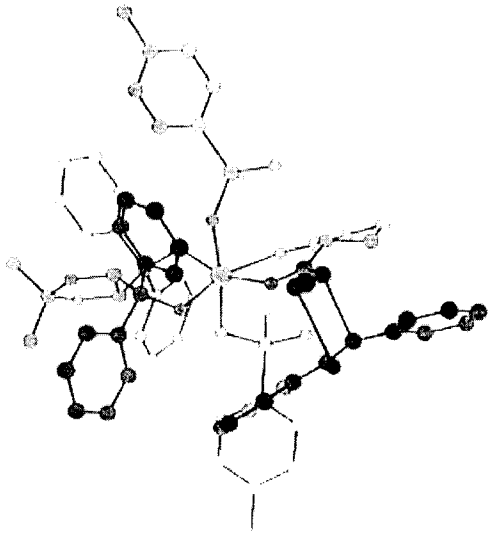


**Figure 2.** Proposed approach of nitrone **2a** to alkene **1a** coordinated to the $Ti(OTos)_2$–TADDOLate catalyst **5f**, leading to *endo*-**3a**.

Gothelf, K, Thomsen, I., Jorgensen, K. J. Am. Chem. Soc. 1996, 118, 59-64.

# Magnesium catalysts

**Table 1. Influence of Different Metal–Ligand Complexes on the Diastereoselectivity of the Reaction of 3-Crotonoyl-1,3-oxazolidin-2-one (1a) with Benzylidenephenylamine *N*-Oxide (2a)[a]**

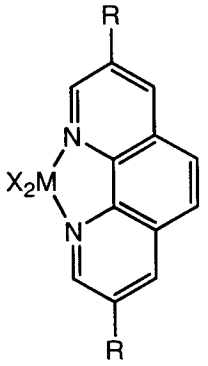
| entry | catalyst[b] | conversion[c] (%) | *endo*-**3a**:*exo*-**3a** |
|---|---|---|---|
| 1 | | <2 | |
| 2 | $Ti(i\text{-}OPr)_2Cl_2$ | 68 | 13:87 |
| 3 | **7** | 91 | 5:95 |
| 4 | **5a** | 63 | 81:19 |
| 5 | **5b**[d] | <2 | |
| 6 | $MgI_2–I_2$ | >90 | 15:85 |
| 7 | **6a** | >90 | >95:<5 |
| 8 | **6b**[d] | >90 | >95:<5 |

[a] Reaction conditions: **1a** (0.1 mmol) and **2a** (0.125 mmol) were mixed in $CH_2Cl_2$ (2 mL) with 50 mg of 4 Å powdered molecular sieves. After the mixture was stirred for 15 min, the catalyst was added. For further details see the Experimental Section. [b] The catalysts were applied in 10 mol %. [c] Reaction time 20 h. [d] 2,9-Dimethylphenanthroline is used as ligand instead of **4a**.

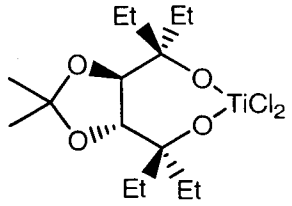
**Table 2. *Endo*-Selective Reactions of Alkenes 1a,b with Nitrones 2a,b in the Presence of 6a as the Catalyst**

| entry | alkene | nitrone | molar scale[a] (mmol) | product | conversion[b] (%) | *endo*:*exo*[c] |
|---|---|---|---|---|---|---|
| 1 | **1a** | **2a** | 0.1 | **3a** | >90 | >95:<5 |
| 2 | **1a** | **2b** | 0.1 | **3b** | >90 | >95:<5 |
| 3 | **1b** | **2a** | 0.1 | **3c** | >90 | >95:<5 |
| 4 | **1b** | **2b** | 0.1 | **3d** | 64 | >95:<5 |
| 5 | **1a** | **2a** | 0.5 | **3a** | 88[d] | 93:7 |
| 6 | **1a** | **2a** | 1.0 | **3a** | 75[d] | 84:16 |

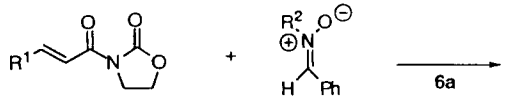
[a] The molar scale is defined from **1** which is mixed with 1.25 mol equiv of **2** in $CH_2Cl_2$ after the addition of 50 mg of 4 Å powdered molecular sieves per 0.1 mmol of **1**. After the mixture was stirred for 15 min, 10 mol % **6a** was added. [b] Reaction time 48 h. [c] Determinated by $^1H$ NMR spectroscopy of the crude product. [d] Isolated yields of the *endo*-isomer.




**5a** M=Cu, R=H, X=OTs
**5b** M=Cu, R=Me, X=OTs
**6a** M=Mg, R=H, X=I
**6b** M=Mg, R=Me, X=I

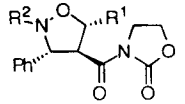



**7**




**1a**: $R^1 = CH_3$
**1b**: $R^1 = CH_2CH_2CH_3$

**2a**: $R^2 = Ph$
**2b**: $R^2 = CH_2Ph$



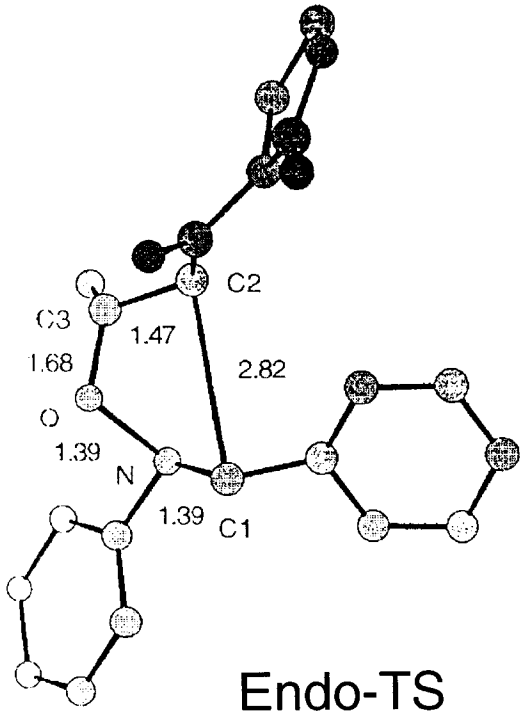

(4)

*endo*-**3**

**3a**: $R^1 = CH_3$, $R^2 = Ph$
**3b**: $R^1 = CH_3$, $R^2 = CH_2Ph$
**3c**: $R^1 = CH_2CH_2CH_3$, $R^2 = Ph$
**3d**: $R^1 = CH_2CH_2CH_3$, $R^2 = CH_2Ph$

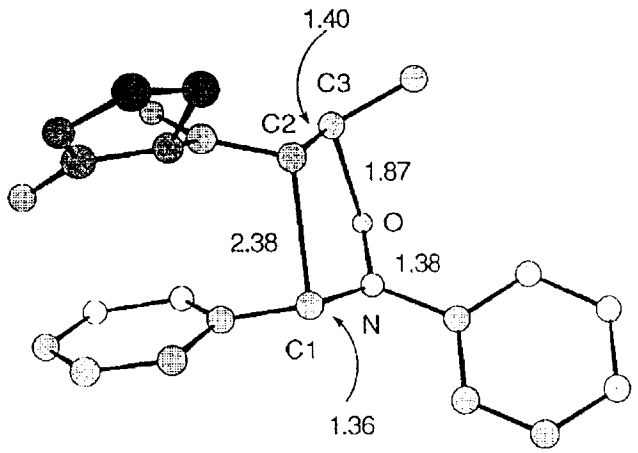
Gothelf, K., Hazell, R., Jorgensen, K. J. Org. Chem. 1996, 61, 346-355.

Uncatalyzed TS:



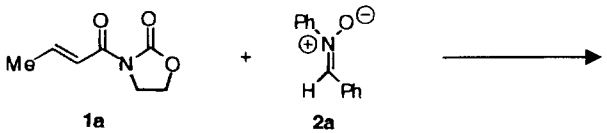

Endo-TS

65kcal/mol

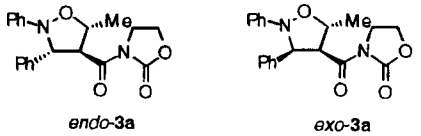



Exo-TS

40 kcal/mol




1a 2a



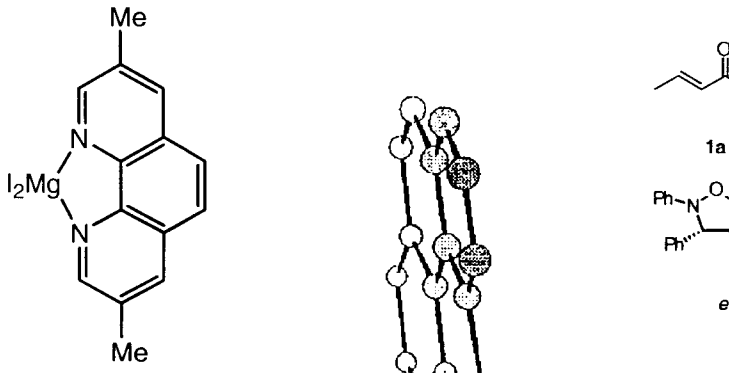

*endo*-3a

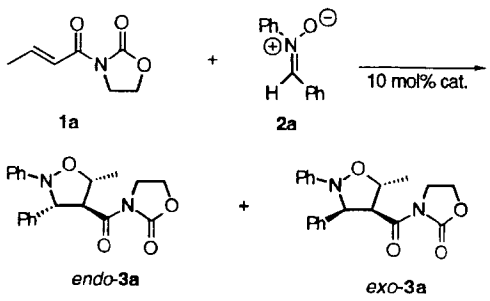



*exo*-3a

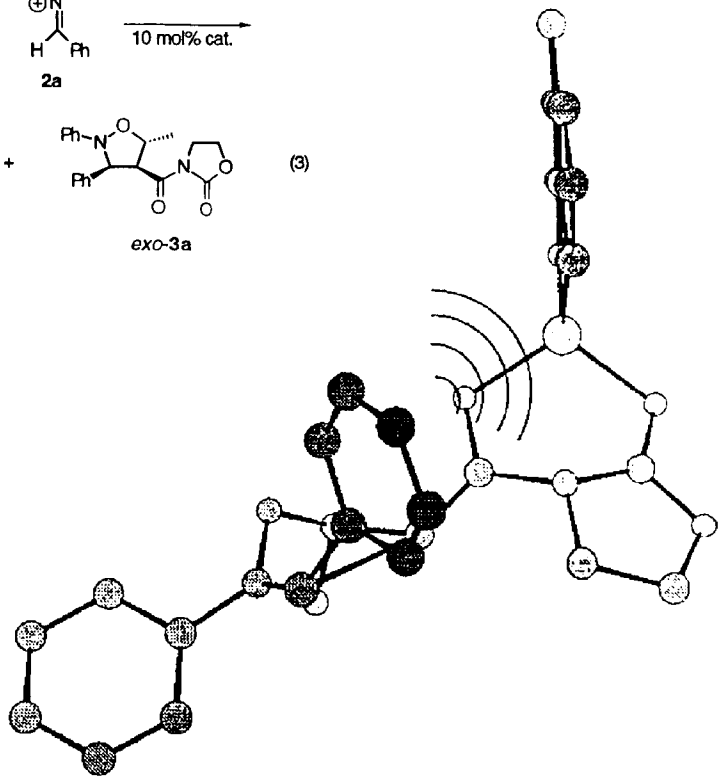
Gothelf, K, Thomsen, I., Jorgensen, K. J. Am. Chem. Soc. 1996, 118, 59-64.

# Transition state for Magnesium Catalyst 6a





Endo-TS

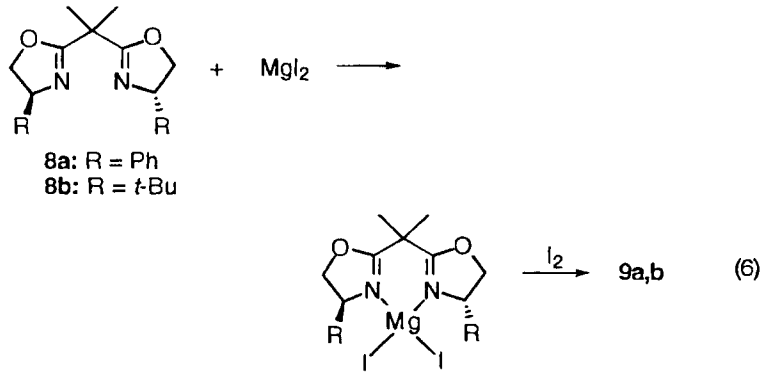
20kcal/mol

Exo-TS

35kcal/mol

Gothelf, K., Hazell, R., Jorgensen, K. J. Org. Chem. 1996, 61, 346-355.

# Enantioselective Mg catalyst



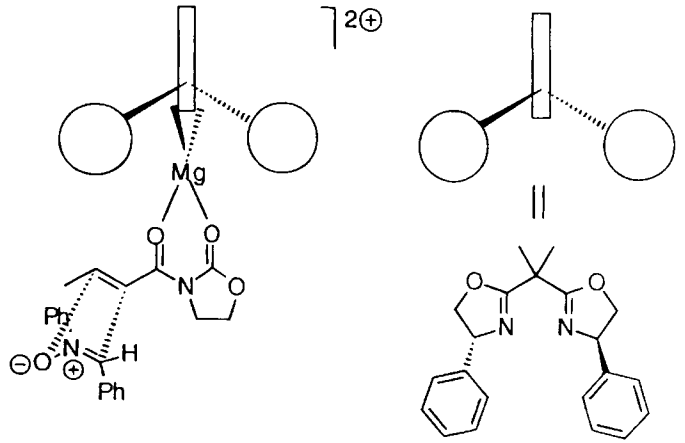




**Figure 4.** Proposed α-*Re* approach of nitrone **2a** to alkene **1a** coordinated to **9a**.

**Table 4. Metal-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition Reactions of 1a,b with 2a,b in the Presence of (*S*)-9a (10 mol %) as the Catalyst**

| entry | alkene | nitrone | molar scale[a] (mmol) | product | conversion (%) | *endo*:*exo* | ee *endo*[c] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | **2a** | 0.1 | **3a** | 72/24 h | 92:8 | 79 |
| 2 | **1a** | **2a** | 0.1[b] | **3a** | 73/24 h | 65:35 | <2 |
| 3 | **1a** | **2a** | 0.5 | (+)-**3a** | >95/48 h | 84:16 | 71 |
| 4 | **1a** | **2a** | 0.5[d] | (−)-**3a** | >95[e]/48 h | 84:16 | 75 (72)[f] |
| 5 | **1a** | **2b** | 0.1 | **3b** | 82/14 d | 89:11 | 0 |
| 6 | **1b** | **2a** | 0.1[d] | (−)-**3c** | >95/14 d | >95:<5 | 82 |
| 7 | **1b** | **2a** | 0.5[d] | (−)-**3c** | >95[g]/14 d | 53:47 | 82 (52)[f] |

[a] The molar scale is defined from **1**. [b] Without 4 Å activated powdered molecular sieves. [c] ee of the *endo*-isomer was determinated by HPLC using a Daicel Chiralcel OD column. [d] (*R*)-**9a** 10 mol % was applied as the catalyst. [e] Isolated yield: 81%. [f] ee of the *exo*-isomer. The ee was determined by $^1$H NMR spectroscopy using Eu(hfc)$_3$ as chiral shift reagent. [g] Isolated yield 66%.

Gothelf, K., Hazell, R., Jorgensen, K. J. Org. Chem. 1996, 61, 346-355.

# Inverse electron-demand reactions

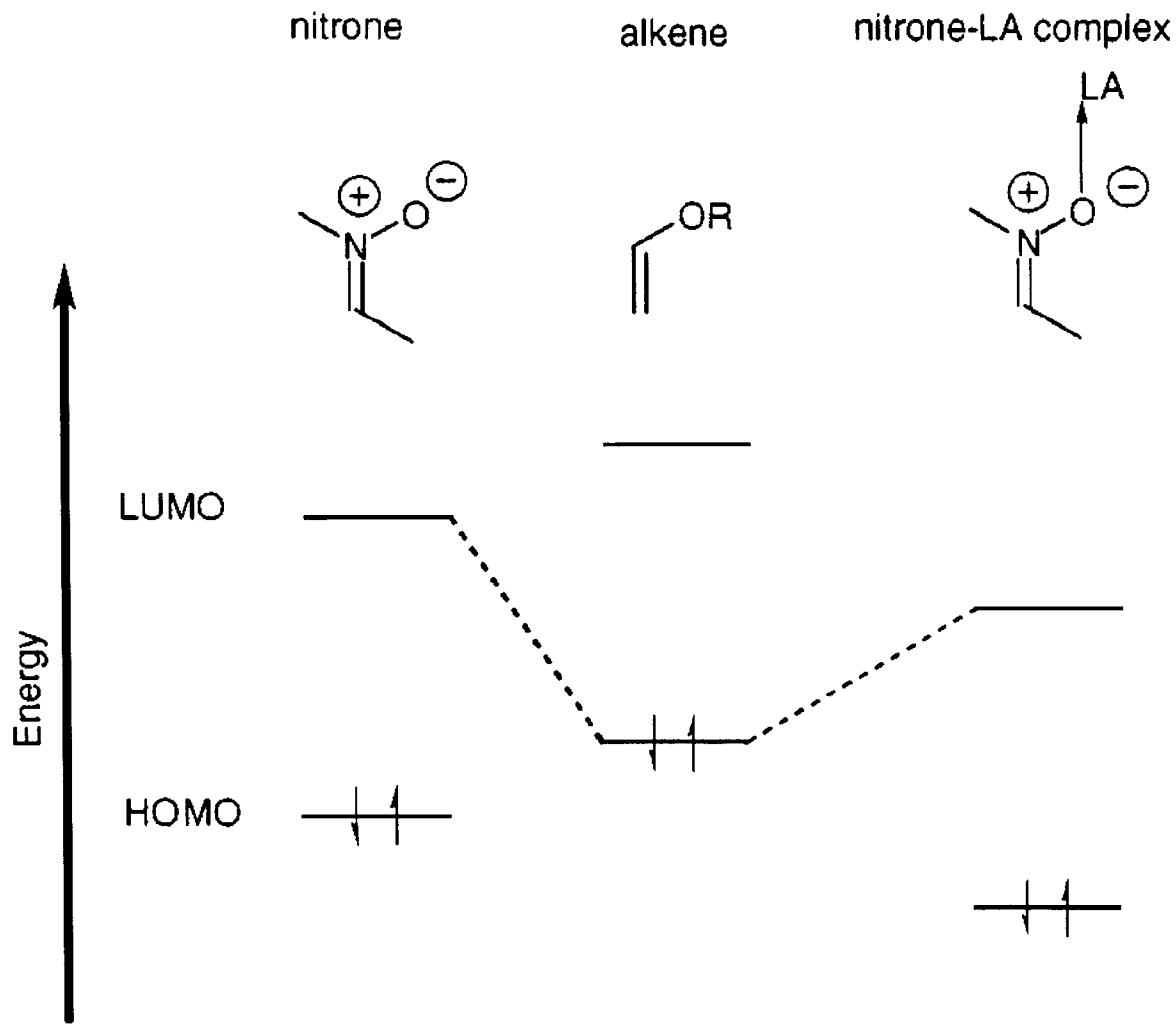
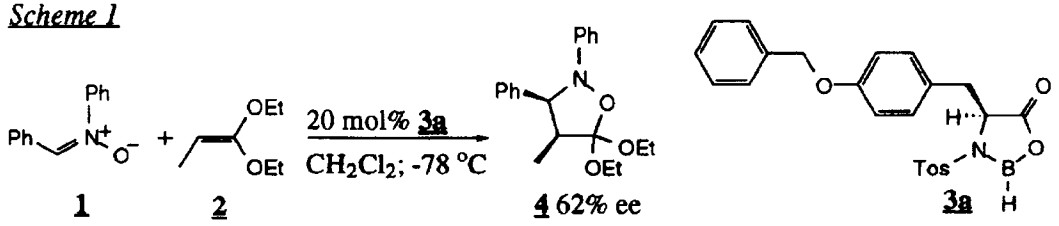



**Fig. 2** The catalytic alteration of the nitrone FMO's in the inverse electron-demand 1,3-dipolar cycloaddition reaction.

Chem. Commun. 2000, 1449-1458.

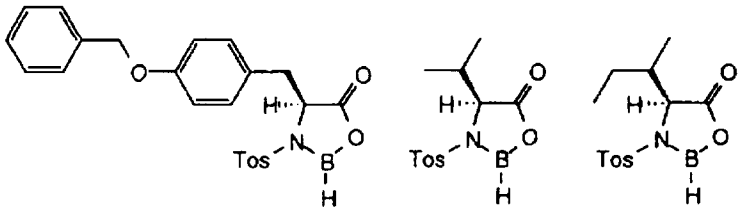
# Boron catalysis

*Scheme 1*




1 2 4 62% ee 3a

Reversal of Enantioselectivity in the Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Nitrone 1 and Ketene Acetal 2 Catalyzed by Oxazaborolidines 3[a].




3a 3b 3c

| borane | e.e. 4 (%) | e.e. 4 (%) | e.e. 4 (%) |
|---|---|---|---|
| $BH_3$-THF | 62 (-) | 4 (-) | 0 |
| $BH_3$-$SMe_2$ | 48 (-) | 70 (+) | 73 (+) |

[a]All reactions were run on a 1.0 mmol nitrone scale with 10 mol% oxazaborolidine 3 (*in situ* prepared from 1M $BH_3$-THF in THF or 1M $BH_3$-$SMe_2$ in $CH_2Cl_2$) and 1.5 eq. ketene acetal in 4 ml solvent at -78 °C.

Influence of Co-solvent on Enantioselectivity of the 1,3-Dipolar Cycloaddition of Nitrone 1 and Ketene Acetal 2 Catalyzed by Oxazaborolidine 3a in $CH_2Cl_2$[a].

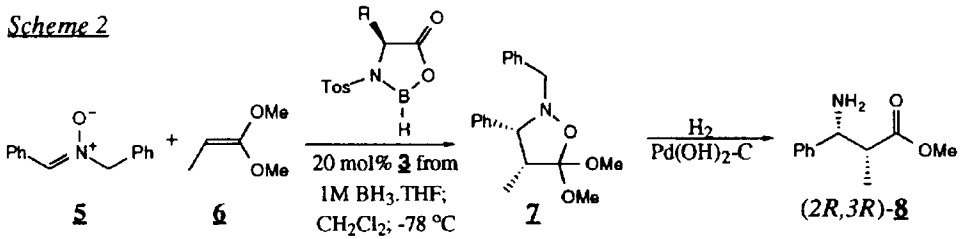
| co-solvent[b] | % ee 4 | co-solvent[b] | % ee 4 |
|---|---|---|---|
| THF | 62 (-)[3a,11] | EtCN | 16 (+) |
| *t*BuOMe | 26 (+) | $EtNO_2$ | 43 (+)<br>60 (+)[e] |
| *n*BuO*n*Bu | 14 (+) | DMSO | 6 (+) |
| PhOMe | 4 (+) | sulfolan | 15 (+) |
| PhOPh | 58 (+)<br>79 (+)[c] | $PhNO_2$ | 33 (+) |
| $PhCH_2OCH_2Ph$ | 33 (+)<br>71 (+)[d] | PhI | 8 (+) |

[a]Reactions were run with 1.0 mmol nitrone and 10 mol% oxazaborolidine 3a (*in situ* prepared from 1M $BH_3$-$SMe_2$ in $CH_2Cl_2$), 1.5 eq. ketene acetal in 4 ml solvent at -78 °C; [b] 0.1 ml (2.5 vol %) co-solvent; [c] 15 vol% co-solvent; [d] 7.5 vol% co-solvent; [e] 10 vol% co-solvent.

Seerden, J.P.; Kuypers, M.; Scheeren, H. Tetrahedron: Asymmetry. 1995, 6(6), 1441-1450.

# Boron

*Scheme 2*




5 6 7 (2*R*,3*R*)-8

Table 3. Chiral Oxazaborolidine Catalyzed Asymmetric 1,3-Dipolar Cycloaddition of Nitrone 5 in $CH_2Cl_2$/THF

| entry | substituent R in 3 | e.e. 8 (%)[a] |
|---|---|---|
| 1 | *i*-Bu | 45 |
| 2 | Ph | 17 |
| 3 | $PhCH_2$ | 11 |
| 4 | $PhCH_2CH_2$ | 59 |
| 5 | 4-($PhCH_2O$)-$PhCH_2$ | 0 |
| 6 | indolyl-$CH_2$ | 46 |

[a] In all cases the (2*R*,3*R*)- 8 enantiomer was formed in excess

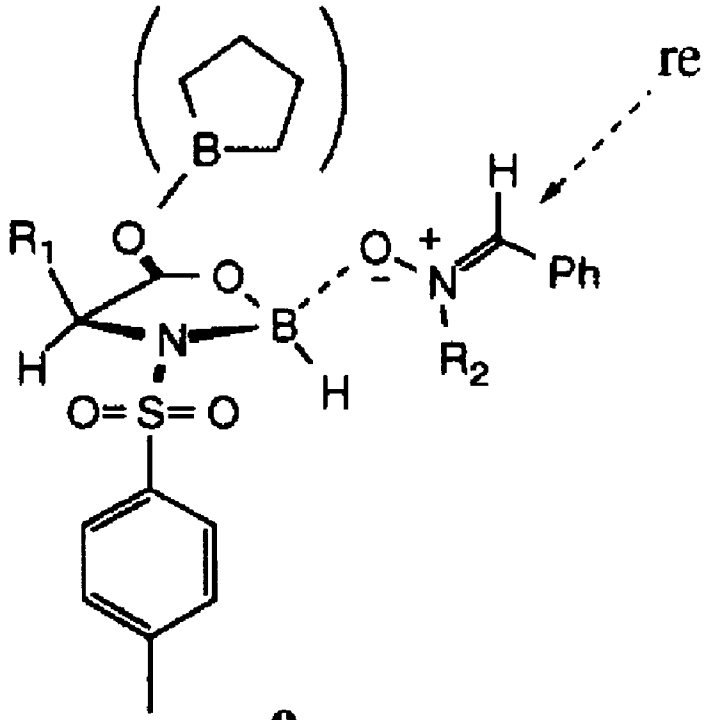
Effect of Co-solvents on Enantioselectivity of 1,3-Dipolar Cycloaddition of Nitrone 5 with Ketene Acetal 6 Catalyzed by Chiral Oxazaborolidines 3[a] Prepared from 1M $BH_3$-$SMe_2$

| entry | catalyst | R | co-solvent[a] | vol% | e.e. (%) 8 |
|---|---|---|---|---|---|
| a | 3a | 4-($PhCH_2O$)-$PhCH_2$ | - | - | 8 (2*R*,3*R*) |
| b | | | $PhCH_3$ | 50 | 18 (2*S*,3*S*) |
| c | | | $PhCH_2OCH_2Ph$ | 2.5 | 34 (2*S*,3*S*) |
| d | 3b | *i*-Pr | - | - | 47 (2*R*,3*R*) |
| e | | | THF | 100 | 21 (2*R*,3*R*) |
| f | | | $PhCH_3$ | 50 | 25 (2*R*,3*R*) |
| g | 3d | $PhCH_2CH_2$ | - | - | 11 (2*R*,3*R*) |
| h | | | PhH | 50 | 15 (2*S*,3*S*) |
| i | 3e | Ph | - | - | 10 (2*S*,3*S*) |
| j | | | $PhCH_2OCH_2Ph$ | 2.5 | 11 (2*S*,3*S*) |
| k | | | PhH | 50 | 34 (2*S*,3*S*) |
| l | | | $PhCH_3$ | 50 | 40 (2*S*,3*S*) |
| m | | | $PhCH_3$ | 97.5 | **74 (2*S*,3*S*)** |
| n | | | $PhCH_3$ | 100[b] | 68 (2*S*,3*S*) |

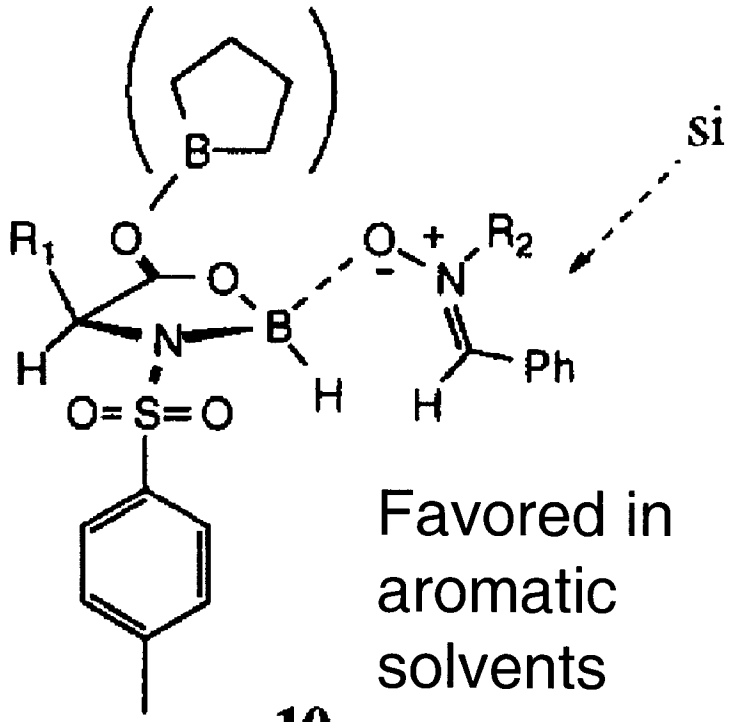
[a] dichloromethane used as standard solvent; catalyst preparation from $BH_3$-$SMe_2$ (1M in $CH_2Cl_2$);
[b] catalyst preparation from $BH_3$-$SMe_2$ (1M in toluene) and reaction in toluene as solvent.

Seerden, J.P.; Kuypers, M.; Scheeren, H. Tetrahedron: Asymmetry. 1995, 6(6), 1441-1450.

Proposed Boron TS




**9**




**10**

Favored in aromatic solvents

# Summary

-Nitrone/Alkene cycloadditions can either be inverse or normal electron demand

-Enantioselectivity and diastereoselectivity can be controlled using catalysis

-Formation of isoxazolidine important for synthetic purposes:

- -Up to 3 stereocenters can be introduced
- -Masked functionality