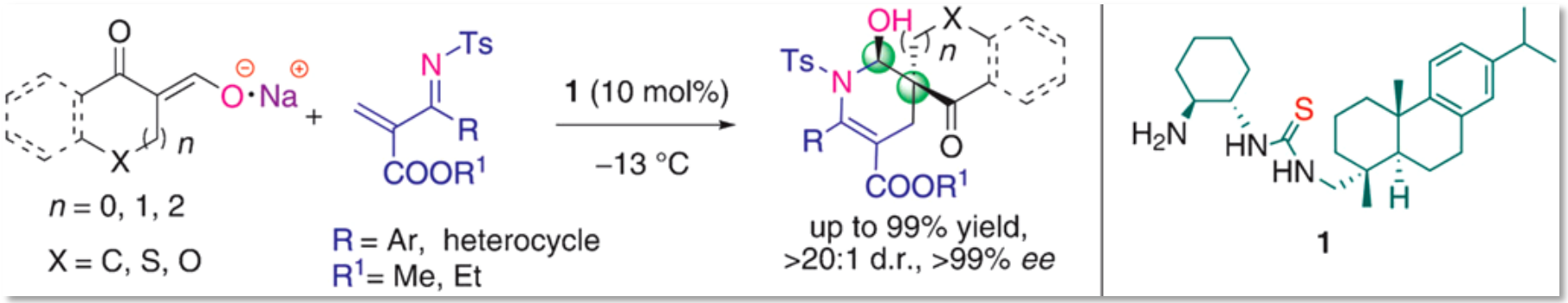
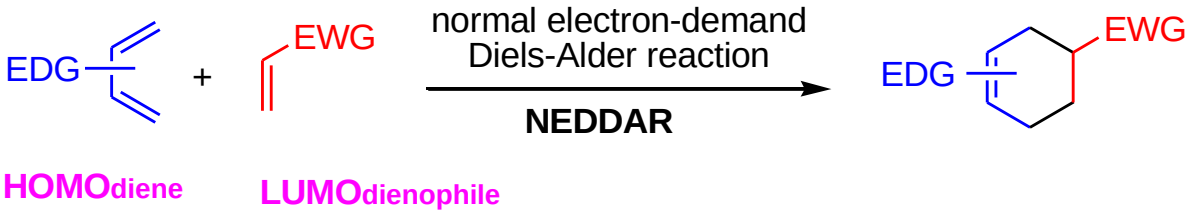
# Bifunctional Organocatalytic Strategy for Inverse-Electron-Demand Diels–Alder Reactions: Highly Efficient *In Situ* Substrate Generation and Activation to Construct Azaspirocyclic Skeletons




The *in situ* generation of the enolate provides a new way in which to use in organic synthesis

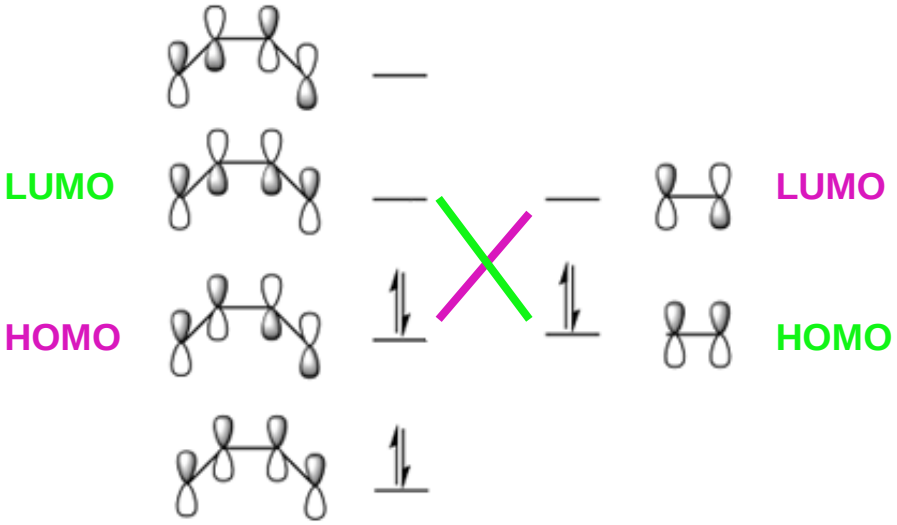
X. Jiang, X. Shi, S. Wang, T. Sun, Y. Cao, R. Wang. *Angew. Chem. Int. Ed*. **2012**, *51*, 1–5.

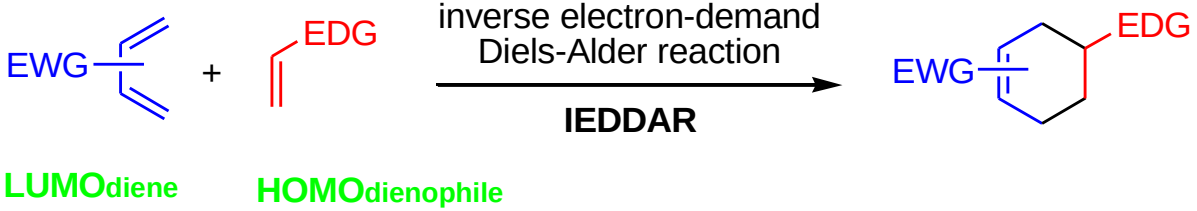
# ¿ Which is the diference between NEDDAR and IEDDAR ?



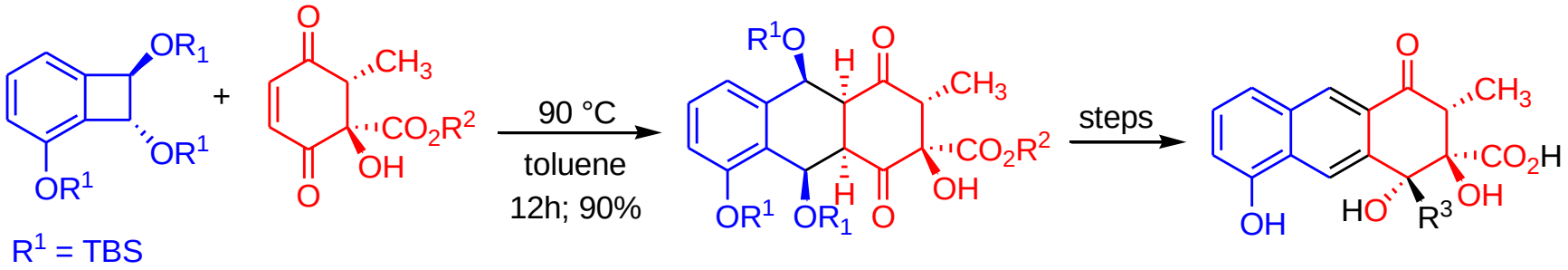

**EDG** (electron-donanting group)
= alkyl, O-alkyl, *N*-alkyl, etc.

**EWG** (electron-withdrawing group)
= CN, $NO_2$, CHO, COR, COAr, $CO_2H$, COCl, etc.



The catalytic asymmetric Diels–Alder reaction (DAR) is among the most powerful protocols for the stereoselective construction of six-membered functionalized cyclic frameworks.




$R^1$ = TBS

$R^3$ = isoamyl

(±)-Rishirilide B

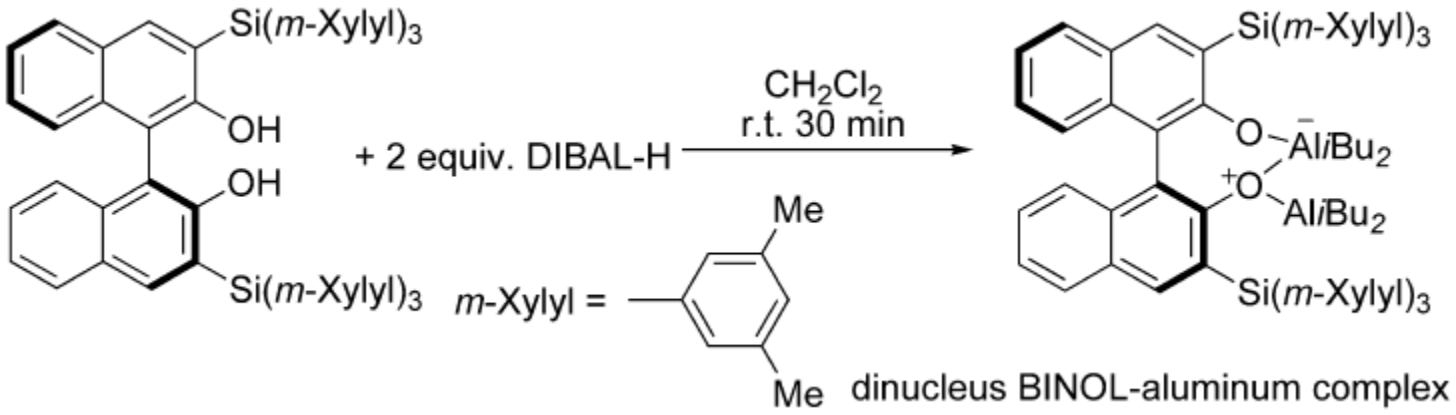
Discover new reaction modes for this cycloaddition

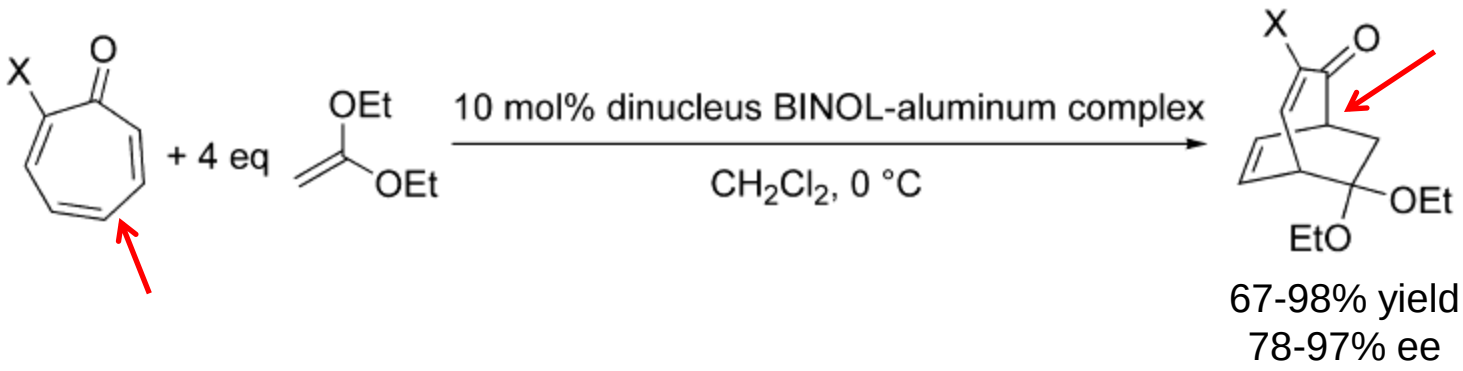
**¿ Which are activation strategies for the IEDDAR ?**

Allen, J. G., Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 351-352

## 1. LUMO$_{diene}$ activation

Activation of dienes through lowering of the LUMO energy by lewis acid



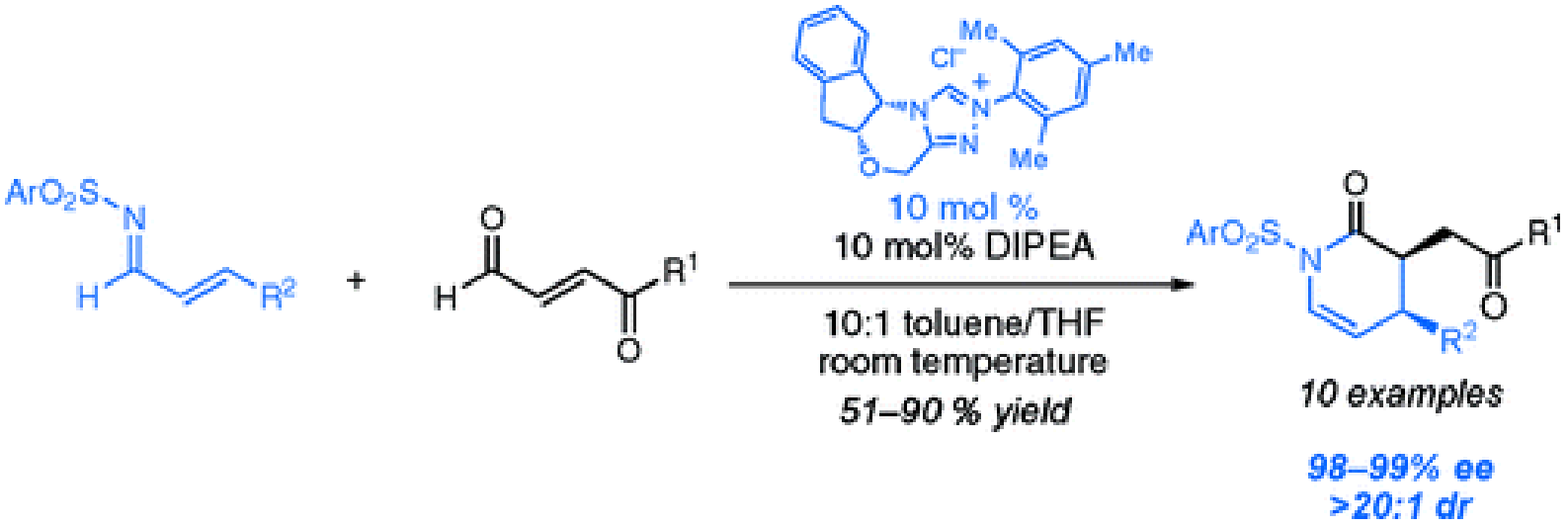




67-98% yield
78-97% ee


• X. Jiang, X. Shi, S. Wang, T. Sun, Y. Cao, R. Wang. *Angew. Chem. Int. Ed.*, **2012**, *51*, 1–5.
• P. Li, H. Yamamoto. *J. Am. Chem. Soc.*, **2009**, *131* (46), 16628–16629.

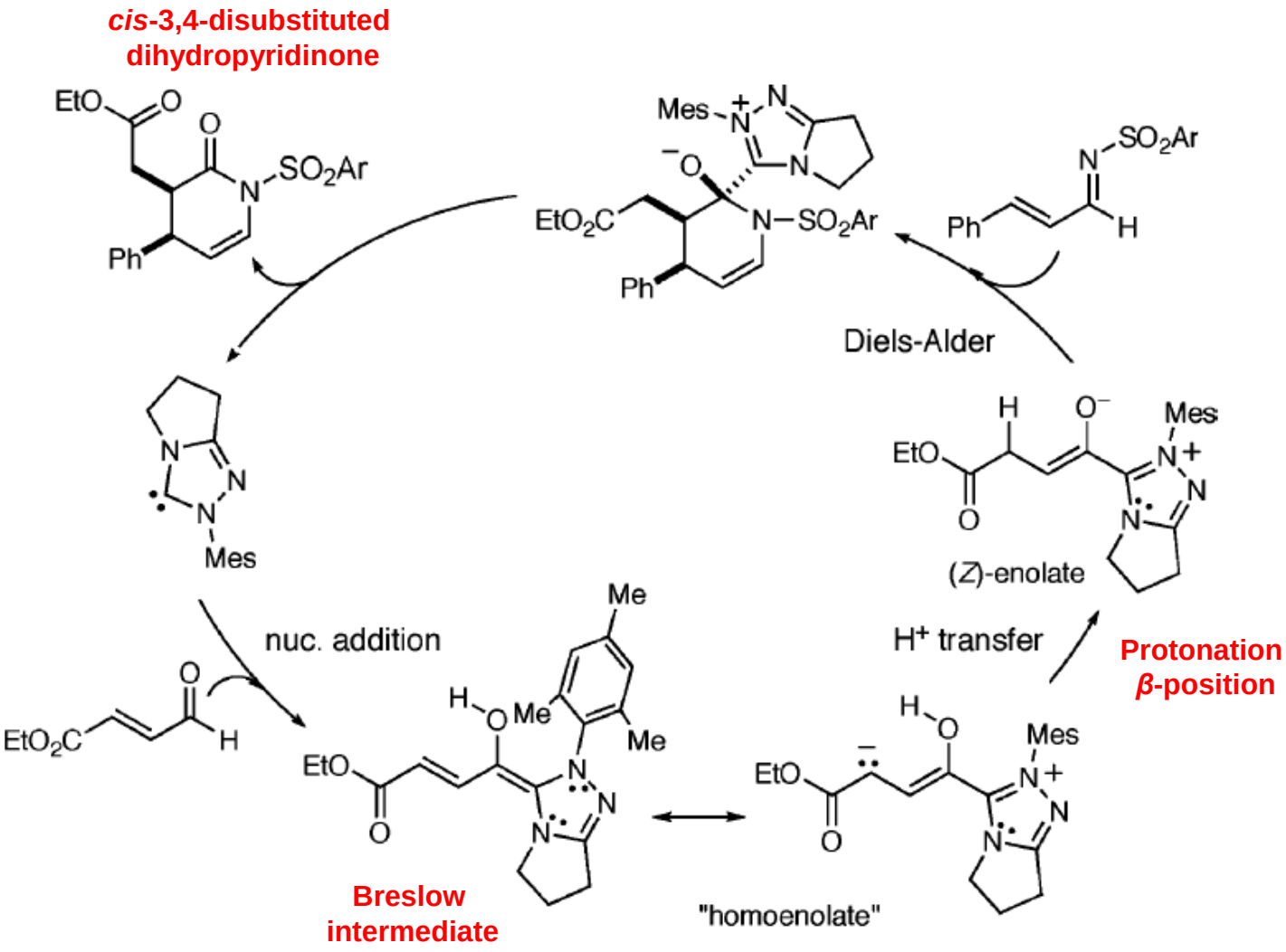
## 1. LUMO$_{diene}$ activation

Activation of dienes through lowering of the LUMO energy by organic molecules

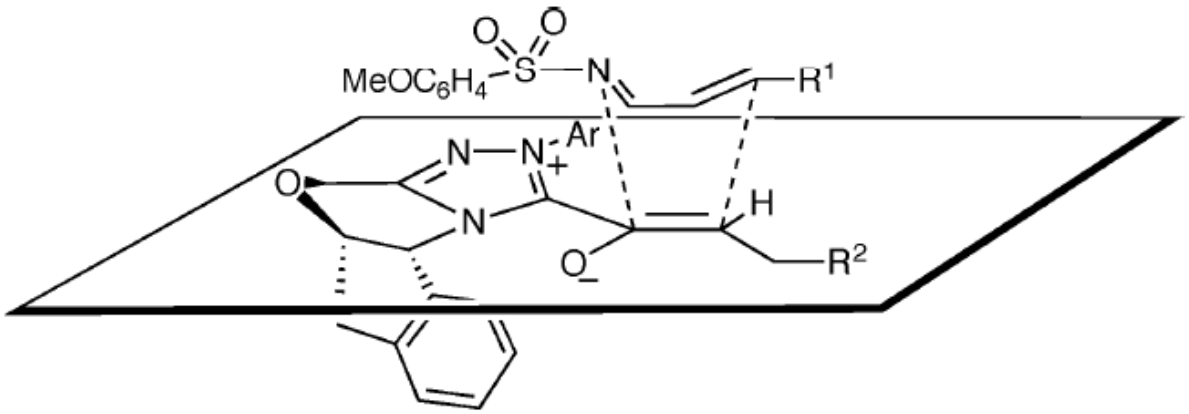


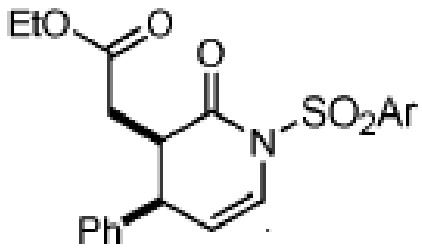

The first N-heterocyclic carbene (NHC)-catalyzed aza-Diels−Alder reactions using a novel chiral triazolium salt serves as an efficient precatalyst for the generation of enolate (HOMO$_{dienophile}$) that undergo IEDDAR with *N*-sulfonyl-α,*β*-unsaturated imines (LUMO$_{diene}$).

M. He, J. R. Struble, J. W. Bode. *J. Am. Chem. Soc.*, **2006**, *128* (26), 8418–8420




M. He, J. R. Struble, J. W. Bode. *J. Am. Chem. Soc.*, **2006**, *128* (26), 8418–8420



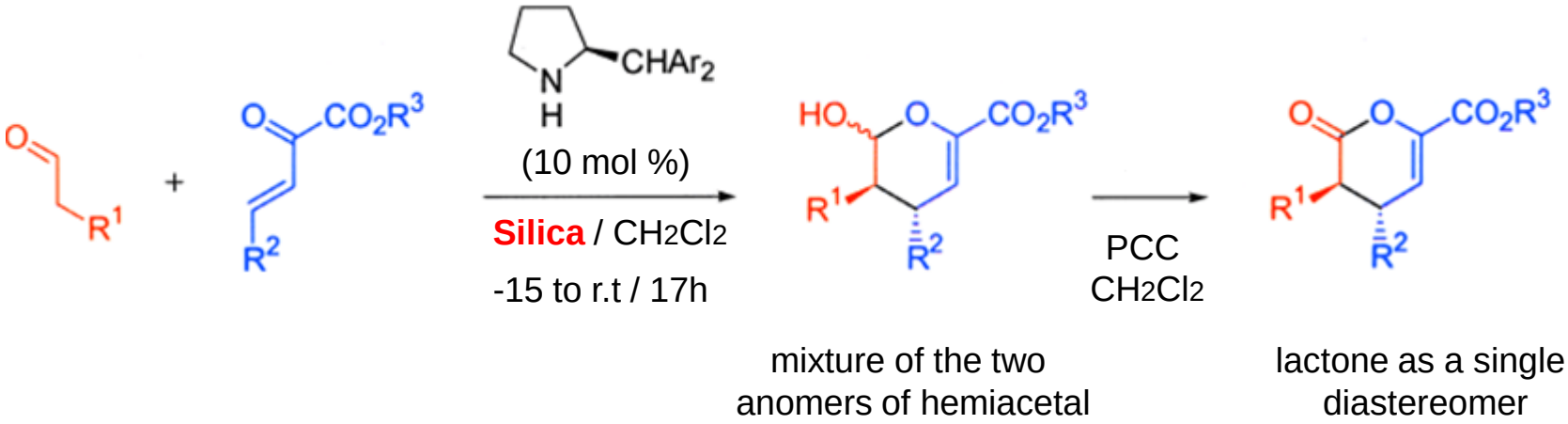

➢ The exceptional diastereoselectivity is rationalized by the high preference for an *endo* transition state, and in the NHC-catalyzed system, this reaction mode is reinforced by the presence of the bulky triazolium moiety in the active dienophile.

➢ The *cis-stereoselectivity would* arise from a (*Z*)-*enolate reacting as the dienophile.*

M. He, J. R. Struble, J. W. Bode. *J. Am. Chem. Soc.*, **2006**, *128* (26), 8418–8420

## 2. HOMO$_{dienophile}$ activation

Activation of dienophiles through raising of the HOMO energy by an enamine activation.

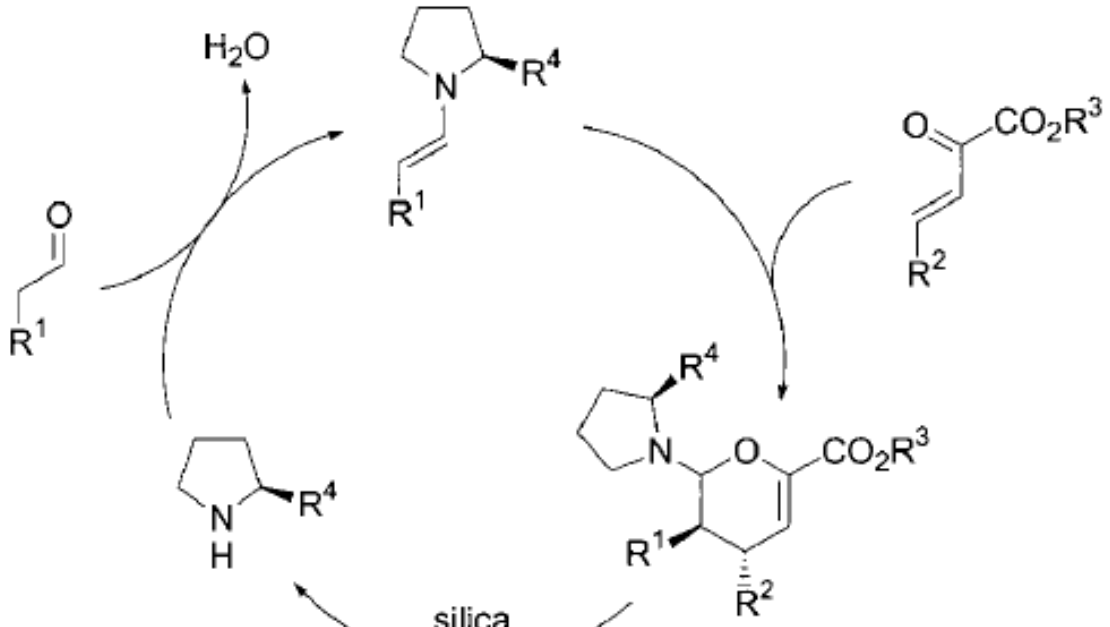


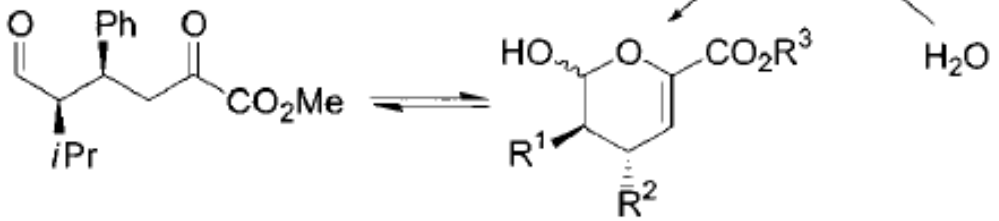

➢ The first catalytic asymmetric hetero-Diels–Alder reaction of aldehydes with enones with excellent diastereo- and enantioselectivity.

➢ The use of a chiral enamine intermediate as an alkene in catalytic asymmetric cycloaddition reactions.

K. Juhl, K. A. Jørgensen., *Angew. Chem. Int. Ed.* **2003**, *42*, 1498 –1501

chiral enamine




aldehyde

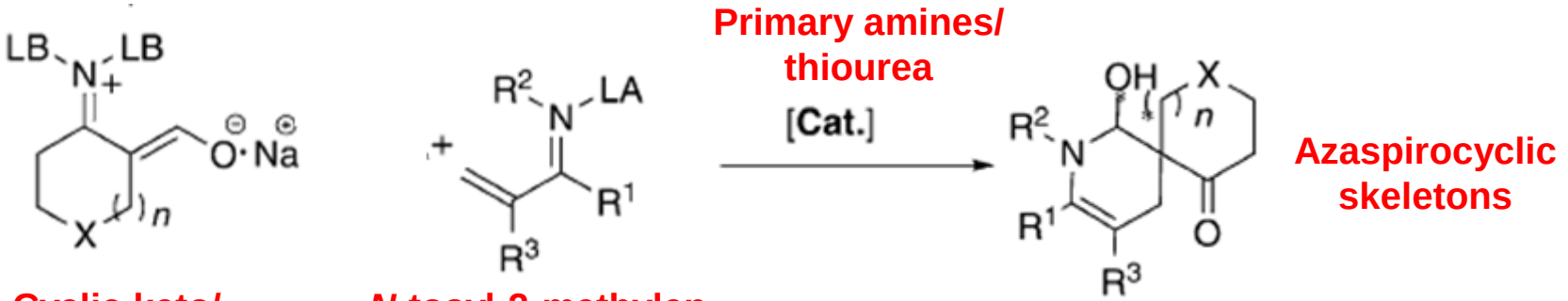
mixture of the two anomers of hemiacetal

the presence of silica would facilitate the hydrolysis step in the catalytic cycle

K. Juhl, K. A. Jørgensen., *Angew. Chem. Int. Ed.* **2003**, *42*, 1498 –1501

## 3. HOMO$_{dienophile}$ and LUMO$_{diene}$: bifunctional activation strategy

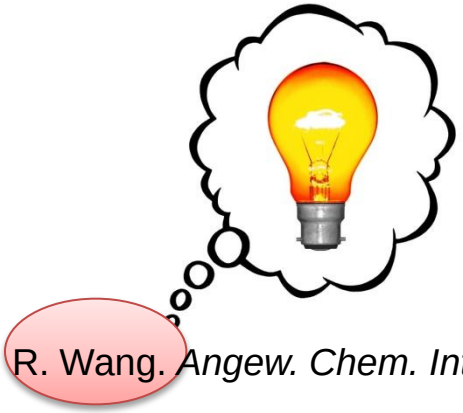
There is no report of an asymmetric IEDDAR that is controlled with a single reactive catalyst through a simultaneous activation of the HOMO$_{dienophile}$ and the LUMO$_{diene}$.




**Cyclic keto/ enolates sodium**

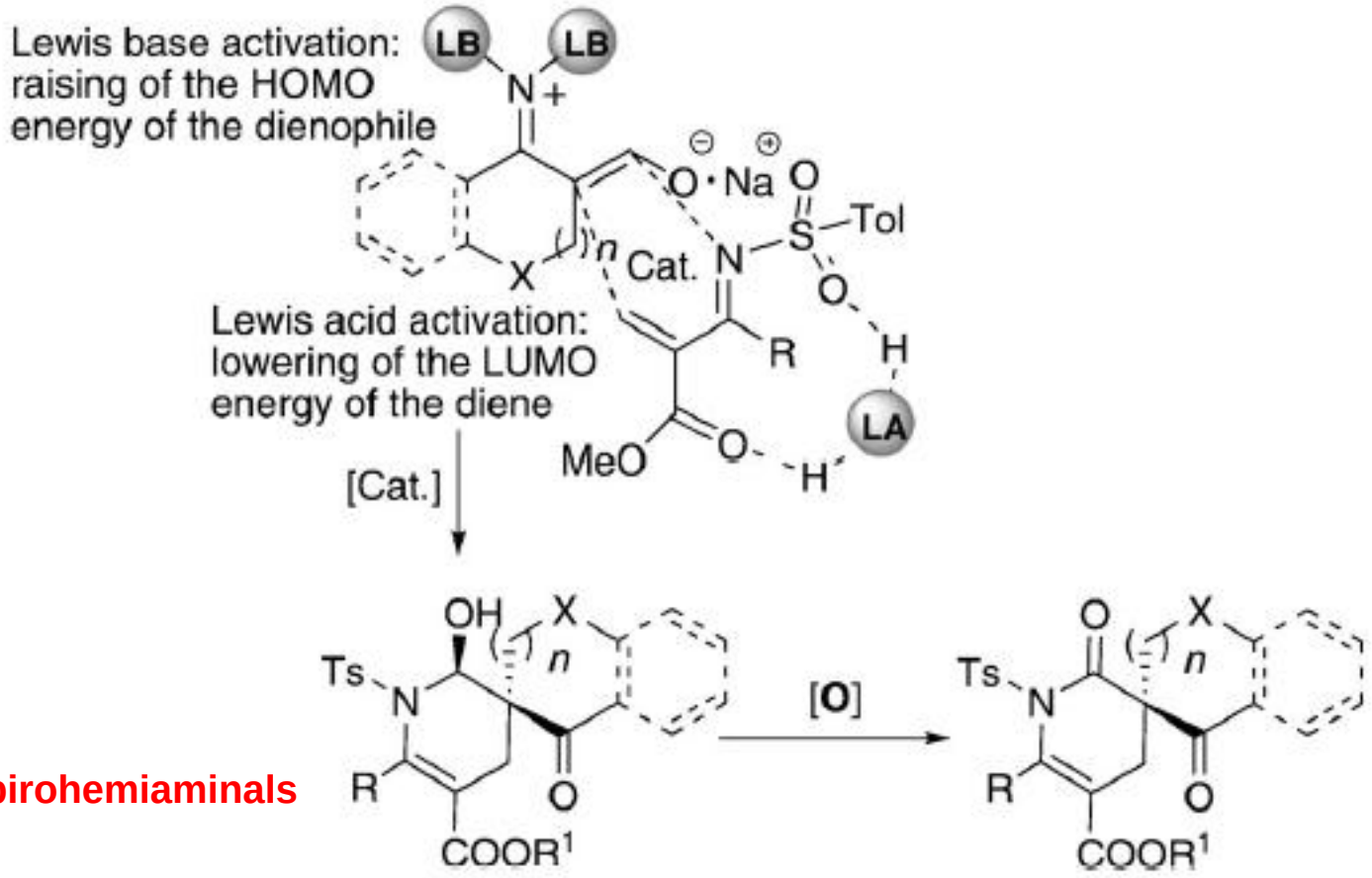
***N*-tosyl-2-methylen but-3-enoates**

**Azaspirocyclic skeletons**



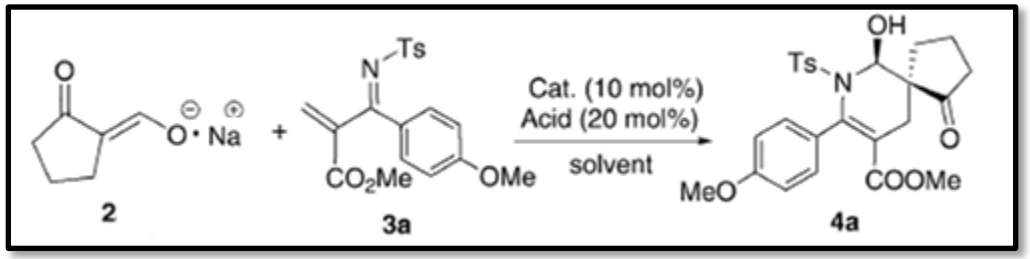
X. Jiang, X. Shi, S. Wang, T. Sun, Y. Cao, R. Wang. *Angew. Chem. Int. Ed*. **2012**, *51*, 1–5.

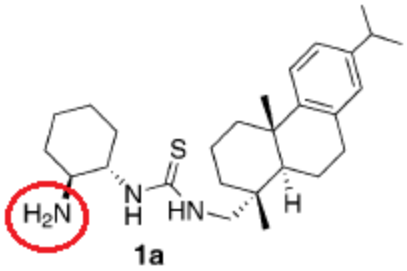
## ¿ Which is the approach bifunctional catalyst for the asymmetric IEDDAR ?




**Spirohemiaminals**

X. Jiang, X. Shi, S. Wang, T. Sun, Y. Cao, R. Wang. *Angew. Chem. Int. Ed*. **2012**, *51*, 1–5.




| Entry | Cat. | Acid | Solvent[b] | Yield [%][c] | *ee* [%][d] |
|---|---|---|---|---|---|
| 1 | 1a | BzOH | toluene/$H_2O$ | 98 | 71 |
| 2 | 1a | AcOH | toluene/$H_2O$ | 99 | 75 |
| 3 | 1a | TFA | toluene/$H_2O$ | 95 | 58 |
| 4 | 1a | AcOH | $CH_2Cl_2/H_2O$ | 99 | 55 |
| 5 | 1a | AcOH | $CHCl_3/H_2O$ | 90 | 31 |
| 6 | 1a | AcOH | $Et_2O/H_2O$ | 93 | 22 |
| 7 | 1a | AcOH | THF/$H_2O$ | 89 | 18 |

**[a]** The reaction was performed on 0.1 mmol scale with **2** (2.0 equiv), **3a** (1.0 equiv), and acid (20 mol%). **[b]** Organic solvent/$H_2O$ (1.0 mL, 1:1). **[d]** Determined by HPLC analysis on a chiral stationary phase, and products were observed with **d.r.>20:1**.

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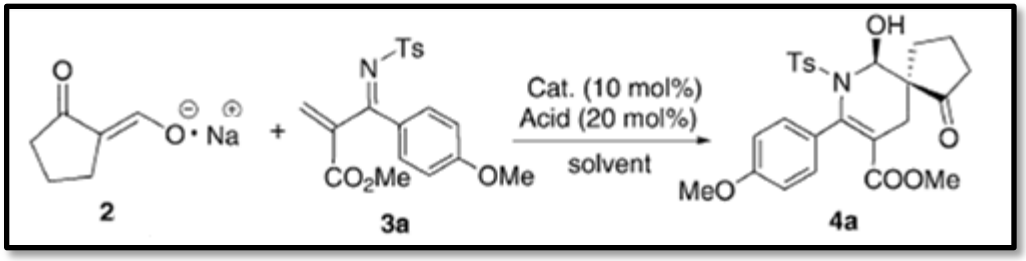
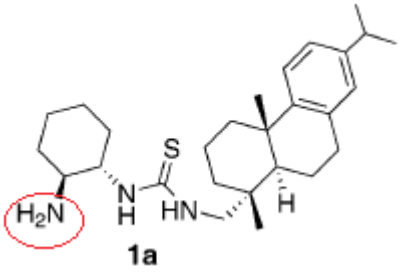
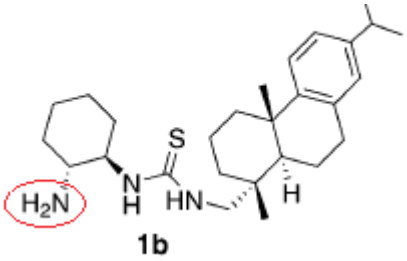



| Entry | Cat. | Acid | Solvent[b] | Yield [%][c] | *ee* [%][d] |
|---|---|---|---|---|---|
| 1 | 1a | BzOH | toluene/$H_2O$ | 98 | 71 |
| 2 | 1a | AcOH | toluene/$H_2O$ | 99 | 75 |
| 3 | 1a | TFA | toluene/$H_2O$ | 95 | 58 |
| 4 | 1a | AcOH | $CH_2Cl_2$/$H_2O$ | 99 | 55 |
| 5 | 1a | AcOH | $CHCl_3$/$H_2O$ | 90 | 31 |
| 6 | 1a | AcOH | $Et_2O$/$H_2O$ | 93 | 22 |
| 7 | 1a | AcOH | THF/$H_2O$ | 89 | 18 |
| 8 | 1b | AcOH | toluene/$H_2O$ | 96 | 55 |
| 9 | 1c | AcOH | toluene/$H_2O$ | 92 | 29 |
| 10 | 1d | AcOH | toluene/$H_2O$ | 83 | 25 |
| 11 | 1e | AcOH | toluene/$H_2O$ | 90 | 61 |
| 12 | 1f | AcOH | toluene/$H_2O$ | 86 | 3 |
| 13[e] | 1a | AcOH | toluene/$H_2O$ | 99 | 83 |
| 14[f] | 1a | AcOH | toluene/$H_2O$ | 99 | 90 |
| 15[g] | 1a | AcOH | toluene/$H_2O$ | 58 | 80 |

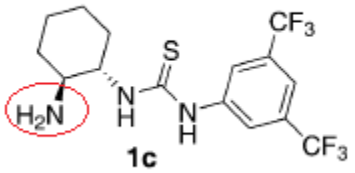
[e] at 0 °C, [f] a -13 °C, [g] at – 40 °C



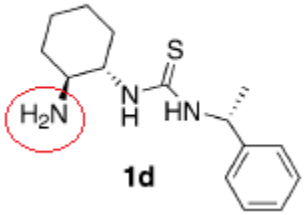
1a



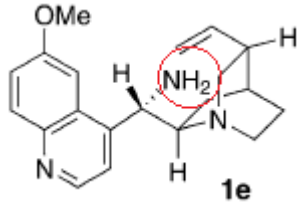
1b



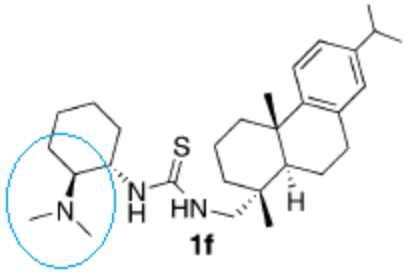
1c



1d

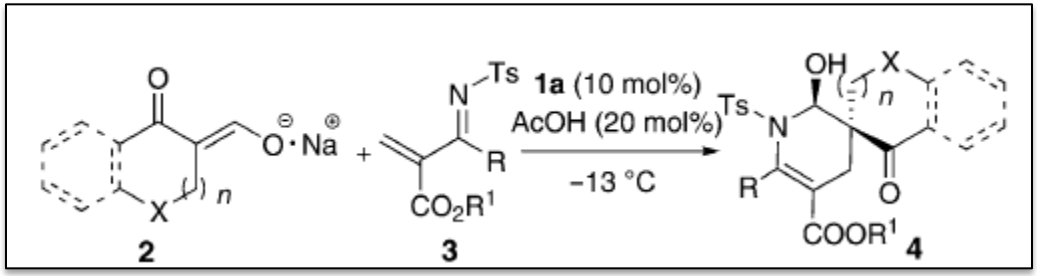


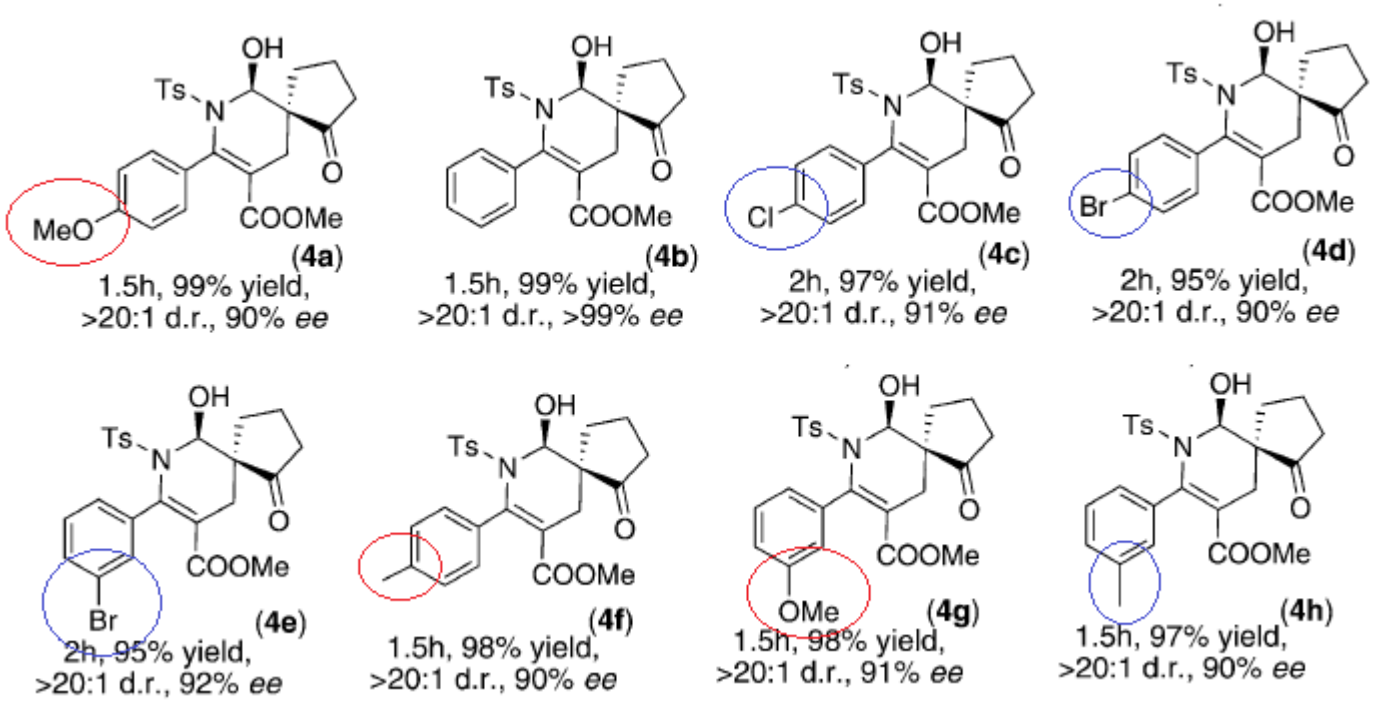
1e



1f

The new method for the synthesis of chiral spirohemiaminals was explored with a variety of substituted *N*-tosyl-2-methylenebut-3-enoates and cyclic keto/enolate sodium.




**4a-h**
Yield 95-99%
> 20:1 dr
88 to > 99% e.e



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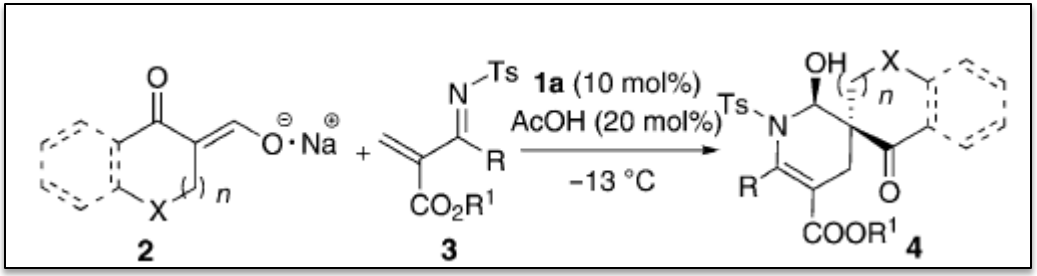
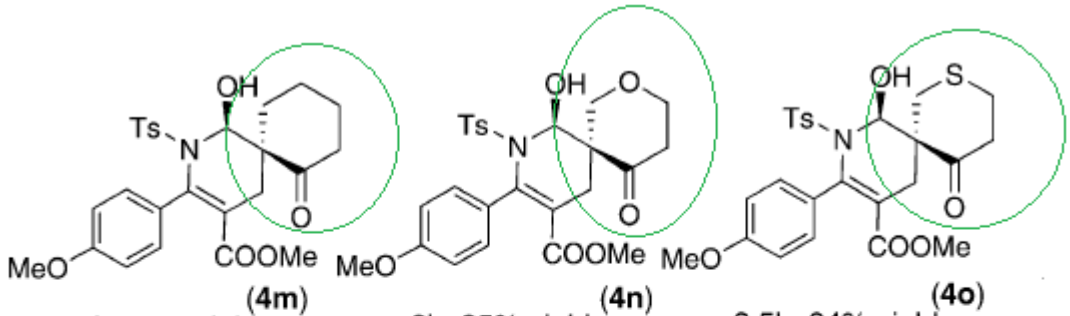
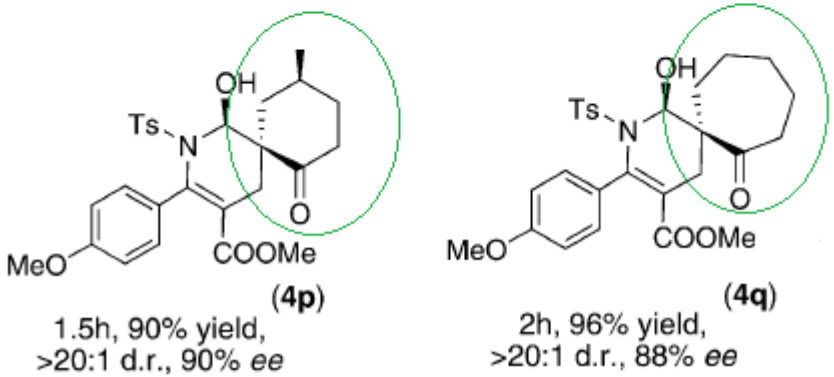


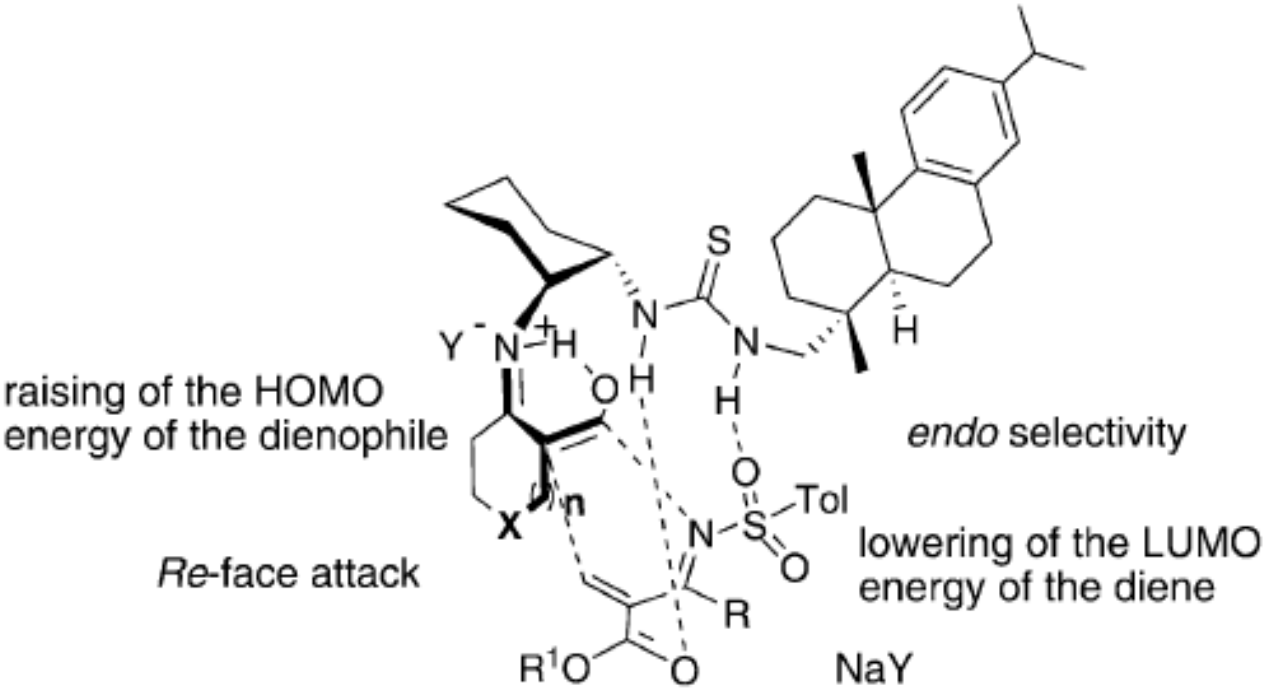




**The diversely structured spirohemiaminals 4m–q**

Yield 84-96%
> 20:1 dr
88 to > 99% e.e

X. Jiang, X. Shi, S. Wang, T. Sun, Y. Cao, R. Wang. *Angew. Chem. Int. Ed*. **2012**, *51*, 1–5.

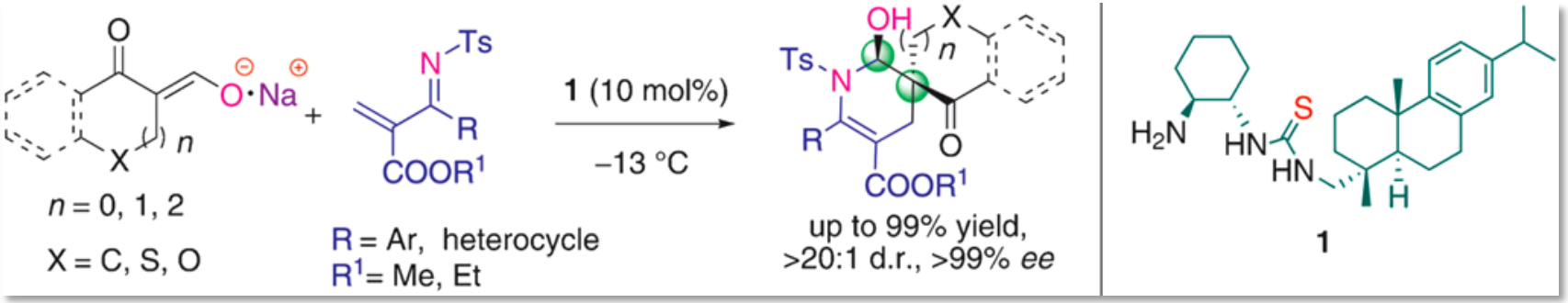
Possible model to explain the stereochemistry of the IEDDAR employing a bifunctional in situ generation/activation strategy.




As a result of the main stereochemical control from the 1,2-diaminocyclohexane moiety and steric hindrance from the dehydroabietic amine moiety of the thiourea, **high Re face and endo selectivity** would be enforced to give the desired chiral product.

X. Jiang, X. Shi, S. Wang, T. Sun, Y. Cao, R. Wang. *Angew. Chem. Int. Ed*. **2012**, *51*, 1–5.

# CONCLUSIONS




➢ Wang and co-workers have disclosed a highly efficient in situ generation/activation strategy that has enabled the development of the ***first highly enantioselective inverse-electron demand Diels–Alder reaction using a bifunctional organocatalyst.***

➢ This process provides a promising method for the enantioselective construction of densely functionalized azaspirocyclic skeletons ***(up to 99% yield, >20:1 d.r., and >99% ee).***

X. Jiang, X. Shi, S. Wang, T. Sun, Y. Cao, R. Wang. *Angew. Chem. Int. Ed*. **2012**, *51*, 1–5.

# Thanks