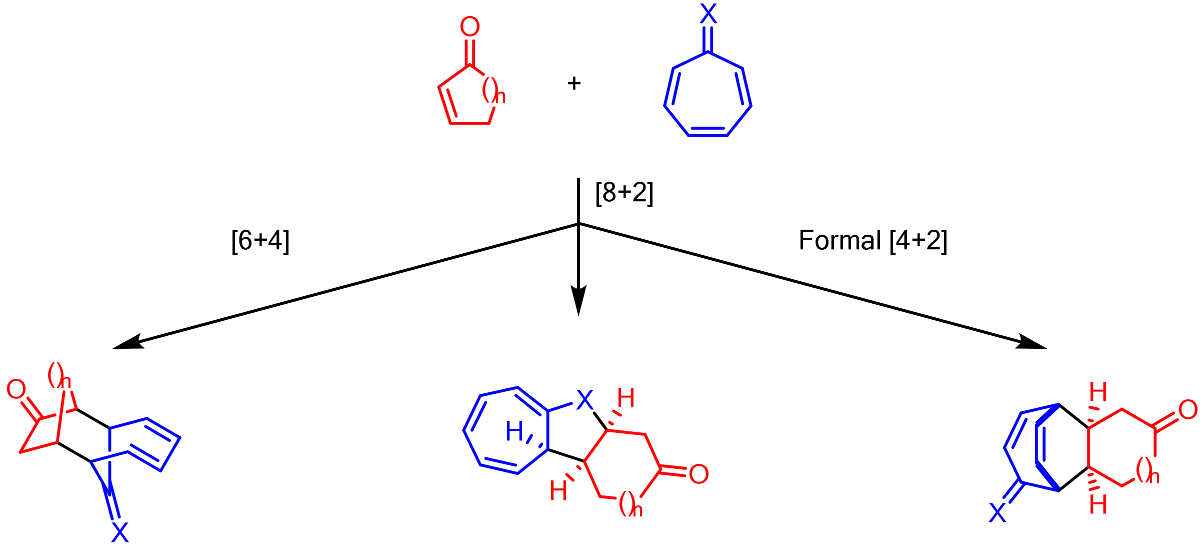
Organocatalytic stereoselective [8+2] and [6+4] cycloadditions



Joel Walker

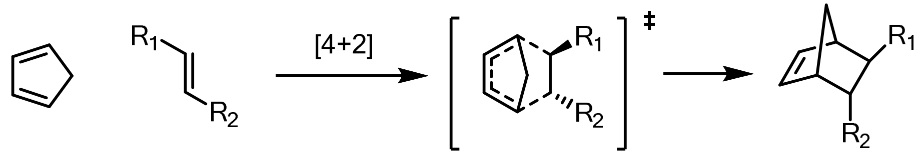
Current Literature

March 4th, 2017

Mose, R.; Preegel, G.; Larsen, J.; Jakobsen, S.; Iversen, E.H.; Jørgensen, K. A. *Nature Chem.* **2016**, Advance online publications

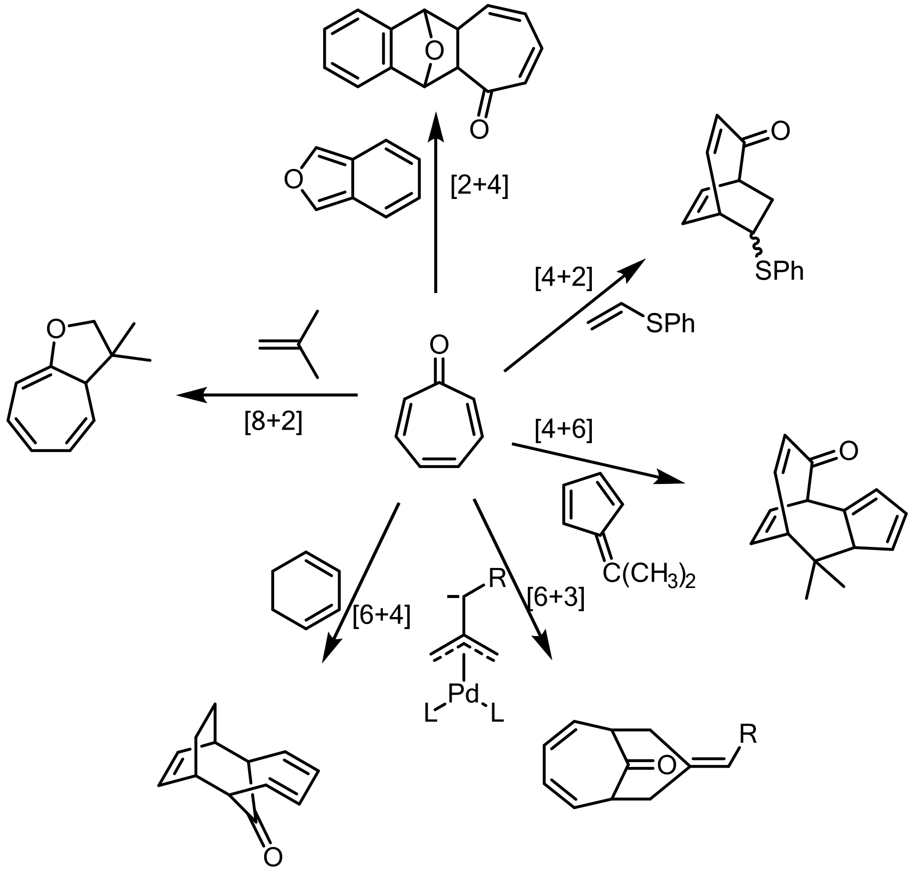
Background: Pericyclic Reactions

- Reactions in which the transition state is cyclic and proceed in a concerted fashion
  - Notable examples are sigmatropic rearrangements (Claisen, Cope) and cycloadditions (Diels-Alder)



Background: Higher-Order Cycloadditions

- Cycloadditions involving more than six π electons (eg. [8+2], [4+6], [6+3], [6+6])
- Struggles with periselectivity



[2+4] Takeshita, H., Wada, Y., Mori, A. & Hatsui, T. *Chem. Lett.* 2, 335–336 (1973).

[4+2] Dahnke, K. R. & Paquette, L. A. *J. Org. Chem.* 59, 885–899 (1994)

[4+6] Houk, K. N., Luskus, L. J. & Bhacca, N. S. *J. Am. Chem. Soc.* 92, 6392–6394 (1970).

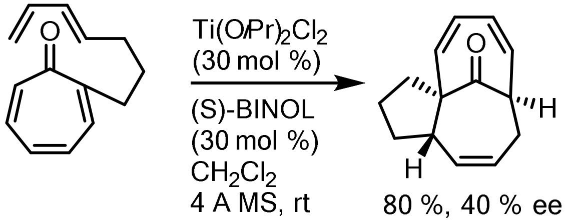
[6+3] Trost, B. M. & Seoane, P. R. *J. Am. Chem. Soc.* 109, 615–617 (1987)

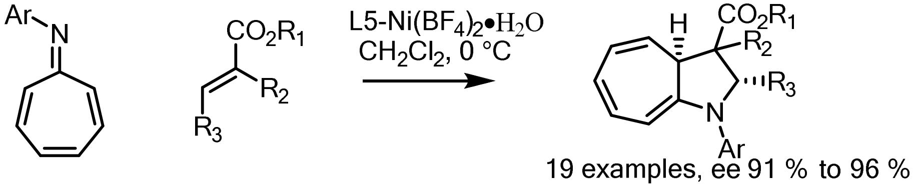
[6+4] Rigby, J. H. & Fleming, M. *Tetrahedron Lett.* 43, 8643–8646 (2002).

[8+2] Cantrell, T. S. *J. Am. Chem. Soc.* 93, 2540–2541 (1971).

Background: Enantioselectivity

- [6+4] additions are *exo*-selective
- [8+2] and [4+2] are *endo*-selective
- Few examples of enantioselective higher-order cycloadditions



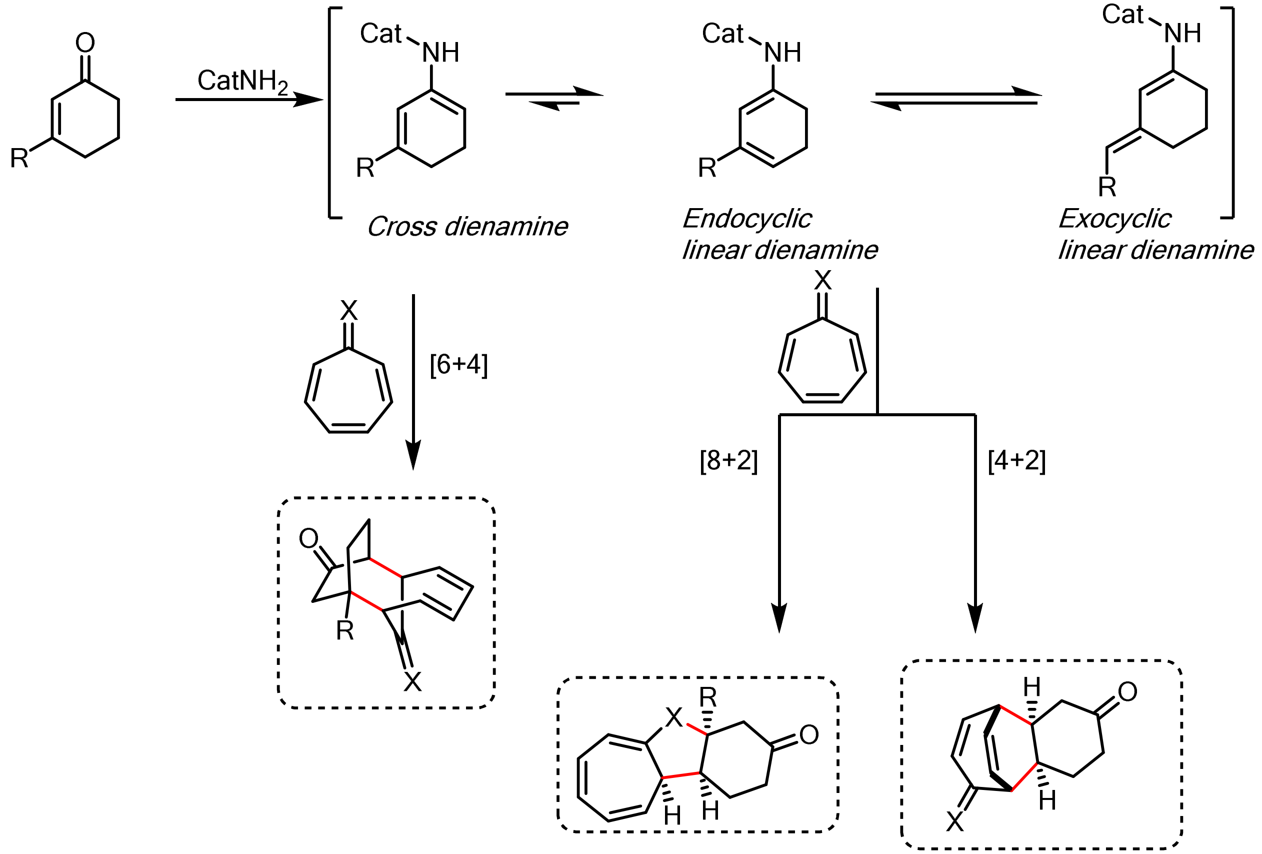


Hoffmann, R. & Woodward, R. B. Selection rules for concerted cycloaddition reactions. J. Am. Chem. Soc. 87, 2046–2048 (1965)

Rigby, J. H. & Fleming, M. *Tetrahedron Lett.* 43, 8643–8646 (2002).

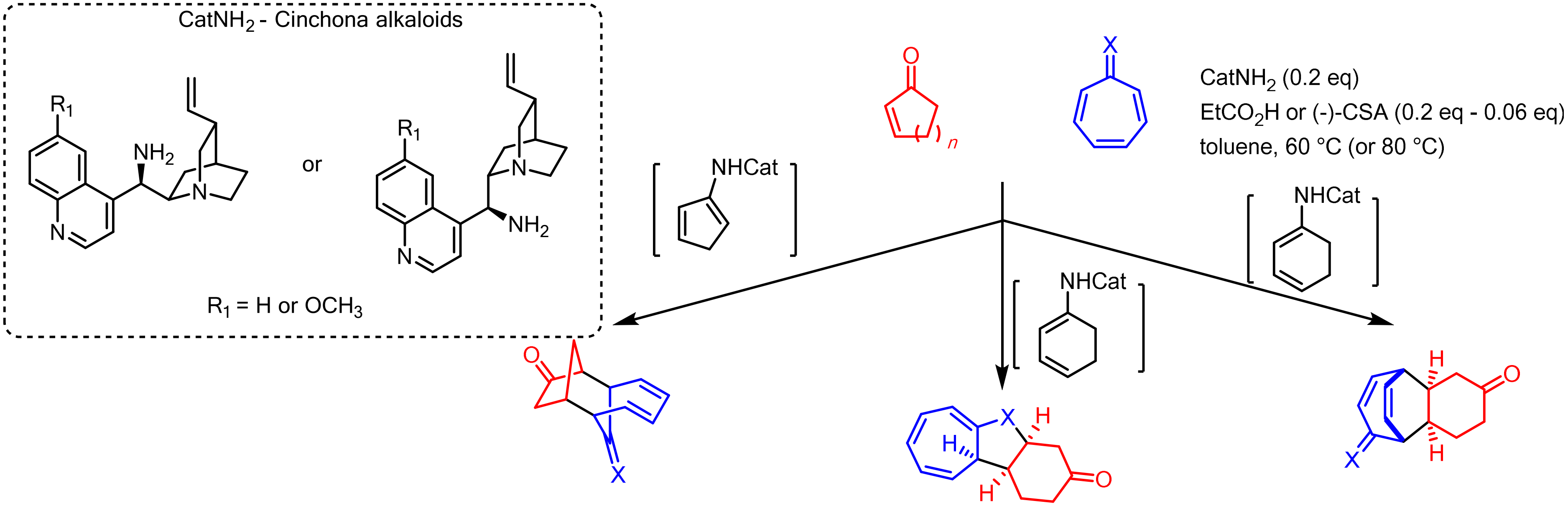
Xie, M. *et al*. *Angew. Chem. Int. Ed.* 52, 5604–5607 (2013).

Initial Vision

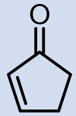
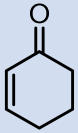
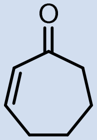


- Different catalytic amounts of dienamine accessible via amino catalyst – can induce periselectivity

Mose, R.; Preegel, G.; Larsen, J.; Jakobsen, S.; Iversen, E.H.; Jørgensen, K. A. *Nature Chem.* **2016**, Advance online publications

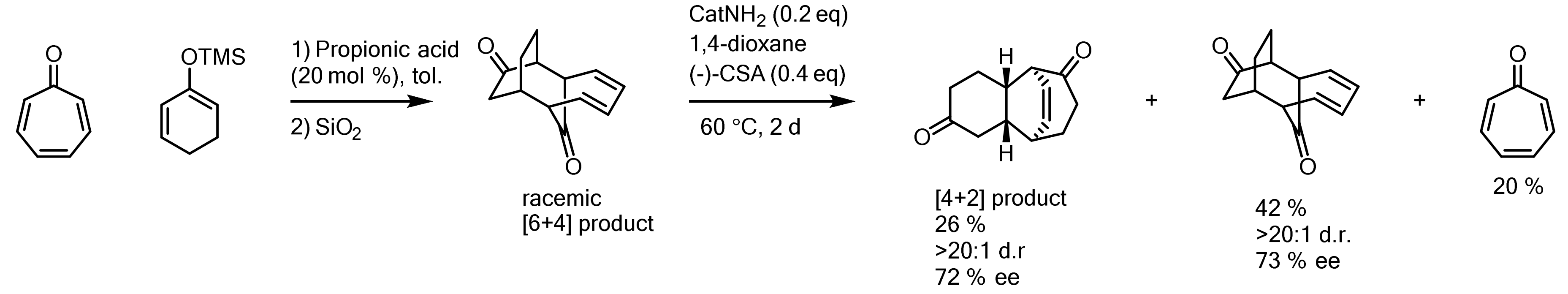


CatNH$_2$ (0.2 eq)
EtCO$_2$H or (-)-CSA (0.2 eq - 0.06 eq)
toluene, 60 °C (or 80 °C)

2-cyloalkenone	X	[6+4] adduct	[8+2] adduct	[4+2] adduct
	O	51 %, 95 % ee, >20:1 d.r.	No product	No product
	C(CN)$_2$	50 %, 42 % ee, >20:1 d.r.	No product	No product
	C(CN)CO$_2$Et	NR	NR	NR
	O	No product	No product	**72 %, 71 % ee, >20:1 d.r.**
	C(CN)$_2$	No product	No product	**56 %, 87 % ee, >20:1 d.r.**
	C(CN)CO$_2$Et	No product	58 %, 98 % ee, 85:15 d.r.	No product
	O	NR	NR	NR
	C(CN)$_2$	5 %, 52 % ee, >20:1 d.r.	48 %, >99 % ee, 9:1 d.r.	No product
	C(CN)CO$_2$Et	No product	61 %, 99 % ee, >20:1 dr	No product

Mose, R.; Preegel, G.; Larsen, J.; Jakobsen, S.; Iversen, E.H.; Jørgensen, K. A. *Nature Chem.* **2016**, Advance online publications

Reaction Pathway Elucidation



- [6+4] product not available in initial tests
- Indication of retro-[6+4] and re-formation of [4+2] product

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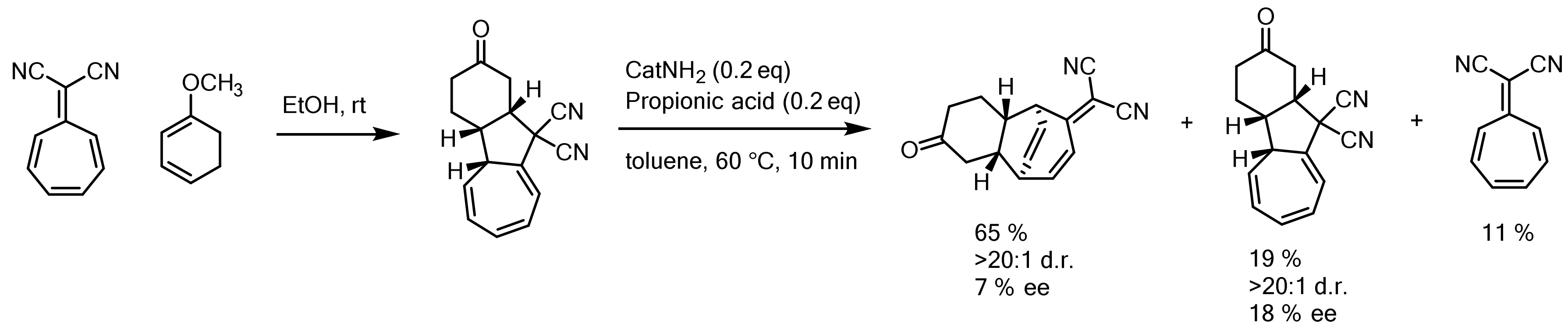
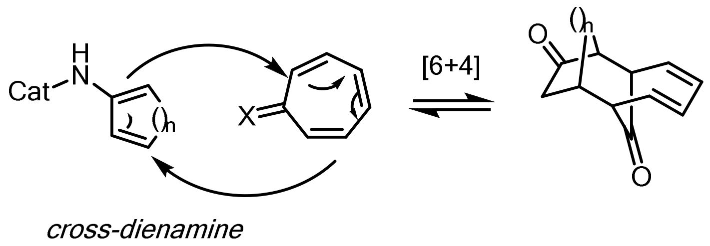
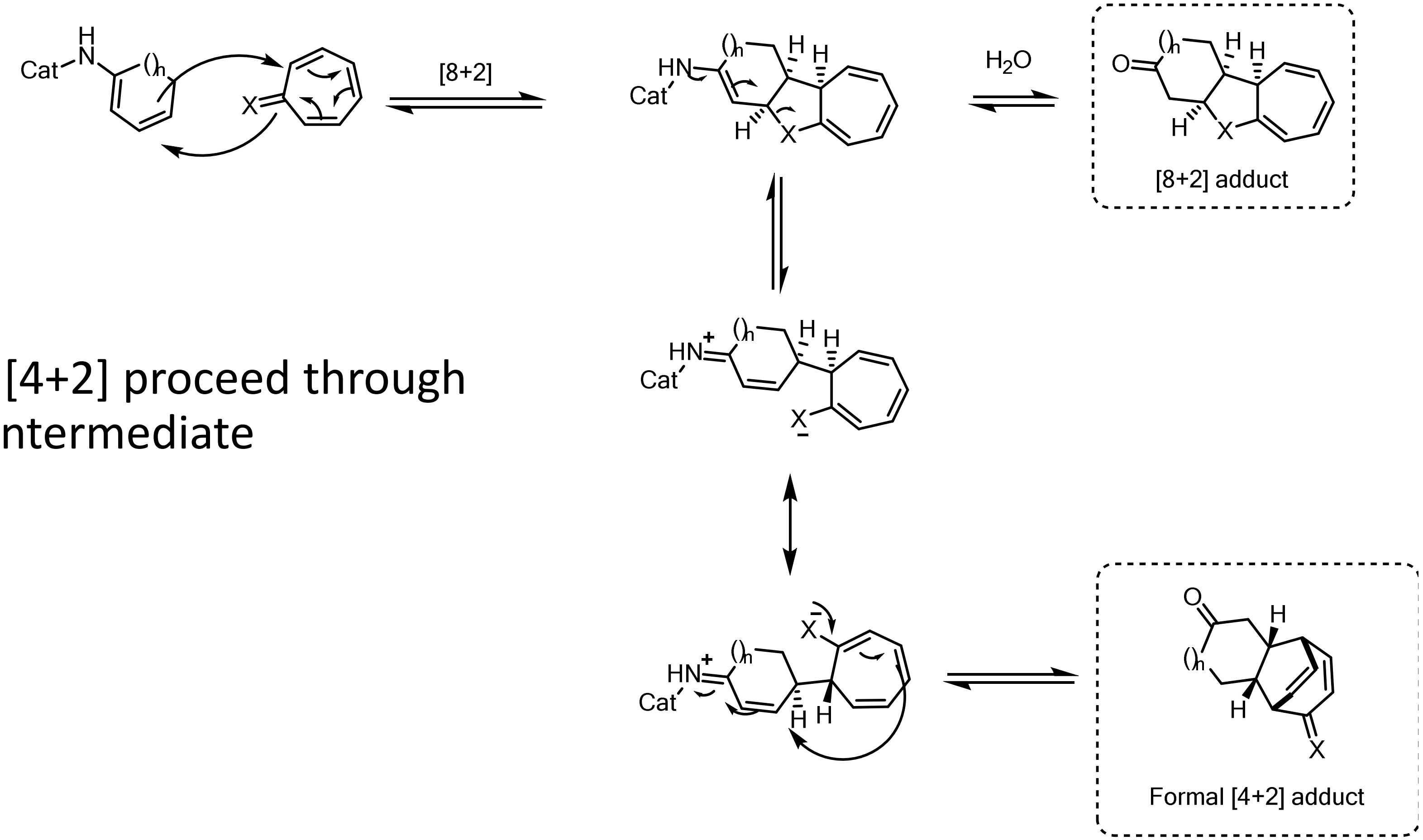


- Interconversion of [8+2] is completely halted without cat.

Mose, R.; Preegel, G.; Larsen, J.; Jakobsen, S.; Iversen, E.H.; Jørgensen, K. A. *Nature Chem.* **2016**, Advance online publications

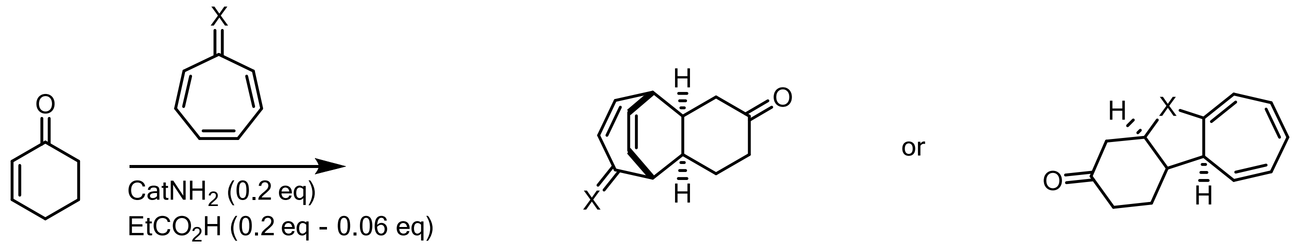


- [6+4] proceeds with cross-dienamine



- [8+2] and [4+2] proceed through common intermediate

Periselectivity

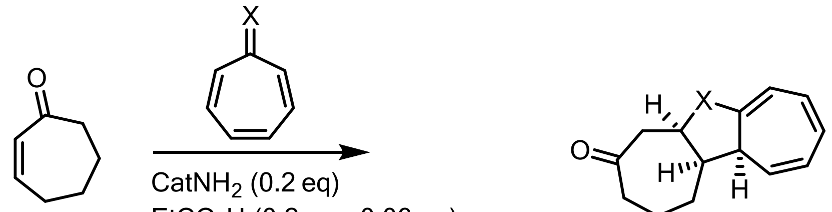


CatNH$_2$ (0.2 eq)
EtCO$_2$H (0.2 eq - 0.06 eq)
toluene, 60 °C

or

X = O: 72 %, 71 % ee
X = C(CN)$_2$: 56 %, 87 % ee

X = C(CN)CO$_2$Et: 58 %, 98 % ee

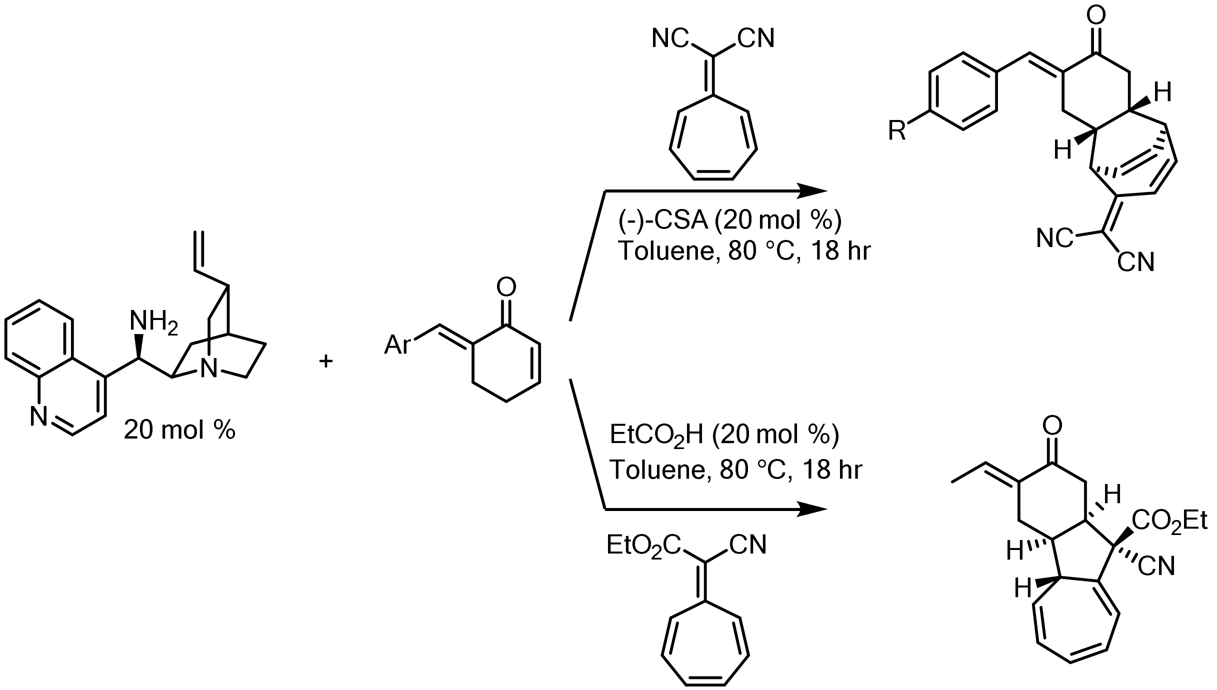


CatNH$_2$ (0.2 eq)
EtCO$_2$H (0.2 eq - 0.06 eq)
toluene, 60 °C

X = O: NR
X = C(CN)$_2$: 48 %, >99 % ee
X = C(CN)CO$_2$Et: 61 %, 99 % ee

- Cyclohexeneone and cyclohepteneone undergo [8+2] cycloaddition initially

Studies on Electronic Effects of Cycloalkenone

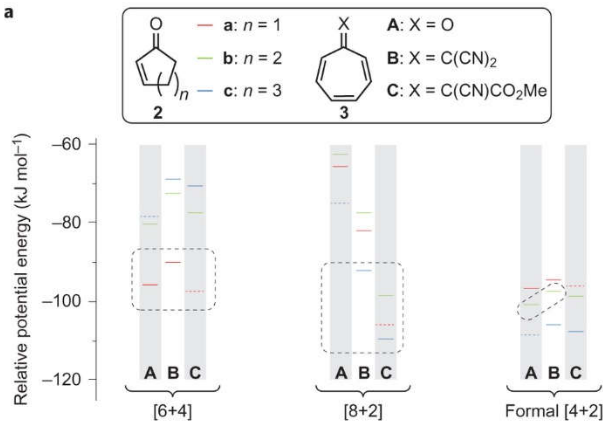


R = CO_2Me: 29 %, >20:1 d.r., 61 % ee
R = H: 53 %, 10:1 d.r., 69 % ee
R = OMe: 69 %, >20:1 d.r., 80 % ee

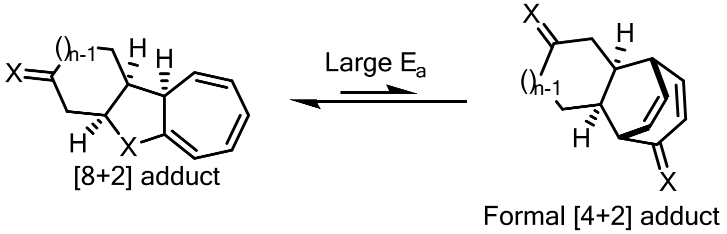
R = CO_2Me: 20 %, >20:1 d.r., 99 % ee
R = H: 55 %, 4:1 d.r., 99 % ee
R = OMe: 52 %,14:1 d.r., >99 % ee
R = Br: 49 %, >20:1 d.r., >99 % ee

- Periselectivity of the 2-cyclohexenone cycloadditions depends on heptafulvene rather than electronic properties of cyclohexenone

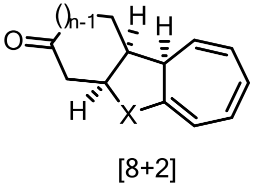
Potential Energies



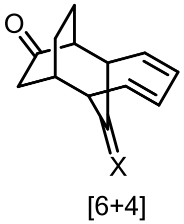
When:



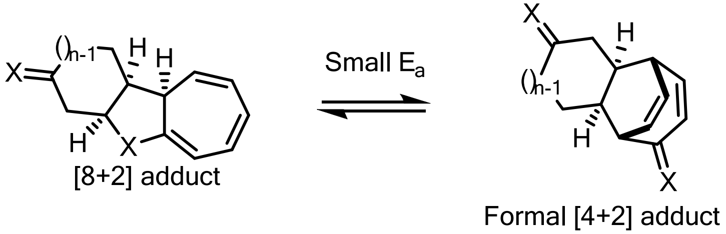
then



or

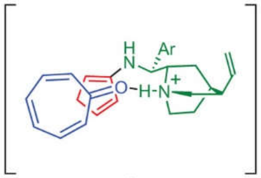


When:

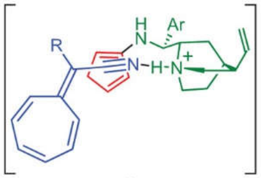


then the most thermodynamically most stable of the 3 products is formed

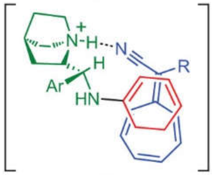
Transition States



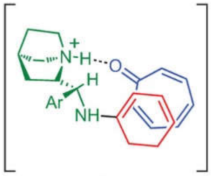
I
[6+4] cycloaddition
Good fit



II
[6+4] cycloaddition
Poor fit



III
[8+2] cycloaddition
Good fit

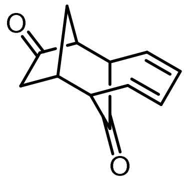


IV
[8+2] cycloaddition
Poor fit

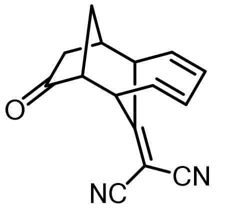
[6+4] – protonated condensation product (cross dienamine is set-up for H-bond with tropone, placing 6π component *exo* (I and II)

[8+2] – protonated condensation product (linear dienamine) is set-up for H-bond through cyano group, placing the 8π component *endo* (III and IV)

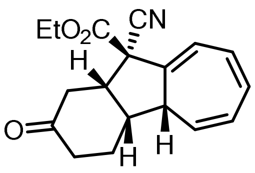
Substrate Summation



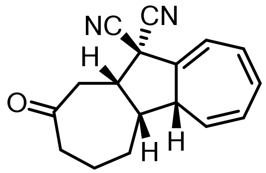
51 %, >20:1 d.r., 95 % ee
First example of catalytic stereoselective [6+4]



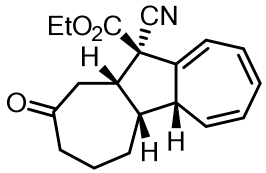
50 %, >20:1 d.r., 42 % ee)



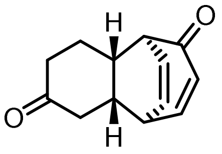
58 %, 85:15 d.r., 98 % ee



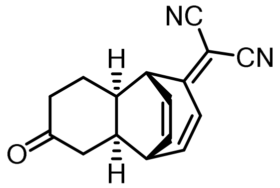
48 %, 9:1 d.r., >99 % ee



61 %, >20:1 d.r., 99 % ee



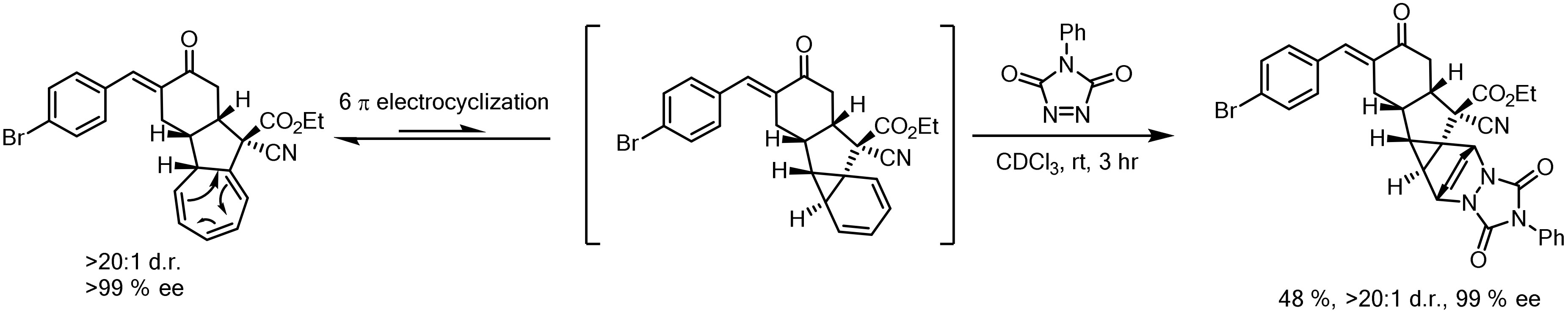
72 %, >20:1 d.r., 71 %

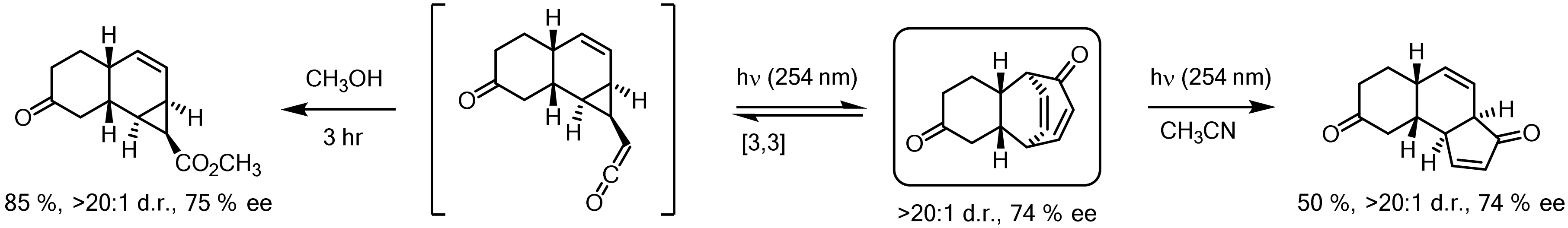


56 %, >20:1 d.r., 87 % ee

- Examples of higher-order, catalytic, stereoselective cycloadditions

Further Uses





- Simple one-step transformations to all-carbon polycyclic compounds

Summary

- Newly developed organocatalytic asymmetrich higher-order cycloaddition reactions
  - [8+2], formal [4+2], and [6+4] cycloadducts produced
  - Highly stereoselective
  - Cinchona alkaloid primary amines as catalysts
  - Periselectivity is controlled by 2-cycloalkenone ring-size and heptafulvene substitution patterns

- Current Limitations
  - Currently limited substrate scope
  - Certain cases where periselectivity is low