

Asymmetric Catalysis for Fine Chemicals Synthesis

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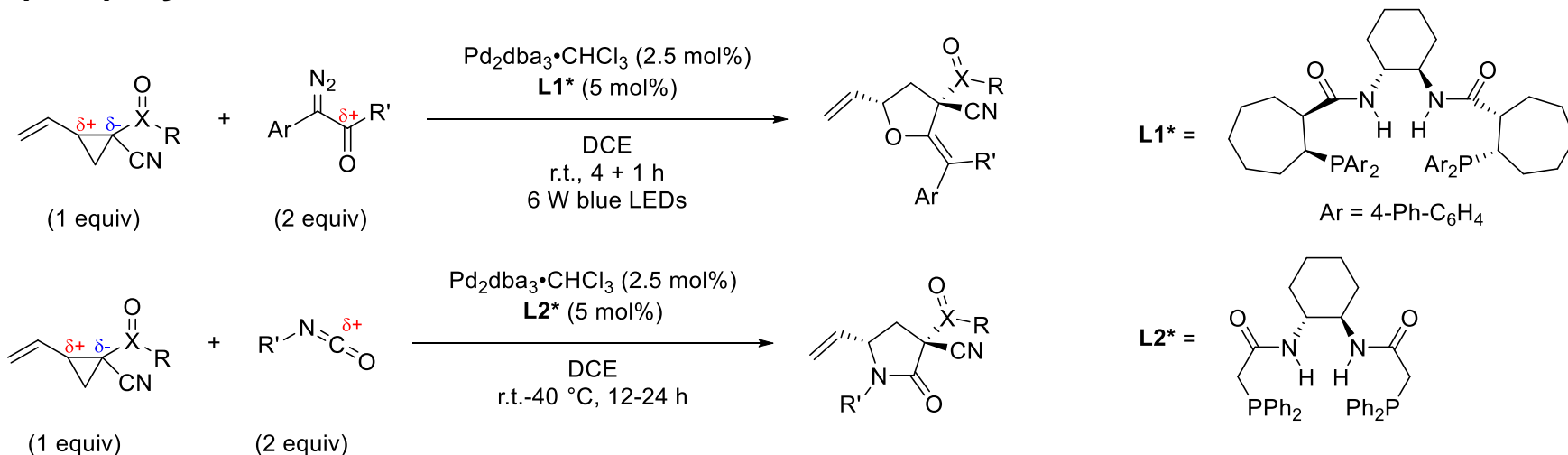


Taming Chiral Quaternary Stereocenters via Remote H-Bonding Stereoinduction in Palladium-Catalyzed (3+2) Cycloadditions

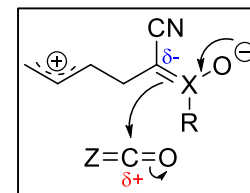
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Introduction: Reaction and Reactivity

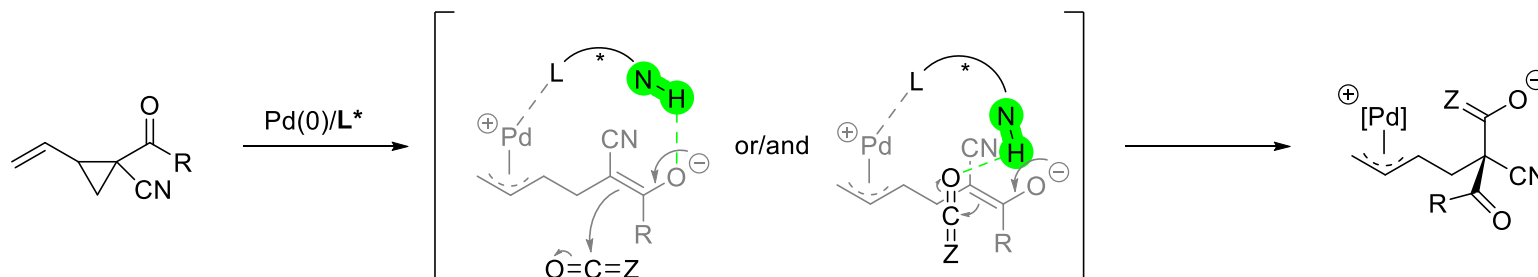
(3+2) Cycloaddition



- The reaction is a **(3+2) cycloaddition**
- **Nucleophile:** dipolar intermediate of ring-opened cyclopropane, nucleophilic in position beta to oxygen
- **Electrophile:** central C-atom of ketene/isocyanate
- **Bond formation:** 1) attack of dipolar intermediate on ketene or isocyanate
2) intramolecular attack of O- or N-nucleophile on π -allyl system
- **Catalyst:** Pd, chiral diphosphine ligand with diamide core

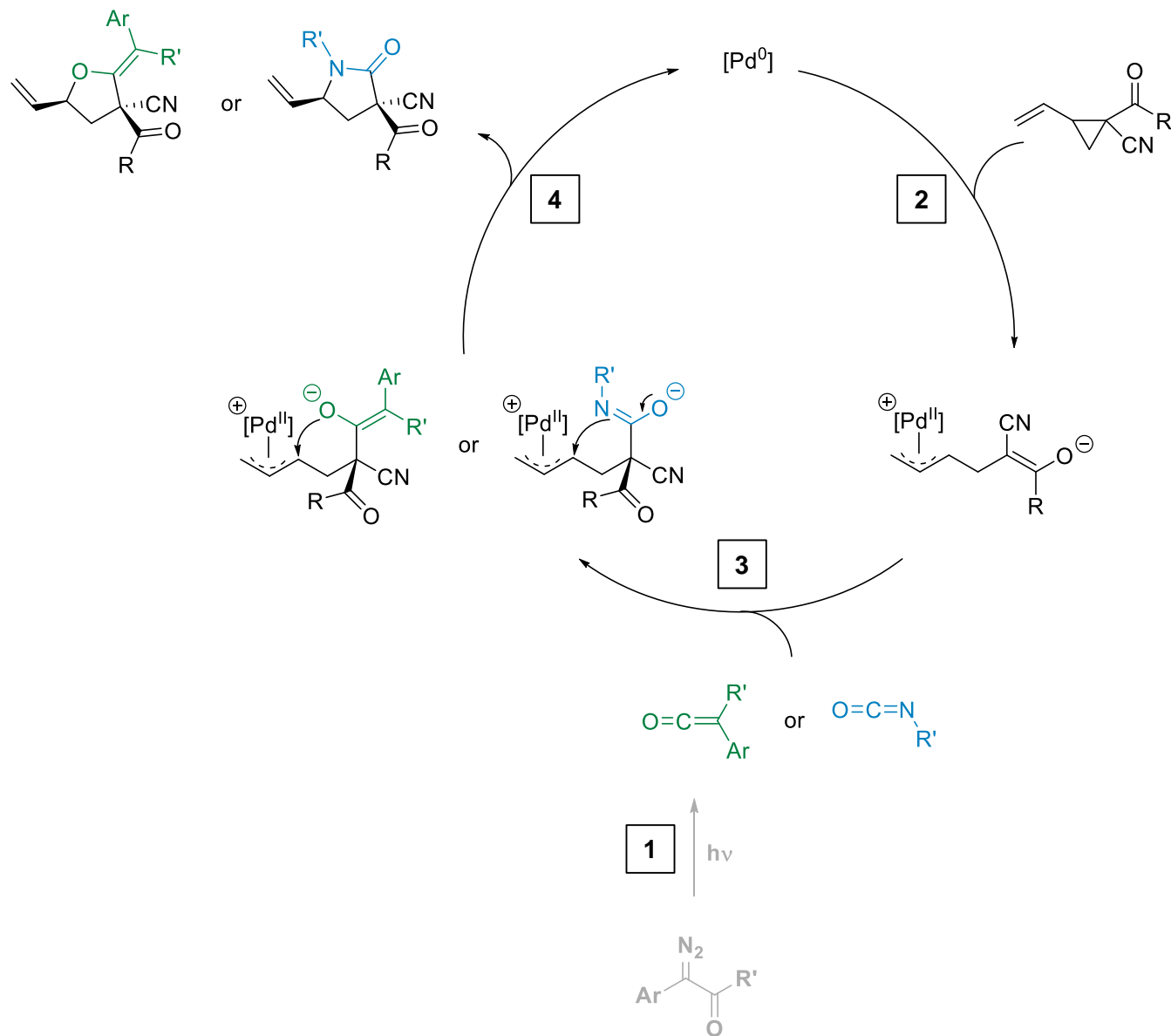


Principle of Activation

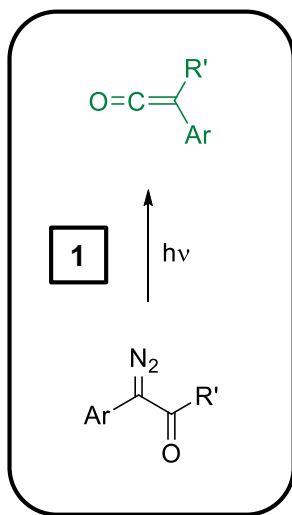


- **Activation of cyclopropane** by push-pull effect of vicinal EDG and EWGs
- **Twofold LUMO activation:**
 - **LUMO activation** through formation of $\text{Pd}-\pi$ -allyl system
 - **Possible LUMO activation** of ketene/isocyanate by H-bonding interaction with ligand
- **Asymmetric induction** by H-bonding interaction between chiral ligand and anionic EWG, and/or the ketene/isocyanate

Catalytic Cycle

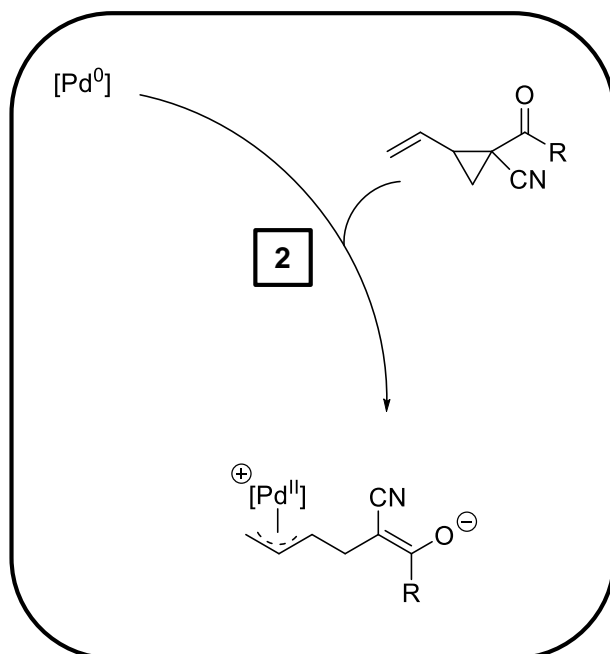


Catalytic Cycle 1



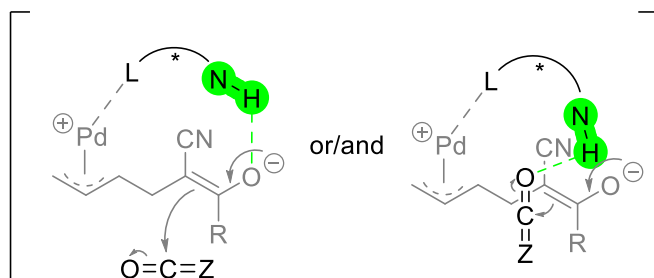
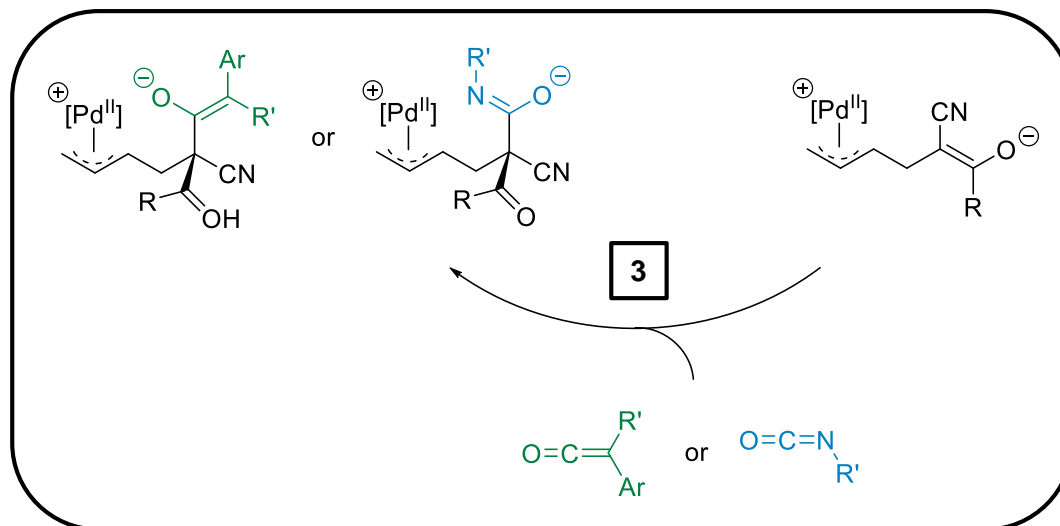
For α -diazoketones: **photoinduced Wolff rearrangement** to produce ketene

Catalytic Cycle 2



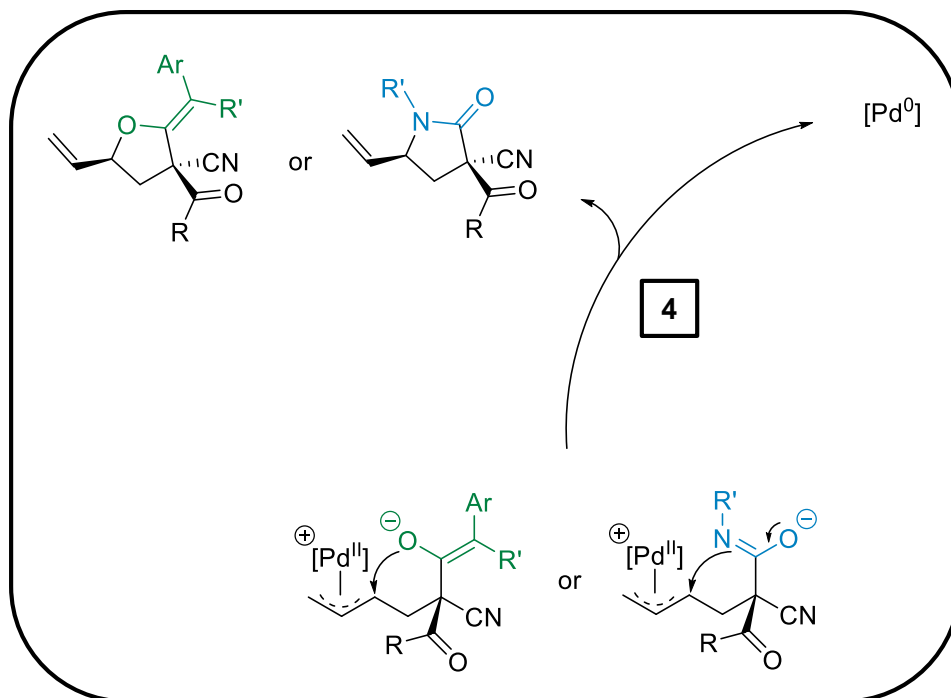
LUMO activation: ring opening and formation of zwitterionic Pd- π -allyl intermediate

Catalytic Cycle 3



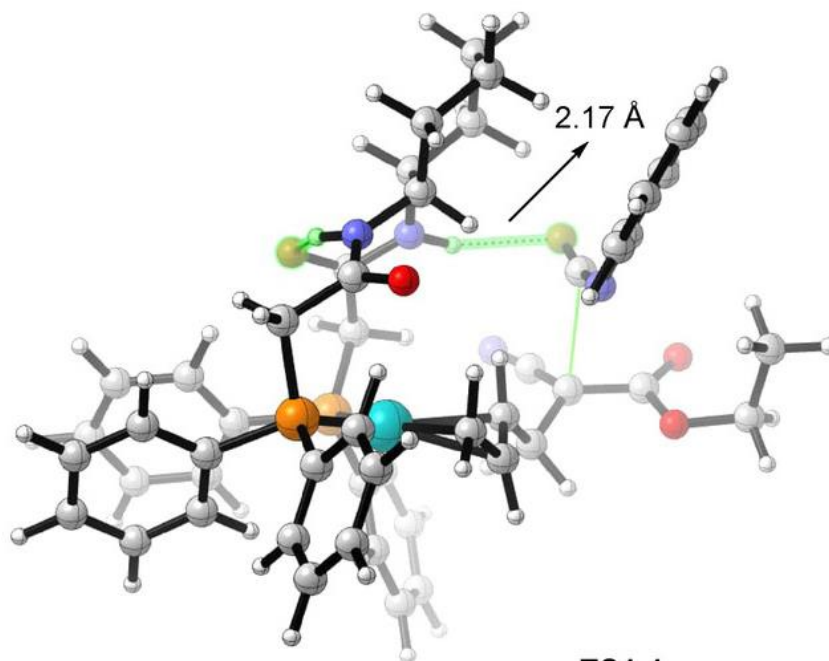
- Rate-determining **C-C bond formation** by attack of dipolar intermediate on (potentially **LUMO-activated**) ketene/isocyanate
- **Asymmetric induction**

Catalytic Cycle 4

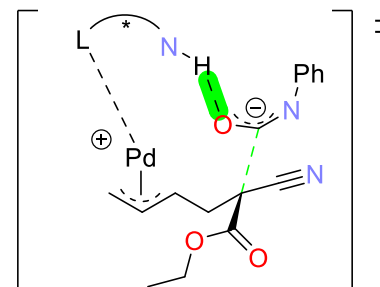


- **C-O or C-N bond formation** by intramolecular attack on Pd- π -allyl system
- **Catalyst turnover**

Asymmetric Induction

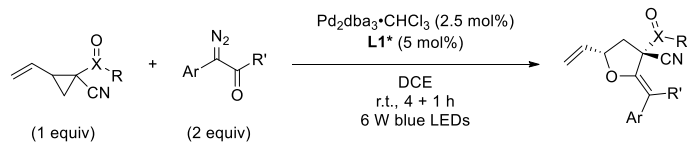


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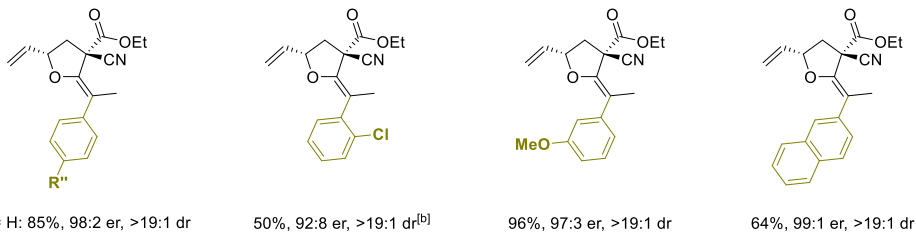


- **H-bonding interaction** between amide in the chiral ligand and phenyl isocyanate
- Suitable spatial orientation of phenyl isocyanate and ester group of π -allyl-Pd intermediate to **avoid unfavoured steric repulsions**

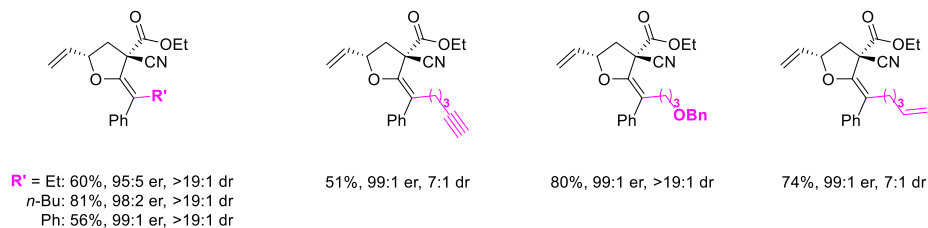
Scope: α -Diazocarbonyl Substrates



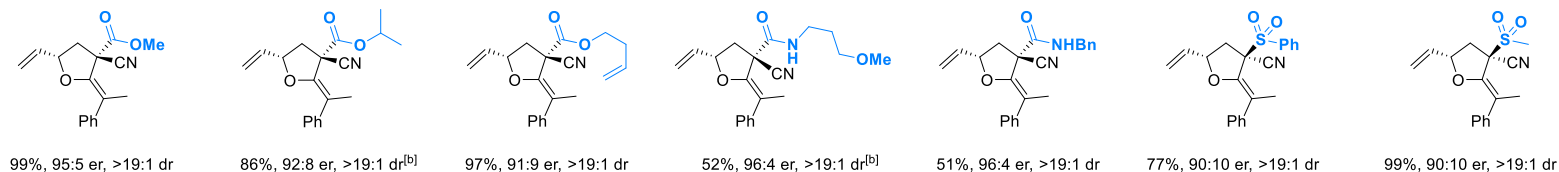
Aryl Substituents



Ketene Substituents



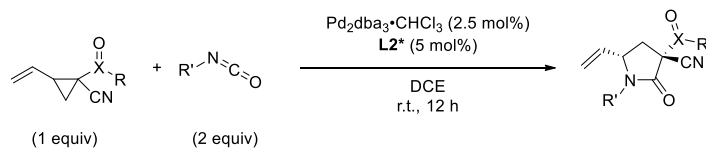
Carbonyl Derivatizations



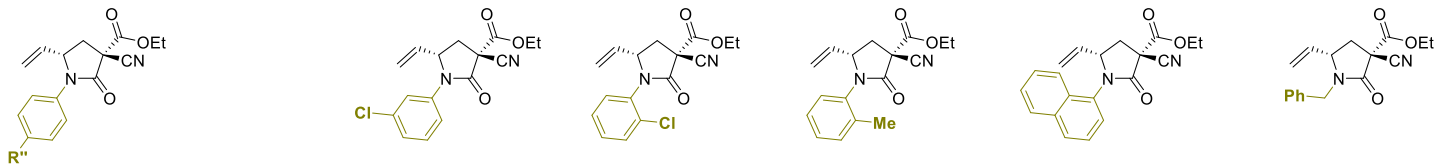
- Generally high yields and good *ers* & *drs* observed
- **Inverted configuration** when sulfones used

[b]: L2^* used

Scope: Isocyanate Substrates



N-Substituents



$\text{R}'' = \text{H}$: 95%, 97:3 er, >19:1 dr
 Me: 99%, 98:2 er, >19:1 dr
 F: 78%, 97:3 er, >19:1 dr
 Cl: 99%, 97:3 er, >19:1 dr

$\text{R}'' = \text{Br}$: 87%, 97:3 er, >19:1 dr
 OCF_3 : 98%, 95:5 er, 14:1 dr
 CF_3 : 87%, 95:5 er, >19:1 dr

99%, 94:6 er, >19:1 dr

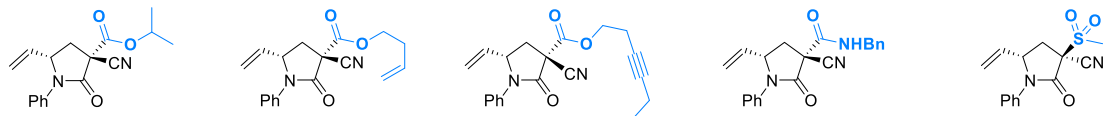
99%, 96:4 er, >19:1 dr

99%, 98:2 er, >19:1 dr

99%, 96:4 er, >19:1 dr

54%, 97:3 er, 11:1 dr
 (carried out at 40 °C, 24 h)

Carbonyl Derivatizations



81%, 96:4 er, >19:1 dr

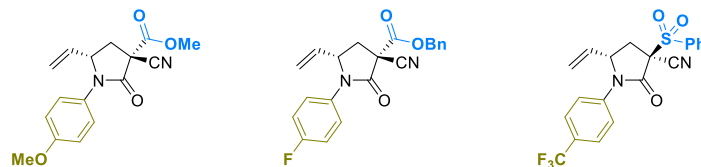
76%, 94:6 er, >19:1 dr

60%, 94:6 er, >19:1 dr

83%, 97:3 er, 5:1 dr

73%, 95:5 er, 7:1 dr

N- and Carbonyl Substitution



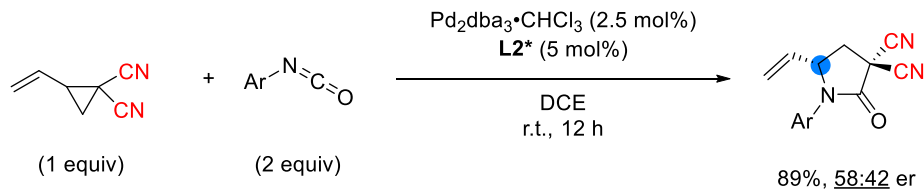
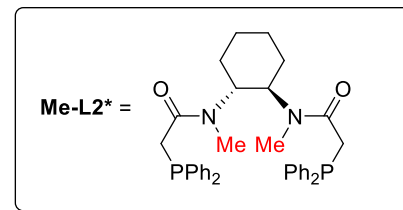
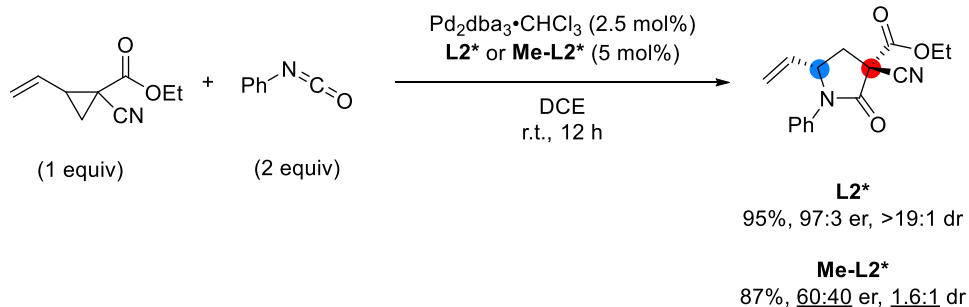
72%, 99:1 er, >19:1 dr

87%, 98:2 er, >19:1 dr

87%, 91:9 er, 4:1 dr

- Generally high yields and good *ers* & *drs* observed
- **Inverted configuration** when sulfones used

Control Studies



- Asymmetric induction via **H-bonding** confirmed
- **Flexibility** of H-bond acceptor on cyclopropane enables stereocontrol

Critical Analysis: Novelty

Strong points

- Control over quaternary stereocenters enabled by use of different EWGs
- First reported simultaneous stereo-handling of donor and acceptor units in D-A cyclopropanes

Weaker points

- Use of known reaction and substrate types
- Common principle of activation
- Importance of H-bond donors in Trost-type ligands established previously

Critical Analysis: Practicability

Strong points

- Mild conditions (mostly rt, mild heating to 40 °C for one scope entry)
- High enantio- and diastereoselectivities, broad scope
- Cyclopropanes accessible in one step

Weaker points

- Use of modified ligands
- Different ligands required depending on substrate
- Restricted EWG substituents on quaternary carbon (H-bonding necessary)
- Need for Schlenk techniques under argon

Critical Analysis: Sustainability

Strong points

- Mild conditions (rt or 40 °C, use of visible light for ketene generation)
- Very good atom economy (no additives; only loss of N₂)

Weaker points

- Harsh ligand synthesis (10 equiv. AlCl₃ & 100 °C required)
- «Red» solvent (DCE) for reaction
- Use of Pd with moderately high loading (2.5 mol%)

Questions

Question 1

Why can this reaction be proposed as an ylide reaction? What would be the relationship between the charges?

Question 2

In the case of π -allyl chemistry, we have distinguished cases where ionization or nucleophilic attack was enantiodetermining: Which one is occurring here?

Question 3

Compare this reaction with the trimethylenemethane (TMM) cycloaddition developed by Trost, which also gives 5-membered rings: What is similar, what is different?