Asymmetric Catalysis for Fine Chemical Synthesis

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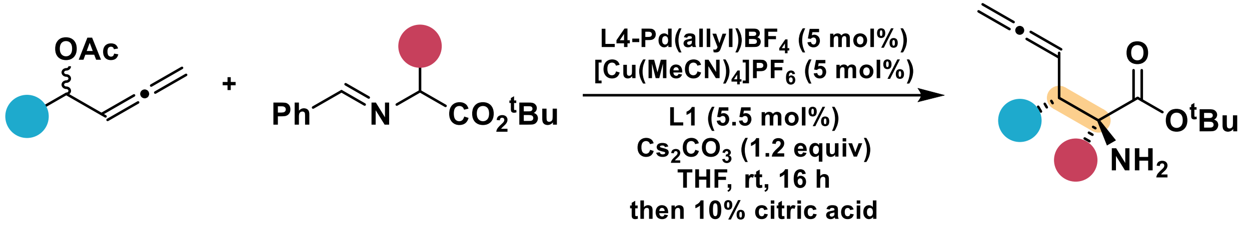
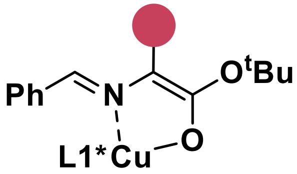
Valentas Olikauskas, Côme Standaert

Stereodivergent Synthesis of Allenes with α,β-Adjacent Central Chiralities Empowered by Synergistic Pd/Cu Catalysis

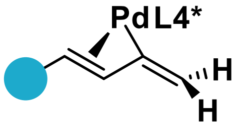
Ling Zhao, Yicong Luo, Junzhe Xiao, Xiaohong Huo, Shengming Ma,* and Wanbin Zhang*

Introduction: Reaction and Reactivity

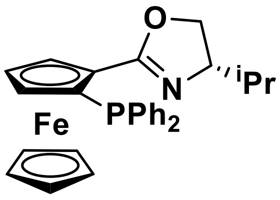




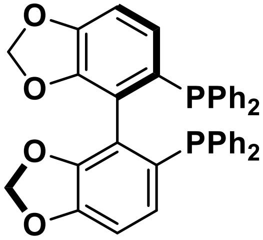
nucleophile



electrophile



(*S*, *S*$_p$)-L1

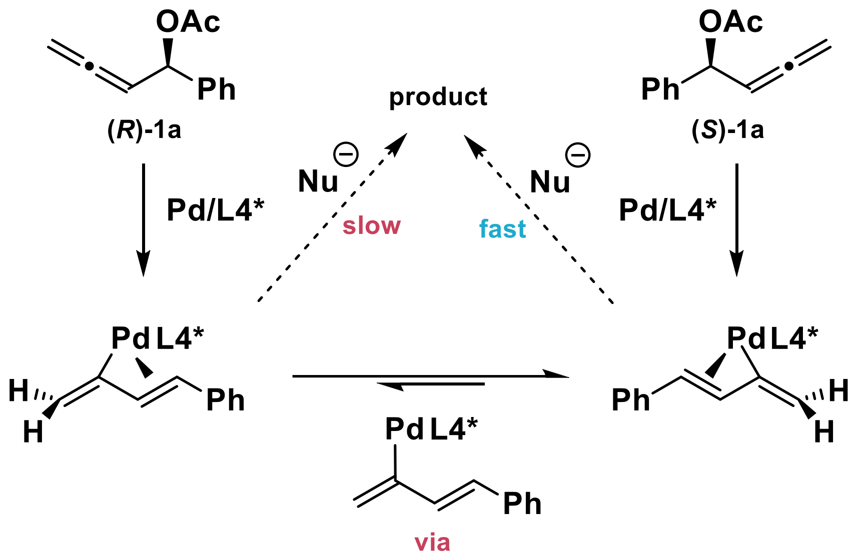


(*R*)-SEGPHOS (L4)

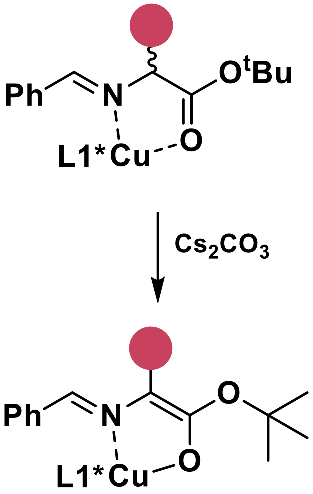
- **This reaction is** an allenylic alkylation with amino-acid derived aldimine esters
- **Nucleophile**: Cu-coordinated deprotonated aldimine ester
- **Electrophile:** Pd-activated η^3-butadienyl allenylic ester
- **Catalyst**: bimetallic catalytic system (Pd/Cu) with chiral ligands on both metal centres
- **Bond formation**: C(α-allene)-C(α-aldimine ester)

Principle of Activation

Electrophile

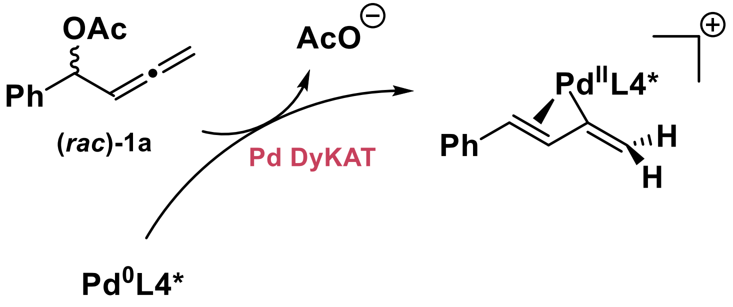


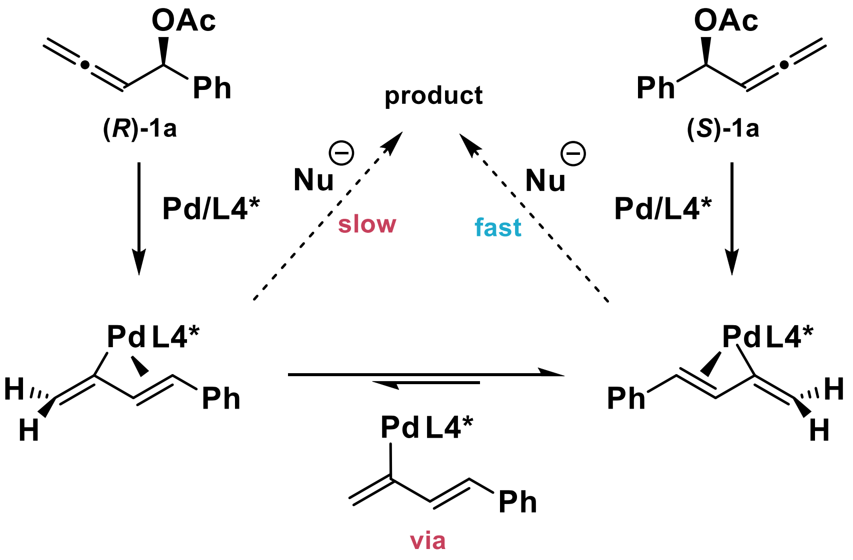
Nucleophile



- **Dual activation** by the bimetallic system
- Activation of the α-acetoxy **allene via** the **DyKAT** process **with Pd** catalyst
- Activation of the **aldimine ester via Cu**-coordination-**enabled deprotonation**
- **Individual stereocentre-control** with Pd and Cu chiral ligands

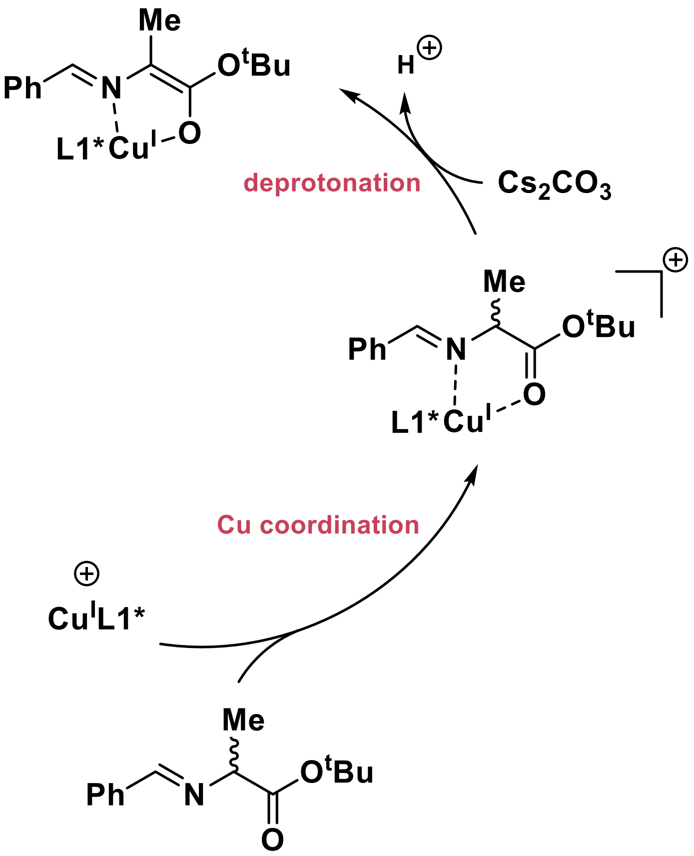
Catalytic Cycle – Pd DyKAT





- Activation of the α-acetoxy allene via the DyKAT process with a chiral Pd catalyst.
- One enantiomer of the electrophile reacts with a nucleophile faster than the other.
- Effectively, the racemic substrate is resolved into a single enantiomer of the active electrophile.

Catalytic Cycle – Nucleophile Activation

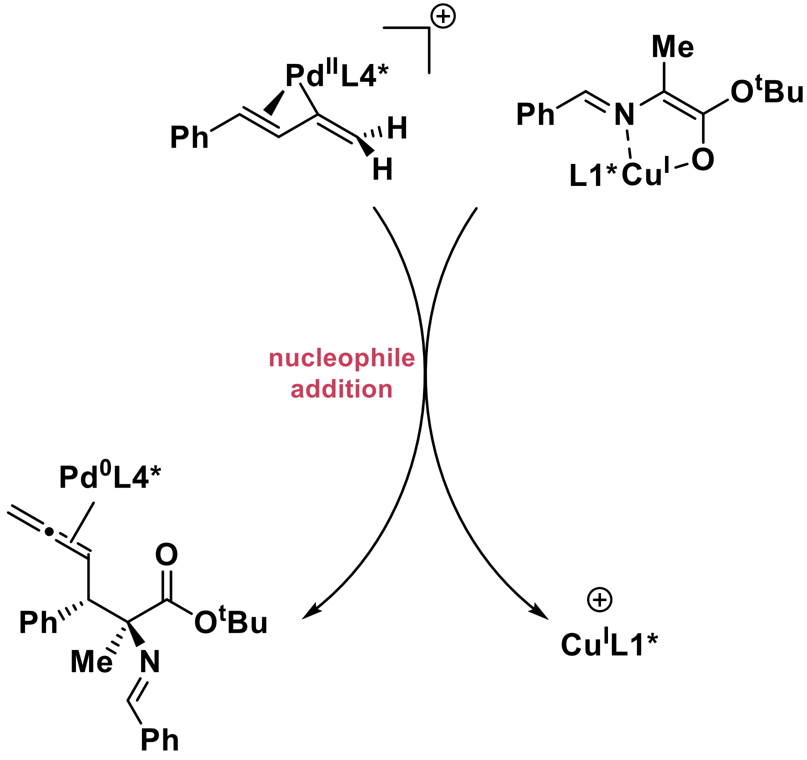


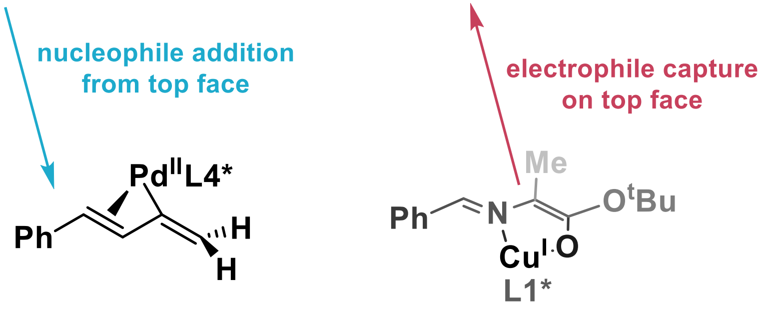
(*rac*)-2a

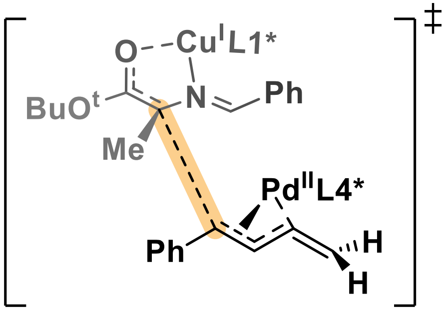
- Activation of the aldimine ester via Cu-coordination-enabled deprotonation.

Catalytic Cycle – Nucleophile Addition

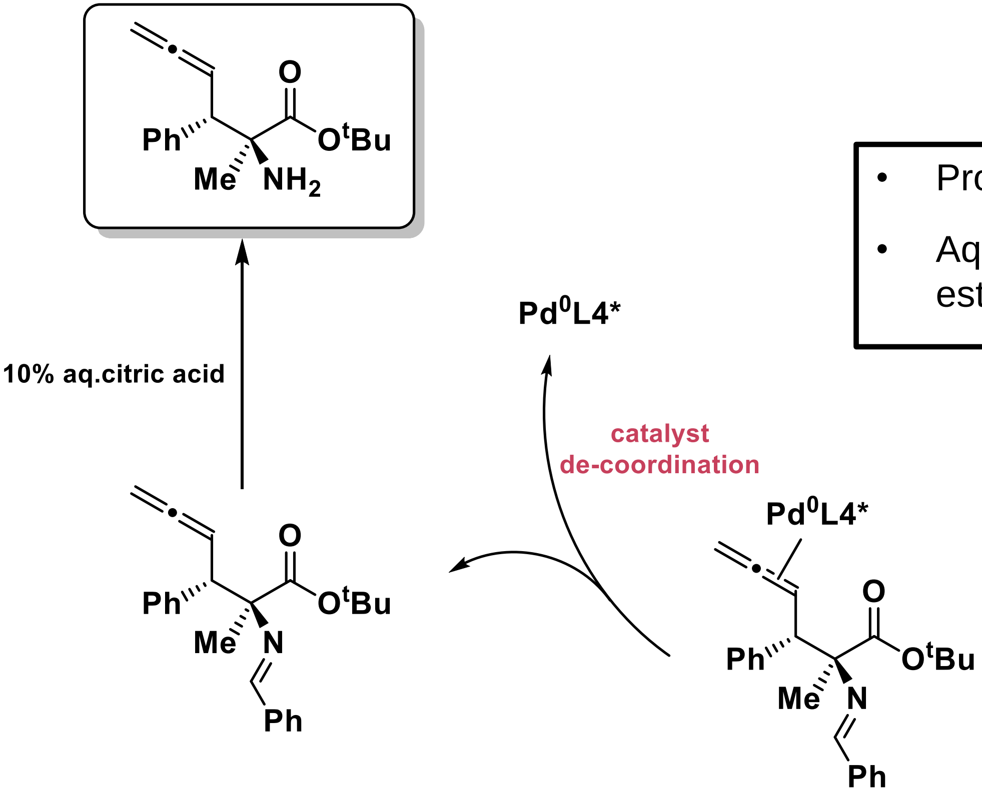
- C-C bond formation.
- Stereo-determining step – two stereocentres formed.
- Individual control of each stereocentre by Pd and Cu ligand choice.
- Possible Cu de-coordination from the aldimine ester before the electrophile capture.





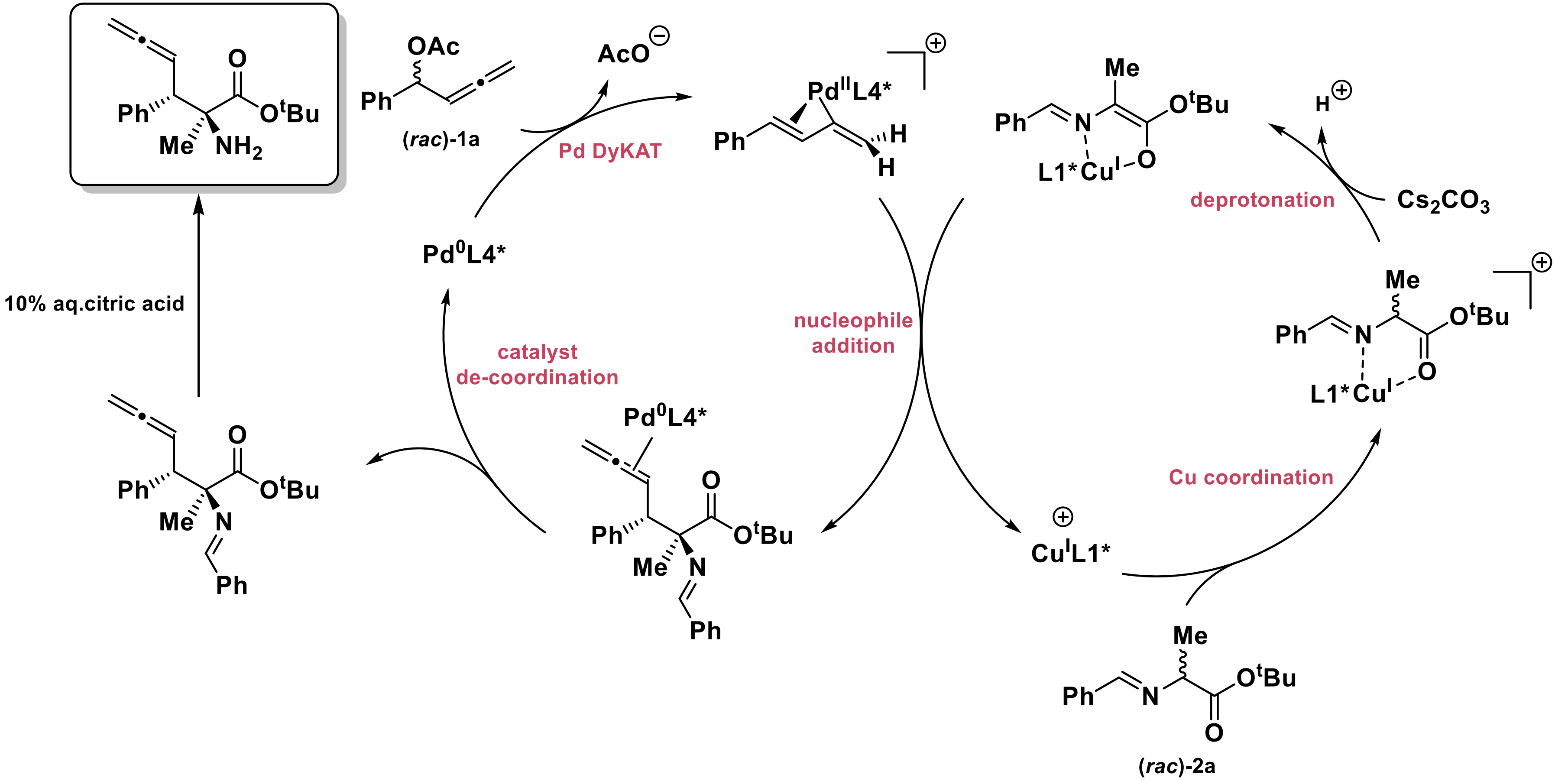


Catalytic Cycle – Pd Catalyst Regeneration



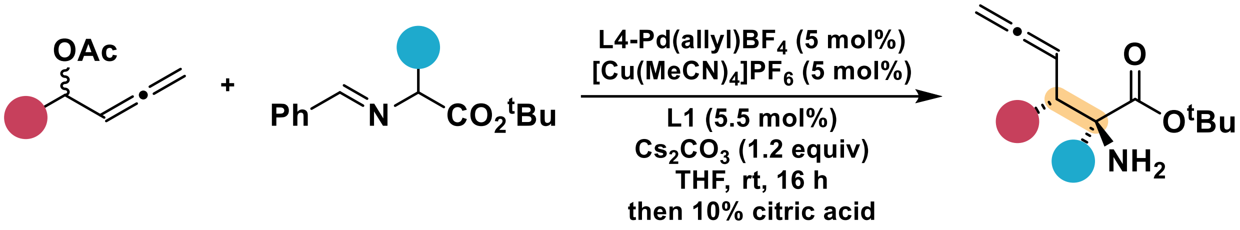
- Product release regenerates the Pd^0 complex.
- Aqueous citric acid work-up yields the α-amino ester product.

Catalytic Cycle

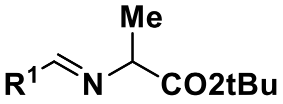


Scope and limitations

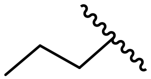
Protecting group effect of aldimine ester



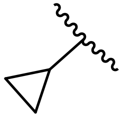
L4-Pd(allyl)BF_4 (5 mol%)
$[Cu(MeCN)_4]PF_6$ (5 mol%)
L1 (5.5 mol%)
Cs_2CO_3 (1.2 equiv)
THF, rt, 16 h
then 10% citric acid



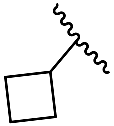
R^1=



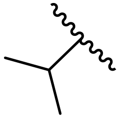
36% yield,
>99% ee



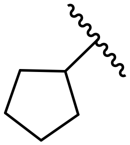
38% yield,
>99% ee



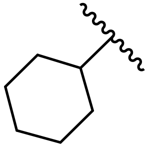
45% yield,
>99% ee



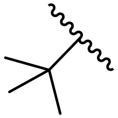
41% yield,
>99% ee



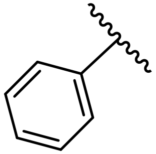
41%
yield,
>99% ee



70% yield,
>99% ee



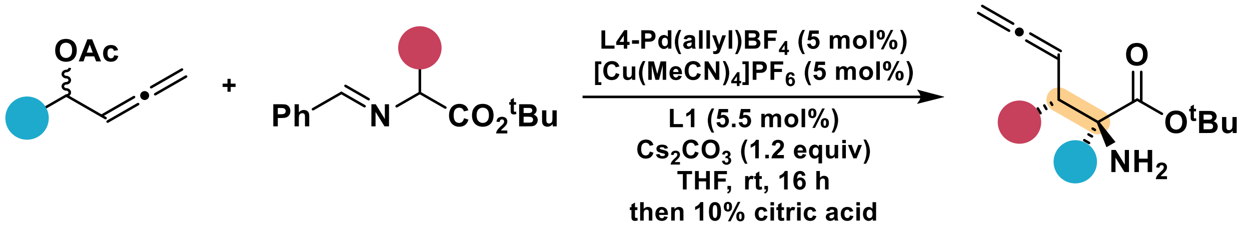
nr



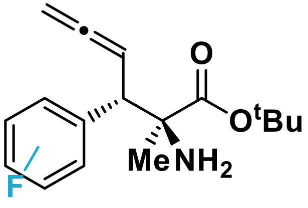
72% yield,
>99% ee

Scope and limitations

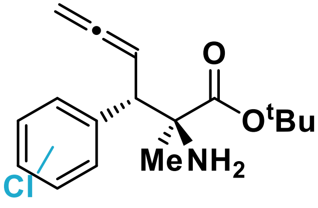
Aryl-substituted allenylic ester



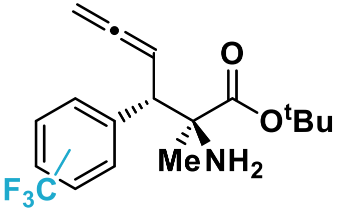
L4-Pd(allyl)BF_4 (5 mol%)
[Cu(MeCN)$_4$]PF_6 (5 mol%)
L1 (5.5 mol%)
Cs_2CO_3 (1.2 equiv)
THF, rt, 16 h
then 10% citric acid



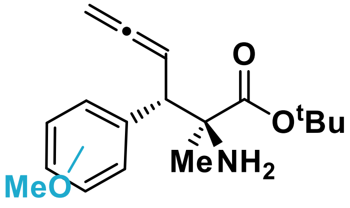
69-72% Yield:
> 20:1 dr, > 99%ee :



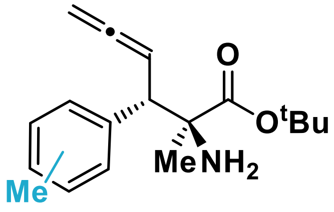
73-76% Yield:
> 20:1 dr, > 99%ee :



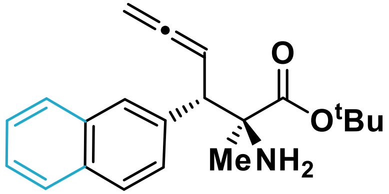
72% Yield:
> 20:1 dr, > 99%ee :



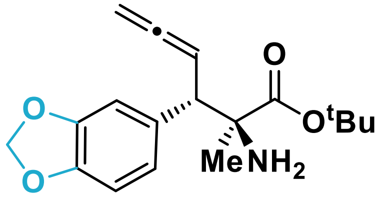
65-71% Yield:
> 20:1 dr, > 99%ee :



74-78% Yield:
> 20:1 dr, > 99%ee :



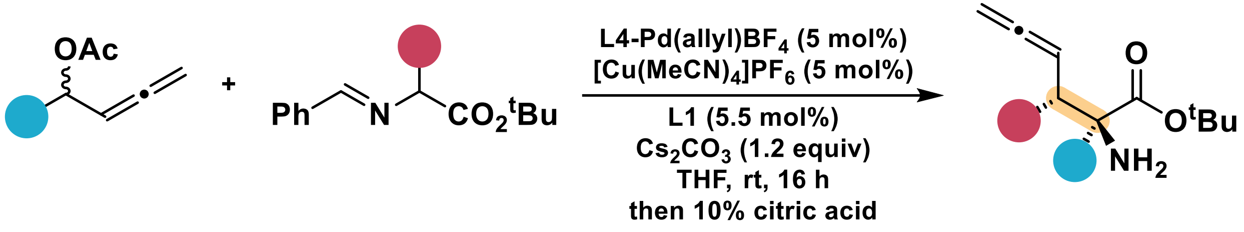
78% Yield:
> 20:1 dr, > 99%ee :

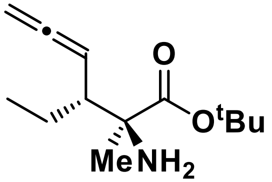


73% Yield:
> 20:1 dr, > 99%ee :

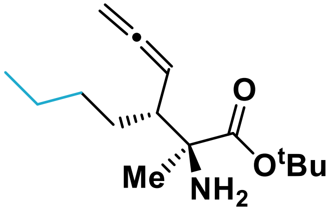
Scope and limitations

Alkyl-susbituted allenylic ester

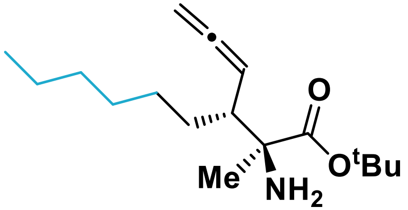




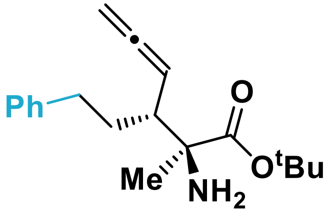
71% Yield
>20:1 dr, >99% ee



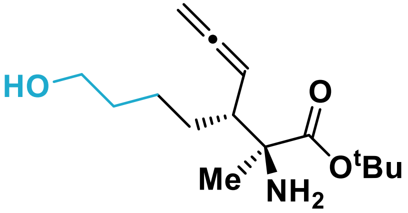
69% Yield
>20:1 dr, >99% ee



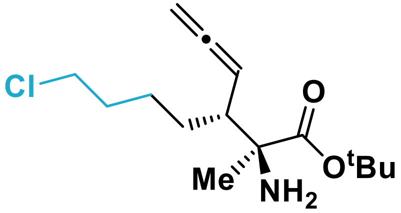
70% Yield
>20:1 dr, >99% ee



62% Yield
>20:1 dr, >99% ee



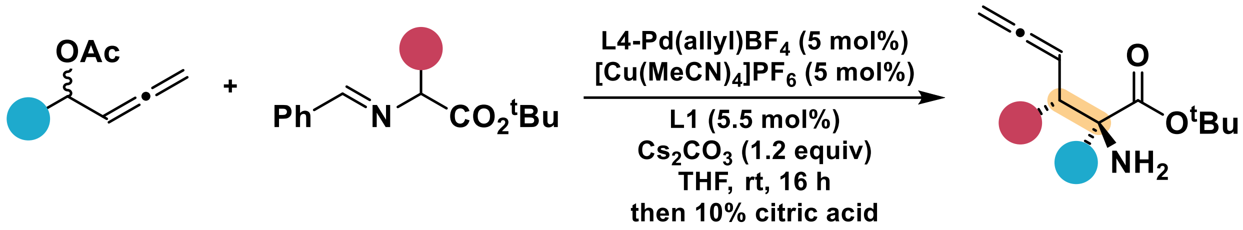
63% Yield
>20:1 dr, >99% ee



69% Yield
>20:1 dr, >99% ee

Scope and limitations

Drug-tethered allenyl acetates



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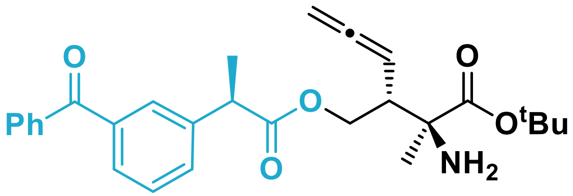
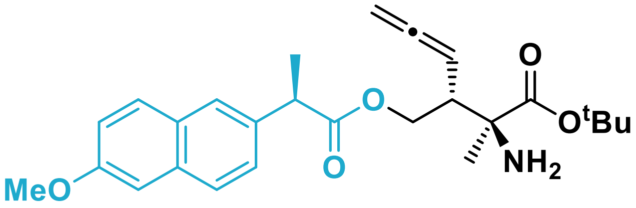
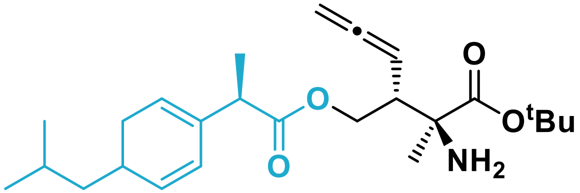
L1 (5.5 mol%)
Cs_2CO_3 (1.2 equiv)
THF, rt, 16 h
then 10% citric acid



52% Yield, >20:1 dr,



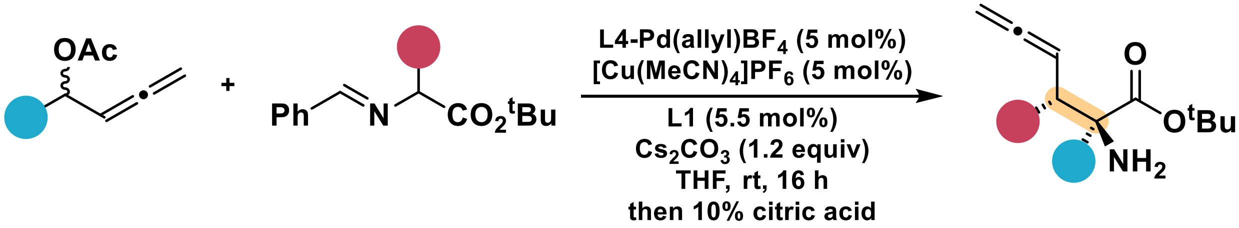
57% Yield, >20:1 dr,



54% Yield, >20:1 dr,

Scope and limitations

Aldimine esters



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[Cu(MeCN)$_4$]PF_6 (5 mol%)
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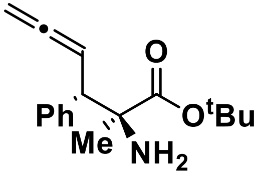
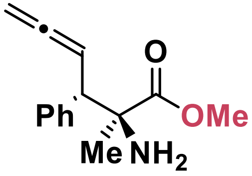
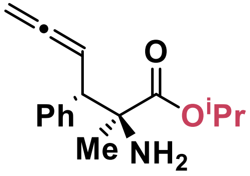


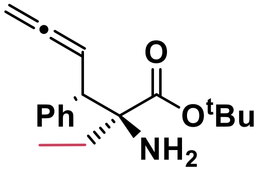
72% Yield
>20:1 dr, >99% ee



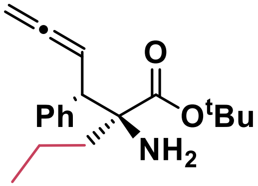
70% Yield
>6:1 dr, >99% ee



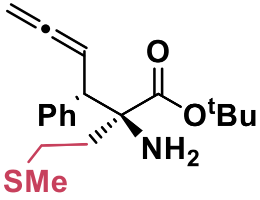
73% Yield
>15:1 dr, >99% ee



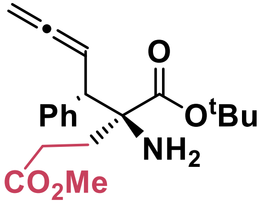
76% Yield
>20:1 dr, >99% ee



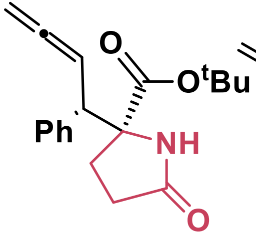
74% Yield
>20:1 dr, >99% ee



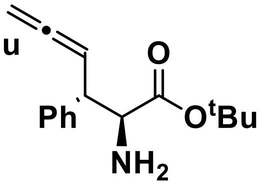
77% Yield
>20:1 dr, >99% ee



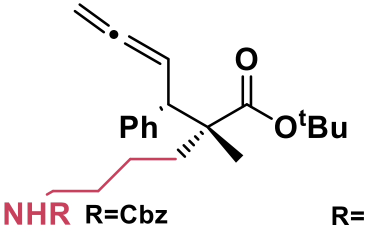
76% Yield
>20:1 dr, >99% ee



72% Yield
>20:1 dr, >99% ee



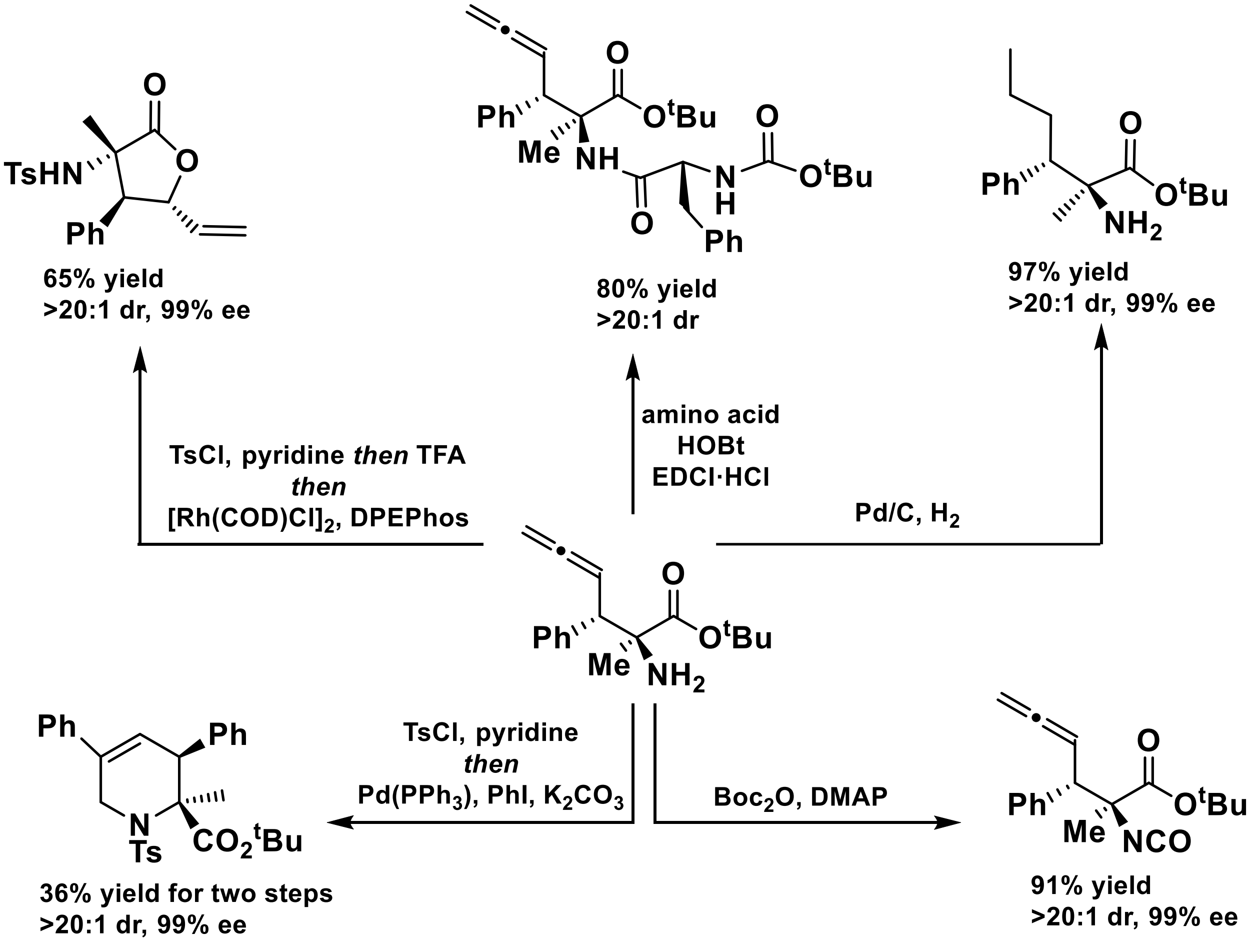
81% Yield
>14:1 dr, >99% ee



R=Cbz
61% Yield
>20:1 dr, >99% ee

R=Boc
65% Yield
>20:1 dr, >99% ee

Transformation of the chiral allenylic product



65% yield
>20:1 dr, 99% ee

80% yield
>20:1 dr

97% yield
>20:1 dr, 99% ee

TsCl, pyridine *then* TFA
then
$[Rh(COD)Cl]_2$, DPEPhos

amino acid
HOBt
EDCI·HCl

Pd/C, H_2

TsCl, pyridine
then
$Pd(PPh_3)$, PhI, K_2CO_3

Boc_2O, DMAP

36% yield for two steps
>20:1 dr, 99% ee

91% yield
>20:1 dr, 99% ee

Critical analysis: Novelty

Strong points

- First method to access all four diastereoisomers of the allene with two adjacent chiral centres
- Independent control of each stereocenter
- Novel η^3-butadienyl Pd intermediate

Weaker points

- Dual catalysis was not a new concept in asymmetric synthesis
- Known ligands were used for asymmetric induction

Critical analysis: Practicability

Strong points

- Chemicals are all available commercially
- Good tolerance for sensitive functional groups (e.g., OH, Sme, NHR)
- High stereoselectivity
- Gives access to enantioenriched valuable products
- Mild conditions

Weaker points

- Moderate yields for complex molecules
- The Cu(I) catalyst is air- and moisture-sensitive
- Inert atmosphere required
- Cs_2CO_3 can be problematic for large-scale reactions
- Relatively complex ligand syntheses for large-scale applications

Critical analysis: Sustainability

Strong points

- Reaction performed under mild conditions
- Solvent used: THF, yellow solvent
- Good atom economy (AcOH by-product)

Weaker points

- Use of expensive and precious palladium metal
- Requires inert atmosphere
- Involves stoichiometric base (Cs_2CO_3) and excess of allenylic acetate compared to nucleophile
- Relatively complex ligand syntheses for large-scale applications

Questions

Question 1

How does the palladium intermediate in this reaction differs from classical pi-allyl palladium intermediates

Question 2

Is there a kinetic resolution in this process? Why?

Question 3

Aldimine esters are popular starting materials in many asymmetric processes. Why?