Asymmetric Catalysis for Fine Chemical Synthesis

Presentation: *J. Am. Chem. Soc.* **2022**, *144,* 15480 - 15487
March 31, 2025.
Valentas Olikauskas & William Pellassy

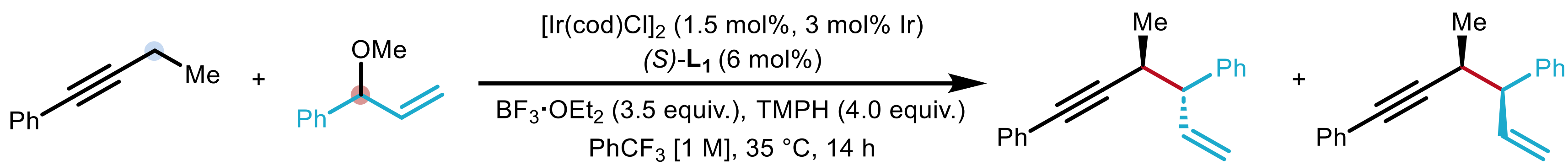
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Enantioselective and Diastereodivergent Allylation of Propargylic C-H Bonds

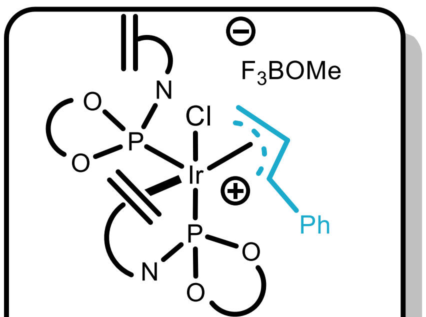
*Jin Zhu, Yidong Wang, Aaron D. Charlack, and Yi-Ming Wang**

Introduction: Reaction and Reactivity

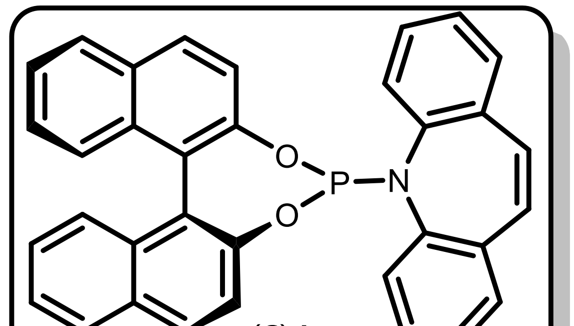
Asymmetric Propargylic Functionalization



>20:1 *dr*, >99% *ee*



Reservoir cat. (Formed *in situ*)



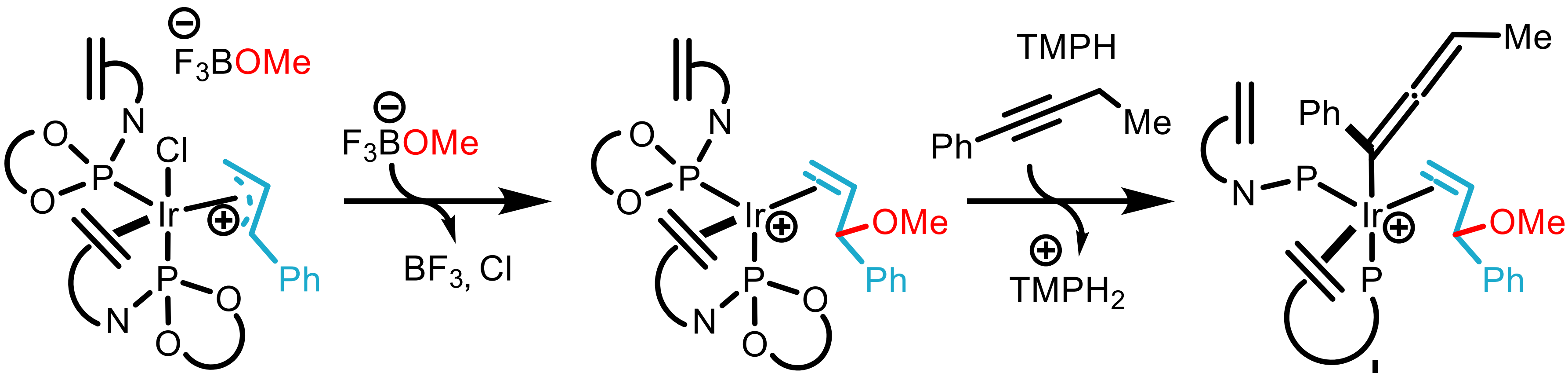
(*S*)-**L$_1$**

- The reaction is an **Alkyne-Allyl Coupling Reaction**.
- **Nucleophile**: Carbon in propargylic position
- **Electrophile**: Carbon in benzylic position
- **Bond formation**: Attack of allenylmetal species on π-allyl electrophile
- **Catalyst**: Phosphoramidite-alkene ligands (*S*)-**L$_1$** coordinated to π-allyliridium complex[1]

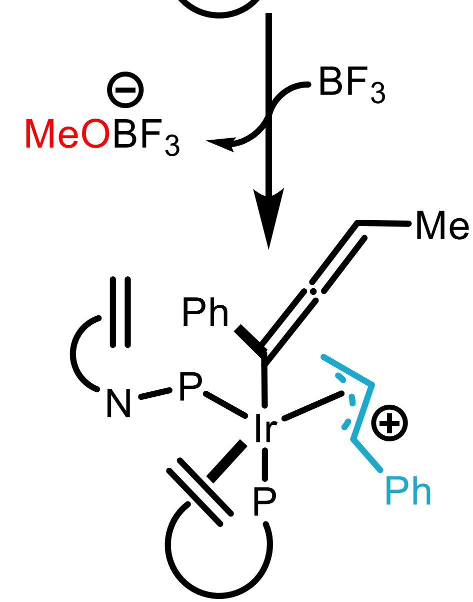
[1] *J. Am. Chem. Soc.* **2017**, *139*, 3603-3606.

Principle of activation

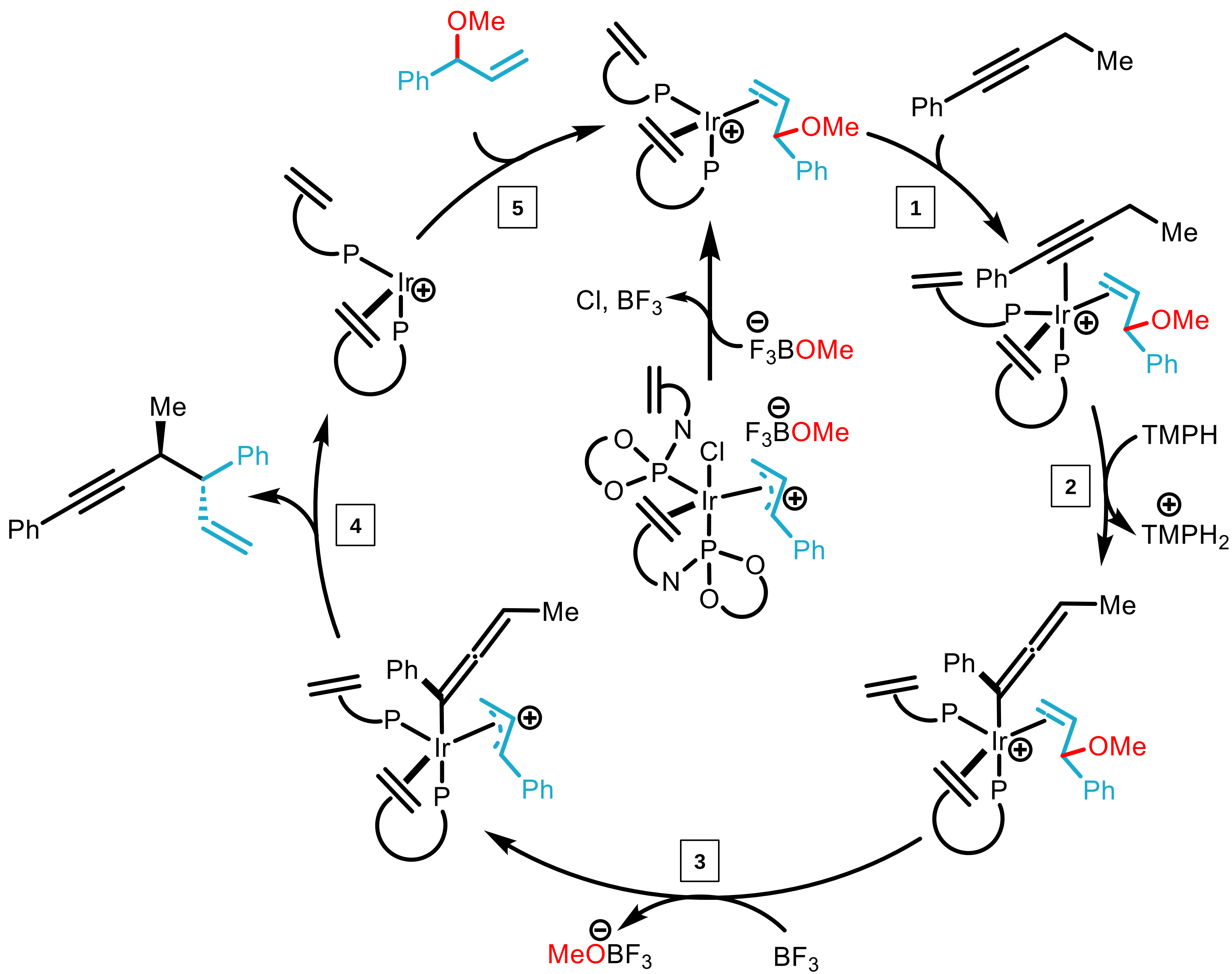
Dual Activation



- **Activation of catalyst** by addition of methoxy boron trifluoride and loss of chloride
- **HOMO Activation**: Alkyne activated by Ir(I) catalyst to deprotonate propargylic proton forming the allenylmetal nucleophile
- **LUMO Activation**: Regeneration of the π-allyliridium complex using boron trifluoride as a Lewis acid

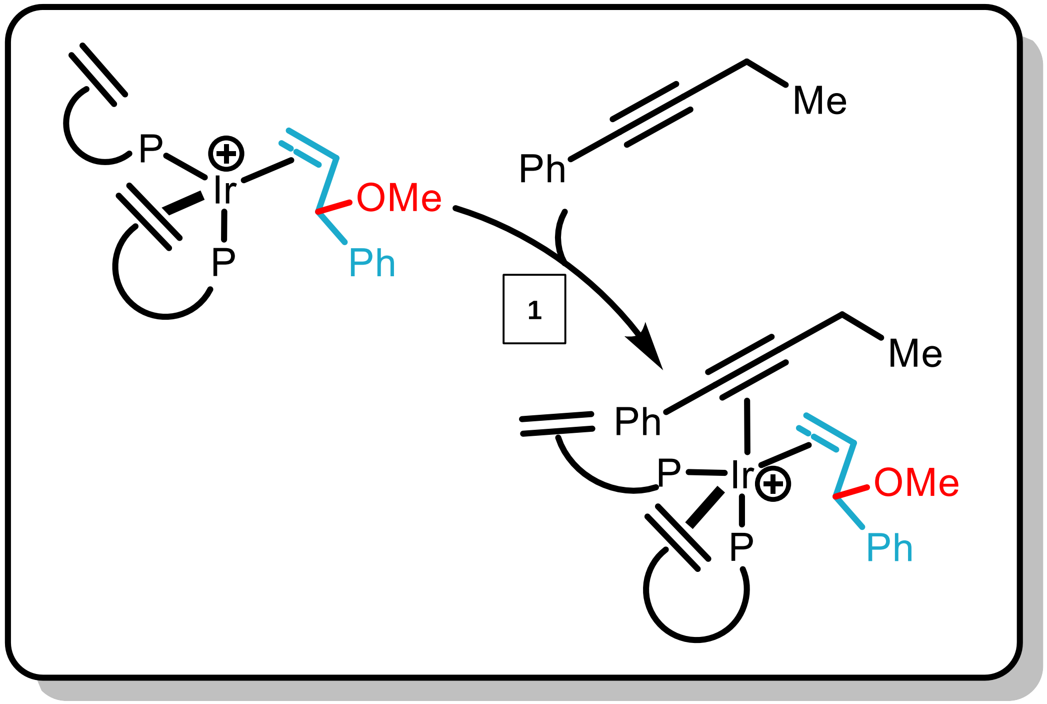


Catalytic Cycle



Catalytic Cycle 1

Alkyne coordination

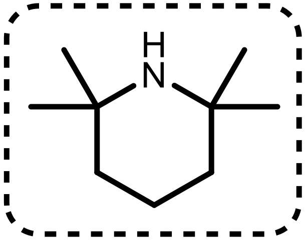


Preactivation of alkyne for propargylic deprotonation

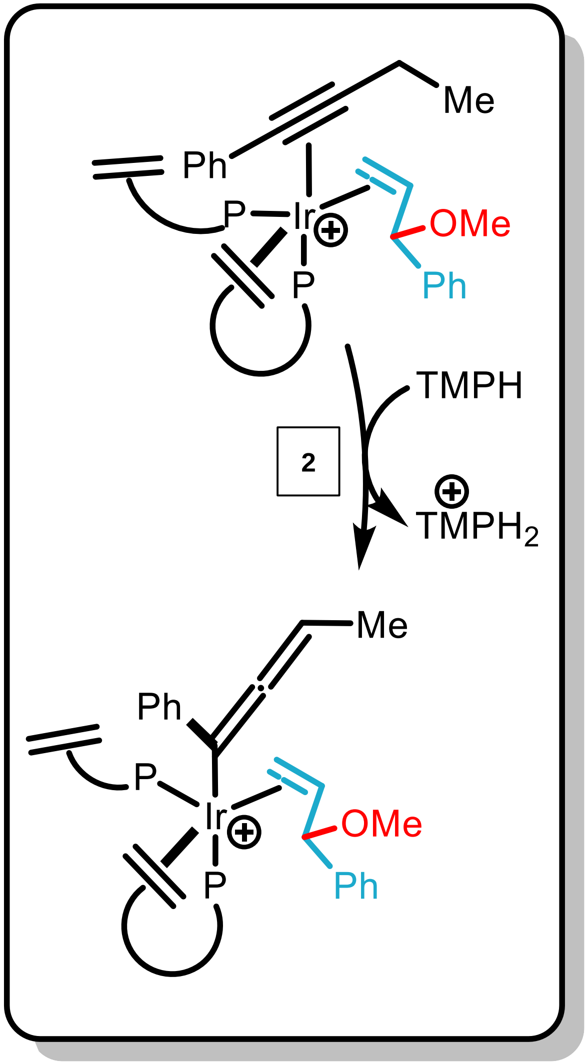
Catalytic Cycle 2

HOMO activation of alkyne

Allenylmetal formation by propargylic deprotonation

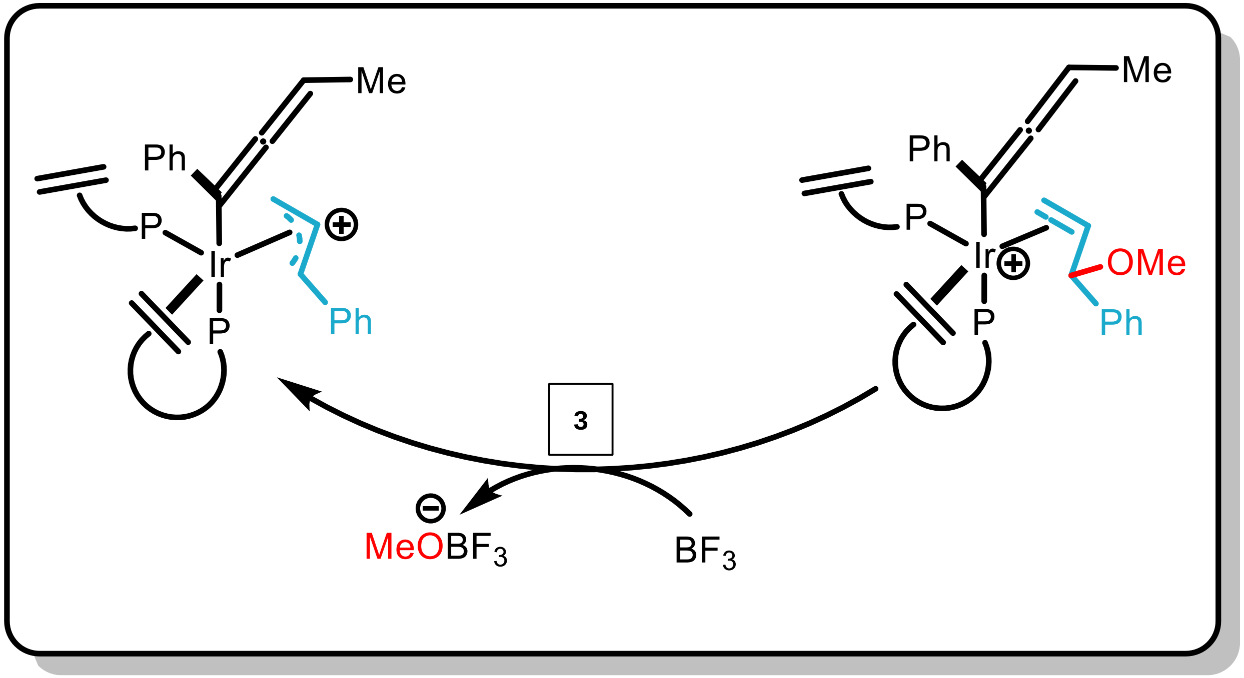


TMPH



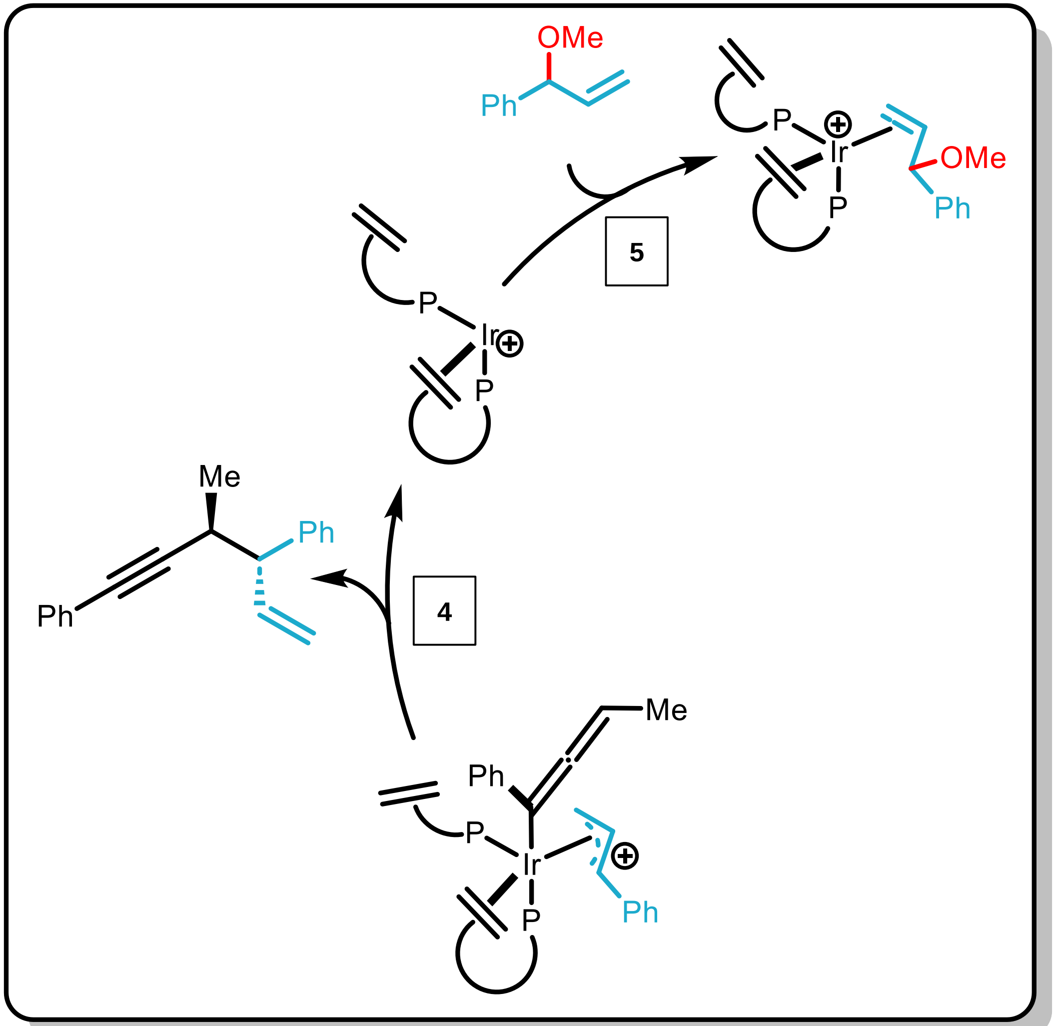
LUMO activation of allyl ether

LUMO activation by departure of methoxy group and formation of π-allyl system. The generated species is a π-allyliridium complex



Catalytic Cycle 4 and 5

Bond formation and **Catalyst turnover**

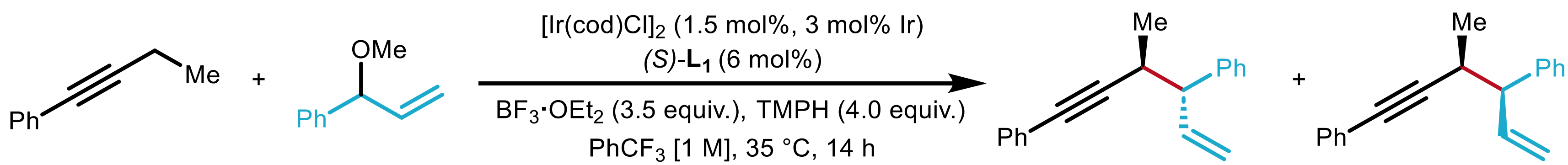


Bond formation by attack of allenylmetal species on π-allyl system

Catalyst turnover

Asymmetric Induction

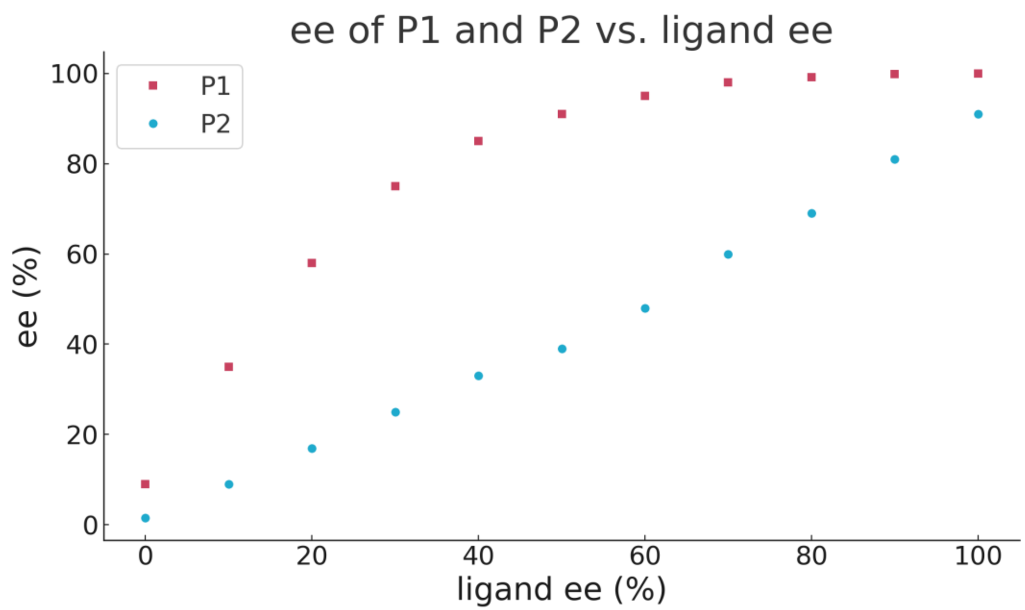
Diastereodivergence



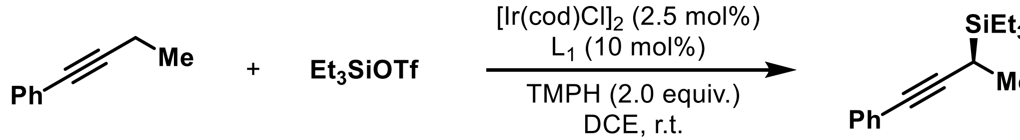
P1 **P2**

variation	% yield (% ee)	P1:P2
none	92 (>99)	>20:1
(±)-L_1 as ligand	99	<1:20

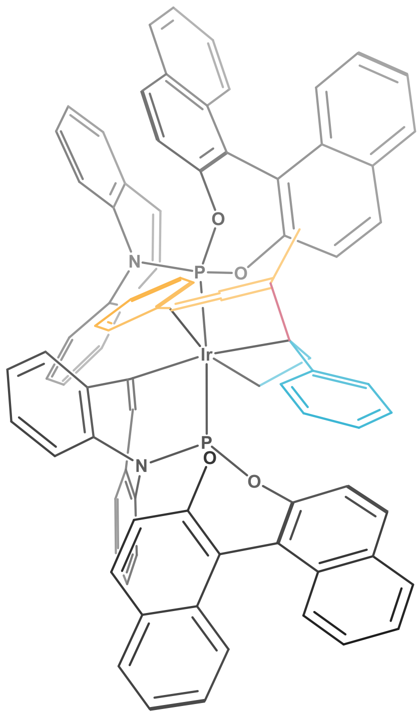
(+)-NLE

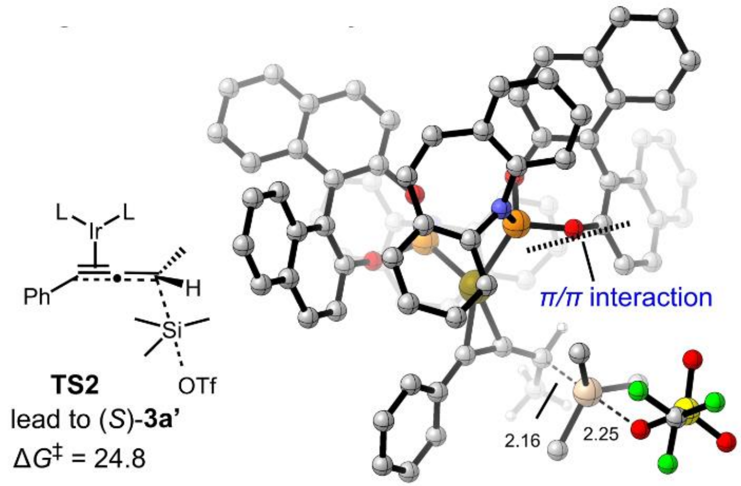


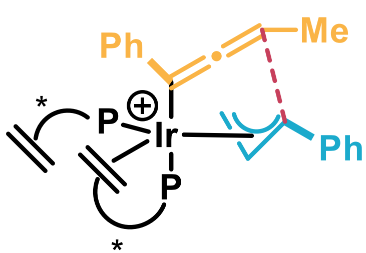
Asymmetric Induction

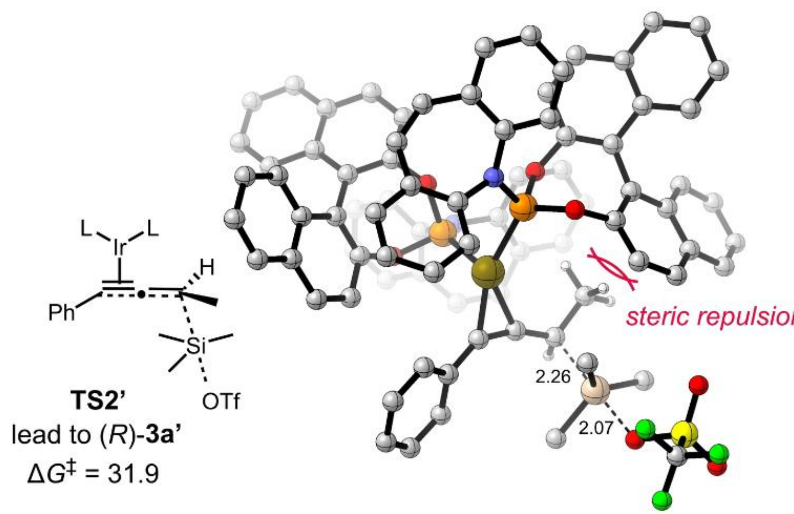


Angew. Chem. Int. Ed. **2024**, *63*, e202318040

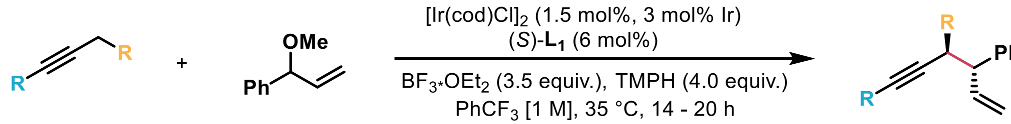


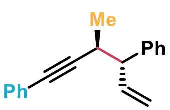




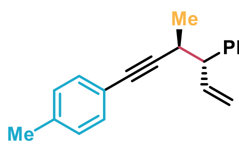


Alkyne Scope

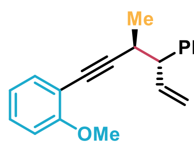




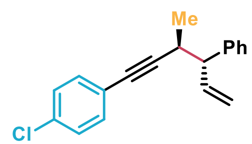
91% yield
>20:1 *dr*, >99% *ee*



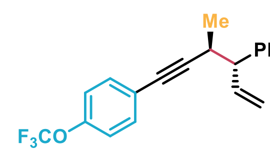
88% yield
14:1 *dr*, >94% *ee*



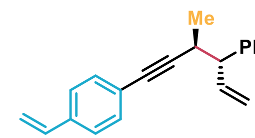
40% yield
9:1 *dr*, >99% *ee*



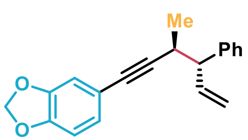
88% yield
>20:1 *dr*, >99% *ee*



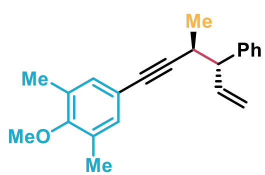
69% yield
>20:1 *dr*, >99% *ee*



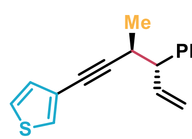
61% yield
>20:1 *dr*, >99% *ee*



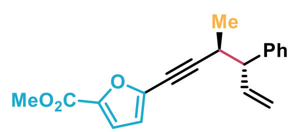
81% yield
15:1 *dr*, >99% *ee*



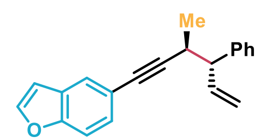
69% yield
16:1 *dr*, >99% *ee*



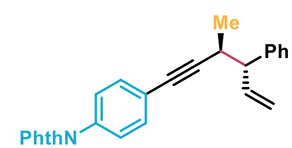
84% yield
11:1 *dr*, >99% *ee*



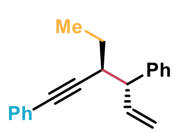
57% yield
11:1 *dr*, >99% *ee*



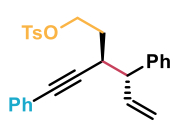
82% yield
16:1 *dr*, >99% *ee*



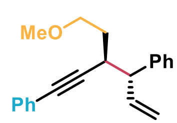
85% yield
>20:1 *dr*, >99% *ee*



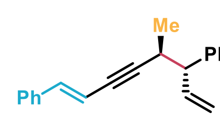
77% yield
>20:1 *dr*, >99% *ee*



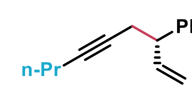
91% yield
>20:1 *dr*, >99% *ee*



48% yield
>20:1 *dr*, >99% *ee*

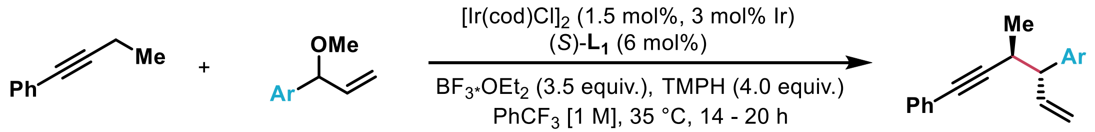


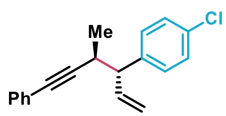
58% yield
>20:1 *dr*, >99% *ee*



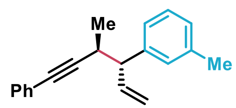
11% yield
>99% *ee*

Allylic Ether Scope

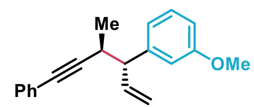




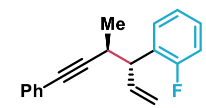
87% yield
>20:1 *dr*, >99% *ee*



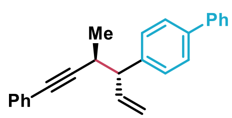
68% yield
>20:1 *dr*, >99% *ee*



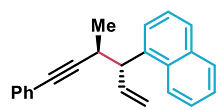
73% yield
>20:1 *dr*, >98% *ee*



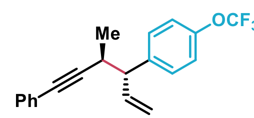
81% yield
>20:1 *dr*, >97% *ee*



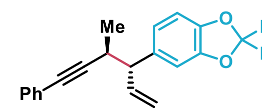
87% yield
>20:1 *dr*, >98% *ee*



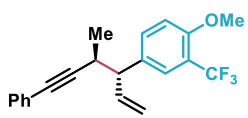
83% yield
>20:1 *dr*, >99% *ee*



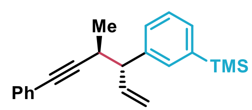
84% yield
>20:1 *dr*, >99% *ee*



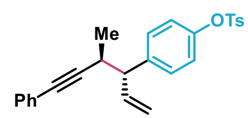
89% yield
>20:1 *dr*, >99% *ee*



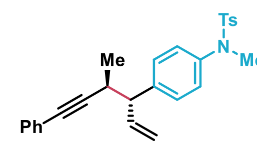
65% yield
>20:1 *dr*, >96% *ee*



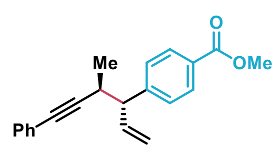
80% yield
>20:1 *dr*, >99% *ee*



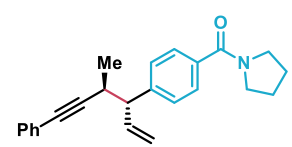
54% yield
>20:1 *dr*, >99% *ee*



41% yield
>20:1 *dr*, >99% *ee*



95% yield
>20:1 *dr*, >99% *ee*



44% yield
>20:1 *dr*, >99% *ee*

Critical analysis: Novelty

Strong points

- Unprecedented dual role of the iridium catalyst
- Complete reverse of diastereoselectivity with a racemic ligand

Weak points

- Both propargylic C-H and allylic ether functionalizations had been reported before
- Known chiral ligands were employed to achieve asymmetric induction

Critical analysis: Practicability

Strong points

- Commercially available iridium precatalyst, ligand, and reaction additives
- Mild reaction conditions (30 - 40 °C)
- C-H functionalization – no need for prefunctionalized substrates
- Two stereocenters formed with excellent regio, diastereo, and enantioselectivity

Weak points

- Expensive uncommon solvent ($PhCF_3$)
- Glovebox required for the reaction set up

Critical analysis: Sustainability

Strong points

- Mild heating (30 - 40 °C)
- Concentrated reaction mixture (1 M)
- C-H functionalization – no need for pre-installed handles
- Two stereocenters formed with excellent regio, diastereo, and enantioselectivity

Weak points

- Perfluorinated expensive solvent ($PhCF_3$)
- Superstoichiometric use of additives – poor atom economy
- Relatively high iridium catalyst loading (for large scale)

Questions

Question 1

Why is $BF_3.OEt_2$ needed in this reaction?

Question 2

What is the rate limiting step of the reaction and which experiment supports it?

Question 3

How is it possible that racemic and enantiopure ligand gives different diastereoisomers of the product?