

IRIDIUM-CATALYZED ALLYLIC SUBSTITUTION: A MECHANISTIC STUDY

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Roadmap

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- Iridium
- Allylic substitution
- Initial Ir Catalyst Systems
- Modern Ir Catalyst
- Enantioselective determination
- Conclusion

Iridium

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- Group 9 element
- Platinum group of metals
- $[\text{Xe}] 4f^{14} 5d^7 6s^2$
- 8th highest melting point
- 2nd most dense (after Os)
- Most corrosion resistant metal
- 0.022 ppb in upper crust (compared to 0.53 ppb Pt)
- Higher concentration in extraterrestrial bodies

| | | | |
|--|---|--|---------------------------------------|
| 44 Ru Ruthenium 101.07 | 45 Rh Rhodium 102.90550 | 46 Pd Palladium 106.42 | 47 Ag Silver 107.8682 |
| | 77 Ir Iridium 192.217 | 78 Pt Platinum 195.084 | 79 Au Gold 196.966569 |

<http://www.dfgoldsmith.com/>



<http://esp.cr.usgs.gov/info/kt/stop2b.html>

Park, J.-W.; et al *Geochim. Cosmochim. Acta* **2012**, 93, 63.

Peucker-Ehrenbrink, B.; et al *Geochem. Geophys. Geosyst.* **2001**, 2.

Uses of Iridium

4

- Former metre standard (1889-1960)

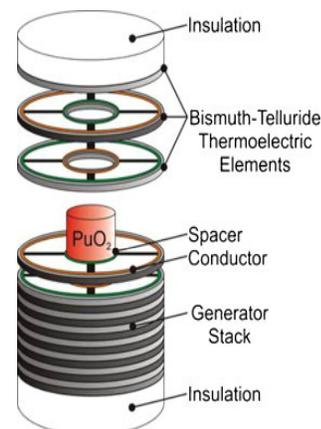
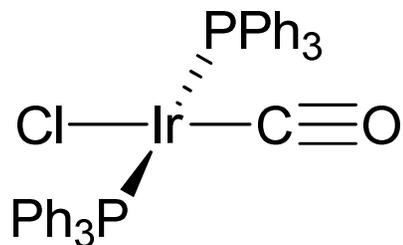
(90% Pt / 10% Ir)

- High performance spark plugs

- Fountain pen nibs

- Insulation for radioisotope thermoelectric generators

- Organometallic catalysts



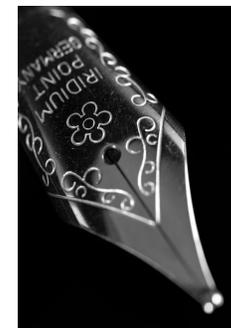
(Whalen, S. A.; et al *J Power Sources* **2008**, 180, 657)



<http://www.nist.gov/pml/wmd/metric/length.cfm>



<http://www.1stautobulbs.com/helpsparkplugs.php#Q15>



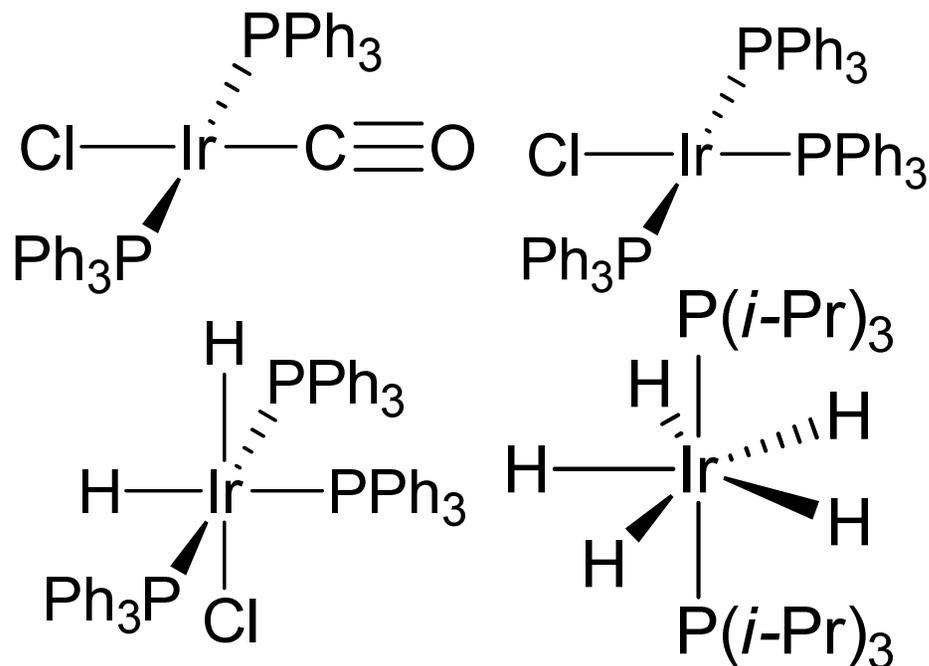
<http://www.chemistryexplained.com/elements/C-K/Iridium.html#b>

Ir Catalysis (early beginnings)

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- “Iridium ... makes a fair catalyst and its lack of use stems partly from neglect and partly from the fact that some platinum metal has usually proved more suitable whenever a comparison was made” –Rylander (Catalytic hydrogenation over platinum metals, 1967)

- Vaska's complex
- Wilkinson's Ir catalyst
- Felkin's dehydrogenation Ir catalyst



Vaska, L. *Acc. Chem. Res.* **1968**, *1*, 335.

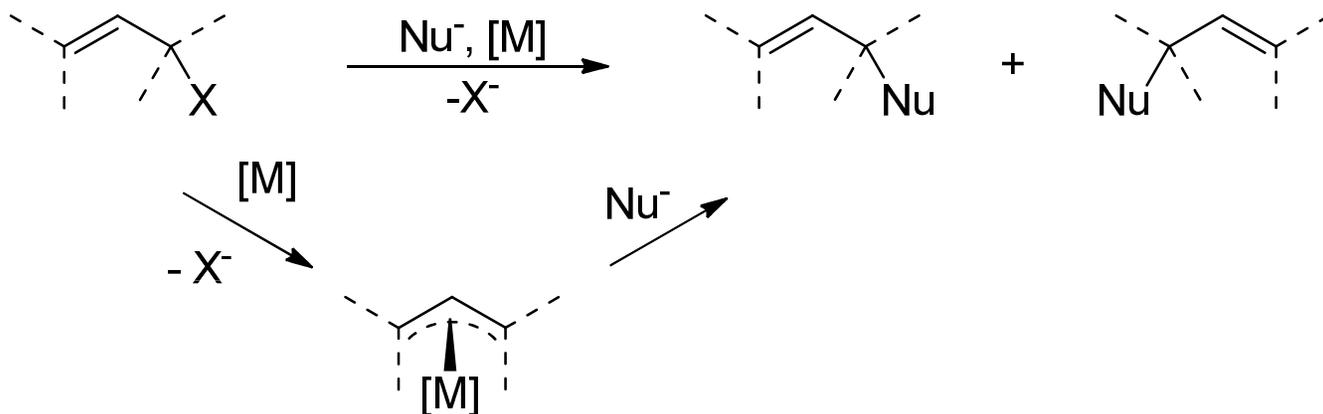
Crabtree, R. H. *Top. Organomet. Chem.* **2011**, *34*, 1.

Felkin, H.; et al *Tetrahedron Lett.* **1985**, *26*, 1999.

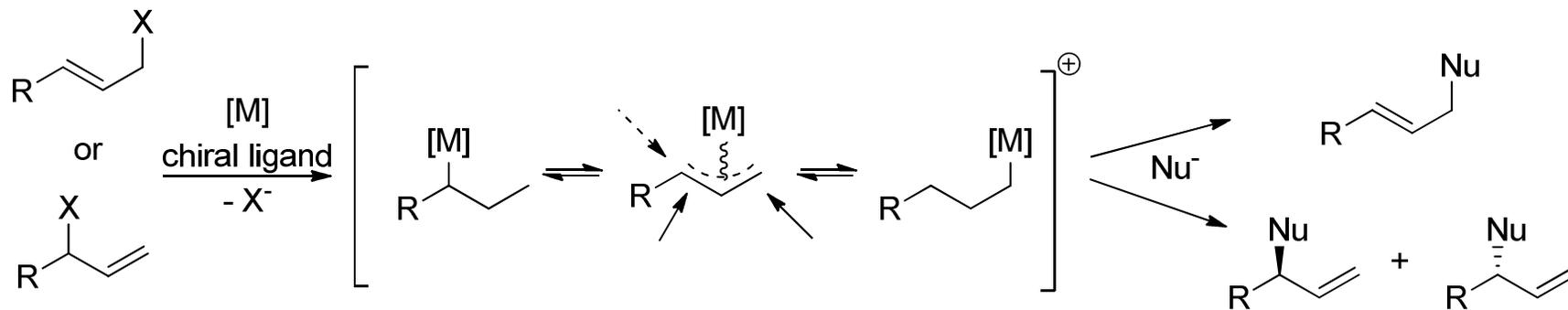
Allylic Substitution

6

□ General reaction:



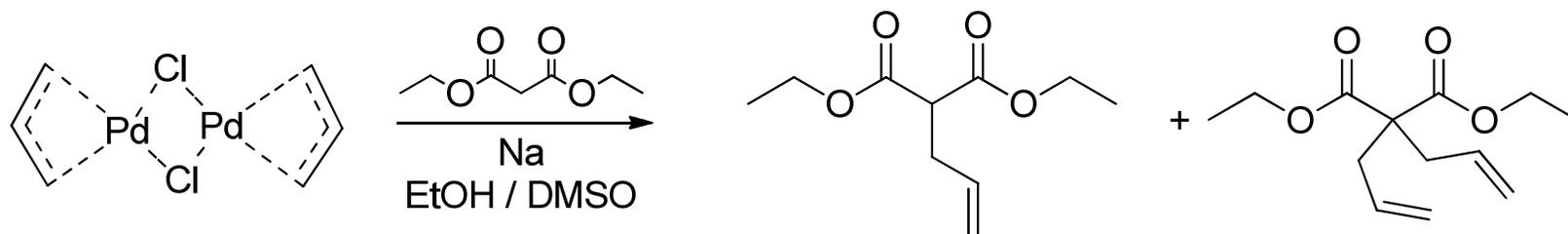
□ Regioselectivity:



Metal catalyzed Allylic Substitution

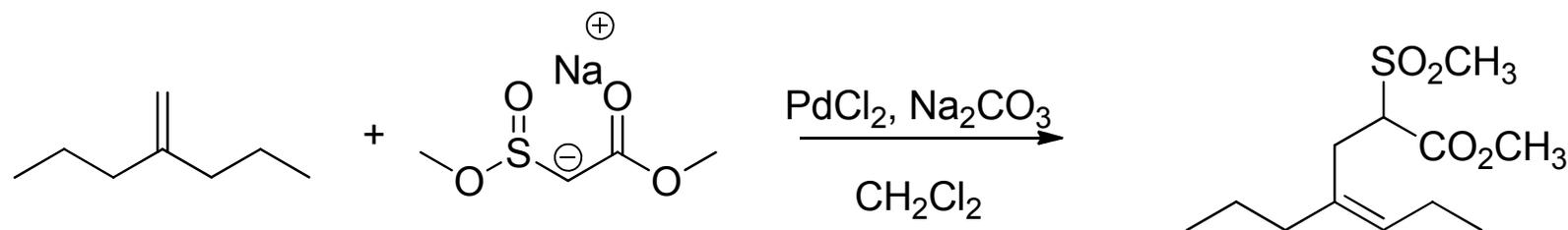
7

- First example of metal mediated allyl substitution



Tsuji, J.; et al *Tetrahedron Lett.* **1965**, 6, 4387.

- Later expanded by Trost

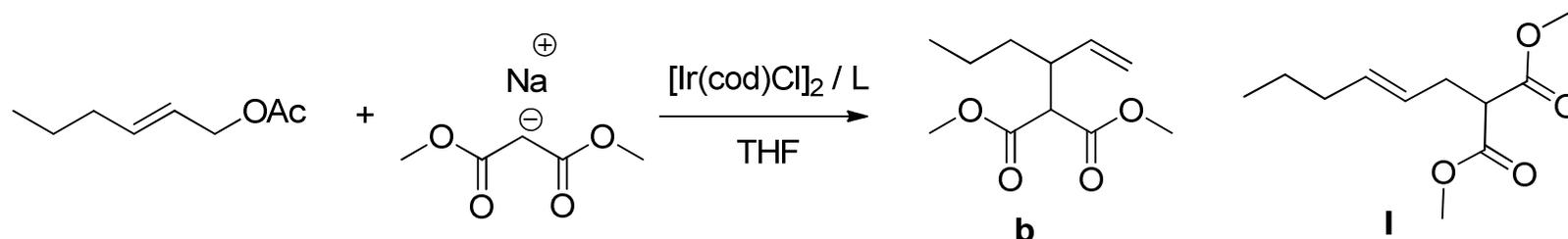


Trost, B. M. et al *J. Am. Chem. Soc.* **1973**, 95, 292.

Ir-catalyzed Allylic Substitution

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□ Takeuchi in 1997



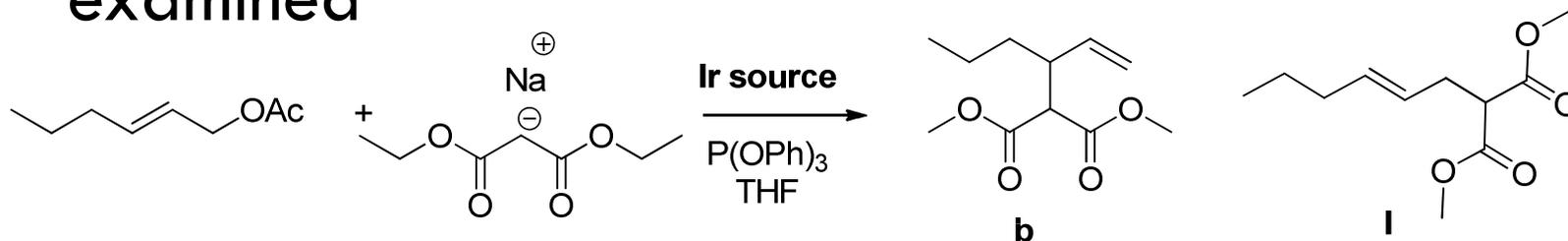
□ Explored effect of achiral ligand

| Entry | Ligand | Conditions | Yield (%) | b:l |
|-------|----------------------------|------------------|-----------|---------|
| 1 | $\text{P}(\text{OPh})_3$ | rt, 3 h | 89 | 96 : 4 |
| 2 | $\text{P}(\text{OEt})_3$ | THF, reflux, 3h | 81 | 59 : 41 |
| 3 | $\text{P}(\text{Oi-Pr})_3$ | THF, reflux, 9h | 44 | 53 : 47 |
| 4 | PPh_3 | THF, reflux, 16h | 6 | 24 : 76 |
| 5 | PnBu_3 | THF, reflux, 16h | 0 | -- |

Effects of Catalyst Precursor

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- Using best ligand, different sources of Ir were examined



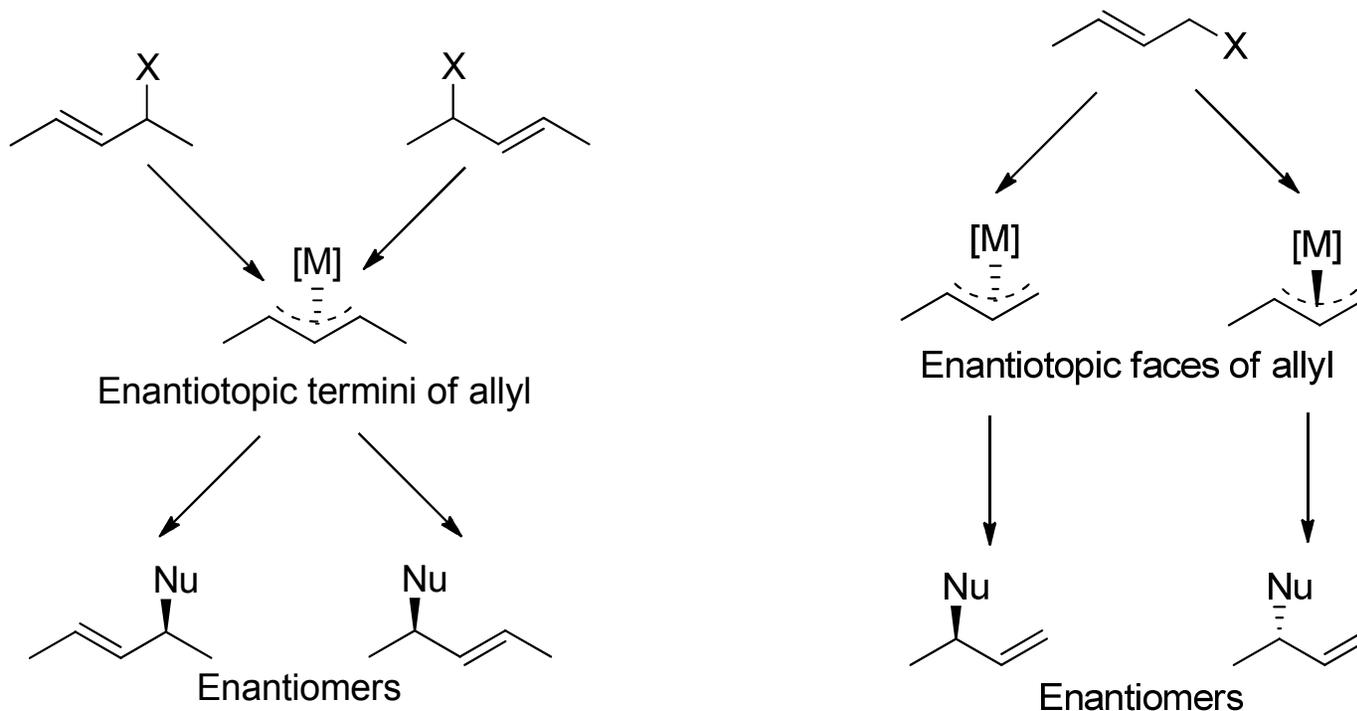
| Entry | Ir source | Conditions | Yield (%) | b:l |
|-------|--------------------|------------------|-----------|---------|
| 1 | $[Ir(COD)Cl]_2$ | rt, 3 h | 89 | 96 : 4 |
| 2 | $[Ir(COD)_2]BF_4$ | THF, reflux, 9h | 90 | 95 : 5 |
| 3 | $Ir(COD)(acac)$ | THF, reflux, 5h | 84 | 72 : 22 |
| 4 | $IrH(CO)(PPh_3)_3$ | THF, reflux, 28h | 64 | 60 : 40 |
| 5 | $Ir_4(CO)_{12}$ | THF, reflux, 9h | 0 | -- |

- Best source is $[Ir(COD)Cl]_2$, despite lower yields

Methods of Stereocontrol

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- Two basic methods to consider

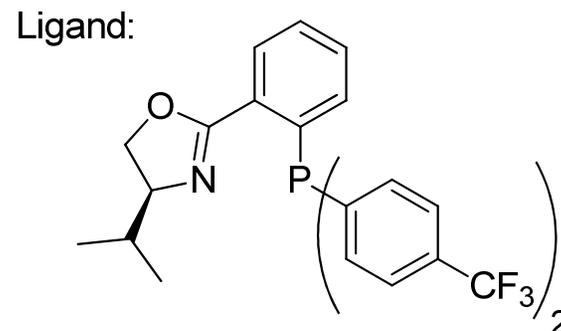
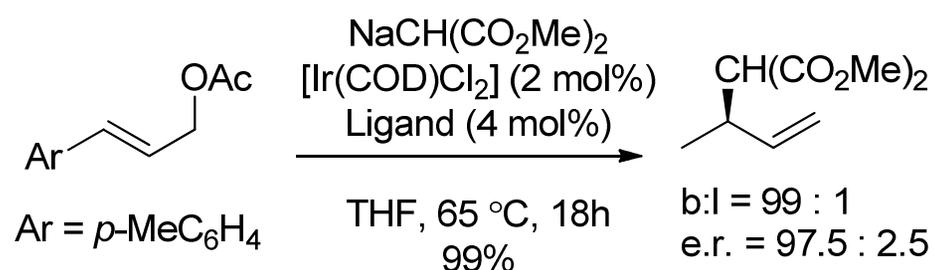


- Initial, selective [M] addition or unselective [M] addition, followed by isomerization

Enantioselective Catalyst Development

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- Helmchen in 1997 using a phosphinooxazoline ligand

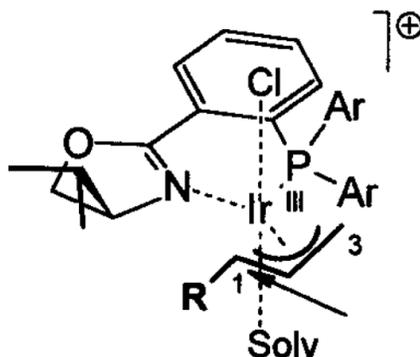


- EWG on ligand important, Ph only gave e.r. = 65:35
- Bulky ligand (3,5-(CF₃)₂C₆H₃) gave e.r. = 86:14

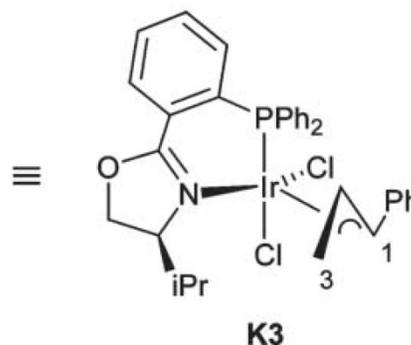
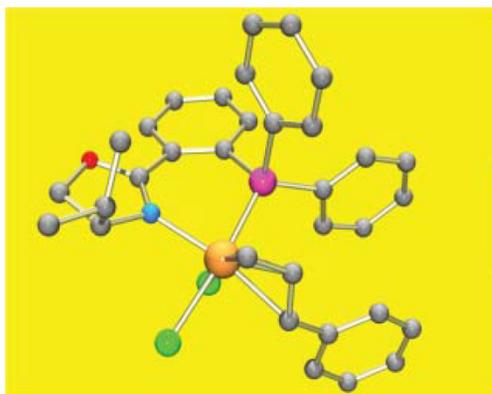
Phosphinoxazoline Intermediate

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- Tentative structure based on Vaska's complex:



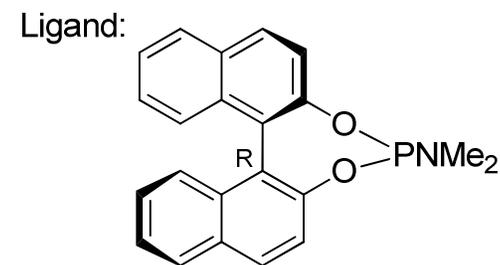
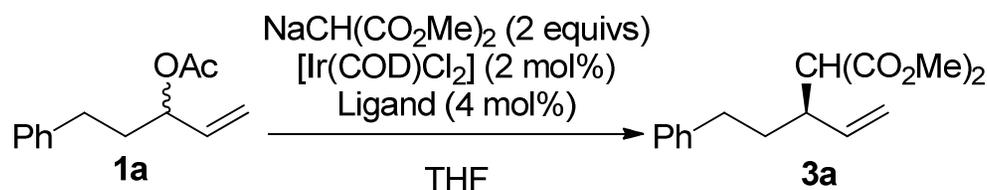
- Later altered by x-ray crystal structure



Helmchen, G. *et al Tetrahedron Lett.* **1997**, 38, 8025.
Helmchen, G. *et al Organometallics* **2004**, 23, 5459.

Ligand / Ir metal ratio

13



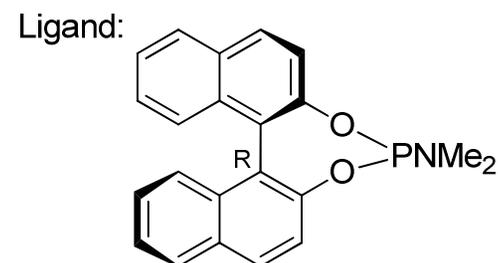
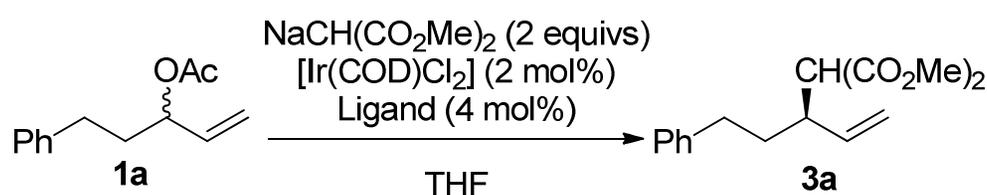
| Entry | Ratio L/Ir | Yield (%) | e.r. | b:l |
|-------|------------|-----------|-----------------|-----------------|
| 1 | 0 : 1 | 66 | -- | 89 : 11 |
| 2 | 1 : 1 | 92 | 85 : 15 | 99 : 1 |
| 3 | 2 : 1 | 66 | 85 : 15 | 99 : 1 |
| 4 | 4 : 1 | 5 | -- ^a | -- ^a |

^a Not determined

□ Optimal ligand to Ir metal ratio appears to be 1:1

Temperature Effect

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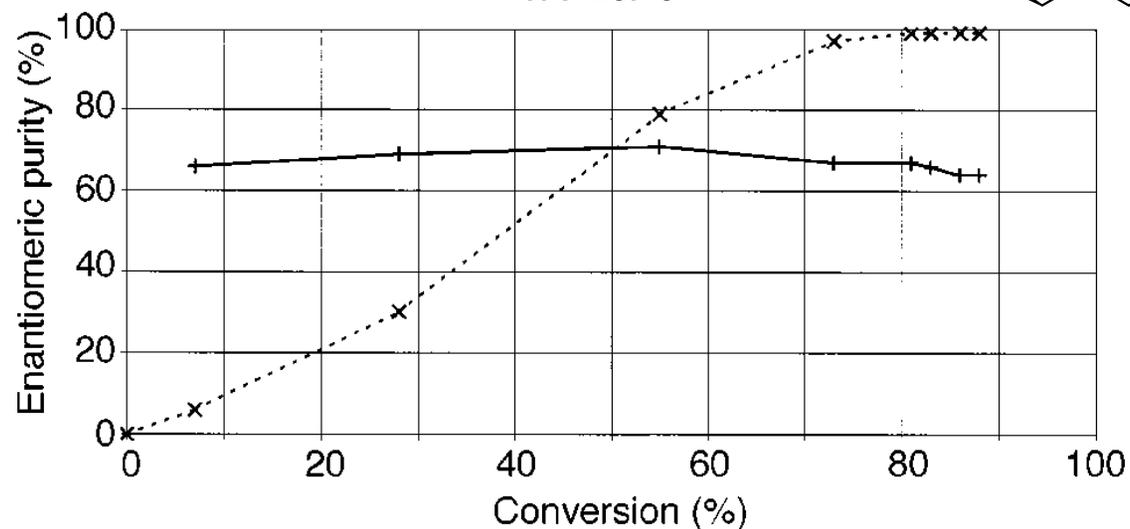
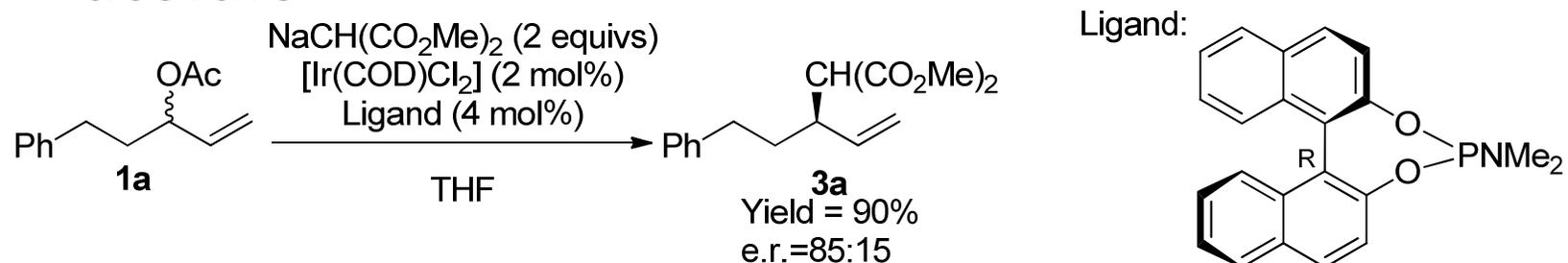
| Entry | Temperature | Time (h) | Yield (%) | e.r. | b:l |
|-------|-------------|----------|-----------|---------|--------|
| 1 | 0 °C | 6 | 74 | 74 : 26 | 99 : 1 |
| 2 | 25 °C | 3 | 92 | 85 : 15 | 99 : 1 |
| 3 | 45 °C | 1 | 99 | 85 : 15 | 98 : 2 |
| 4 | 60 °C | 1 | 98 | 85 : 15 | 98 : 2 |

- No real change in yield, e.r., or b:l ratio after reaction reaches rt and above

Kinetic Resolution

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Investigation of relative rates of racemic allyl acetate

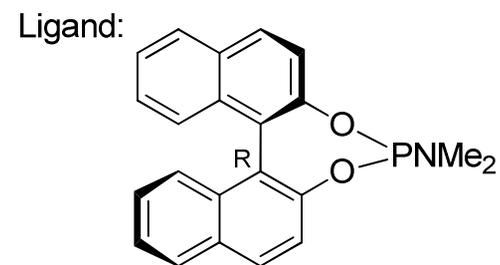
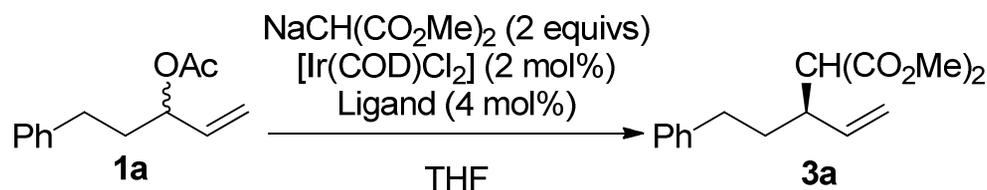


X = enantiomeric purity of **1a**; + = enantiomeric purity of **3a**

Salt Effect

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□ Addition of Li salts to reaction



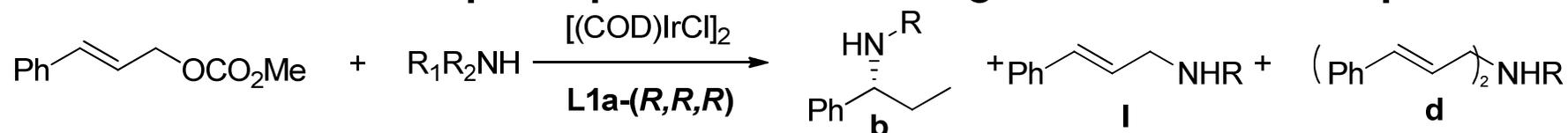
| Entry | Salt | Yield (%) | e.r. | b:l |
|-------|------|-----------|---------|---------|
| 1 | None | 90 | 85 : 15 | 98 : 2 |
| 2 | LiF | 99 | 79 : 21 | >99 : 1 |
| 3 | LiCl | 83 | 93 : 7 | >99 : 1 |
| 4 | LiBr | 68 | 92 : 8 | 98 : 2 |

□ Increase in e.r., but decrease in overall yield

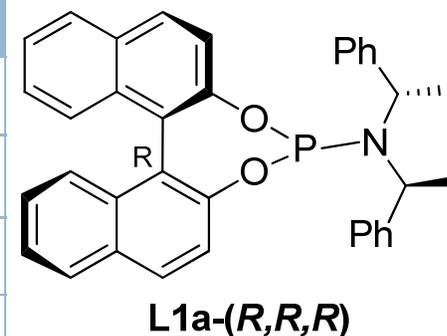
Phosphoramidite Catalyst

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- First use of phosphoramidite ligand for Ir complexes



| Entry | R | R ₂ | Yield (%) | e.r. | b:l:d |
|-------|-------------------------|----------------|-----------|------------|------------|
| 1 | $C_6H_5(CH_2)_2$ | H | 84 | 97.5 : 2.5 | 98 : 1 : 1 |
| 2 | $p-CH_3OC_6H_4(CH_2)_2$ | H | 80 | 97 : 3 | 99 : 0 : 1 |
| 3 | nC_6H_{13} | H | 88 | 98 : 2 | 98 : 2 : 0 |
| 4 | $CH_2=CHCH_2$ | H | 76 | 98.5 : 1.5 | -- |
| 5 | CH_3CH_2 | CH_3CH_2 | 83 | 98.5 : 1.5 | 98 : 2 |

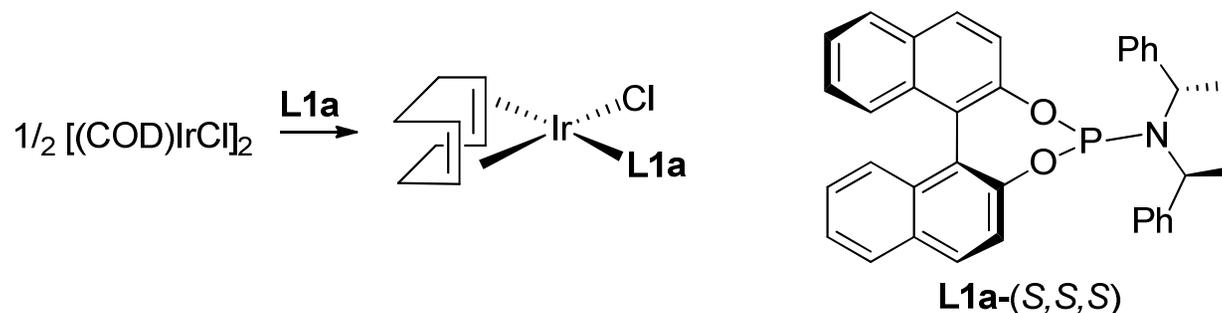


- Shows very high e.r. and branch selectivity

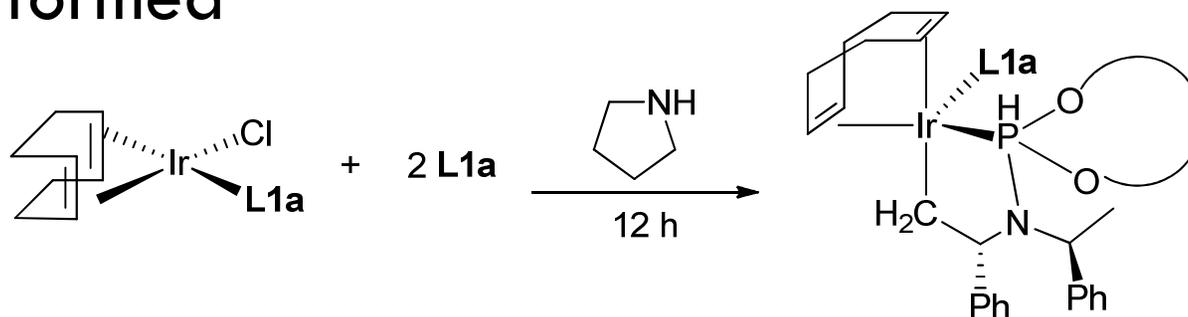
Isolation of Catalytic Intermediate

18

- Isolation of square planar complex



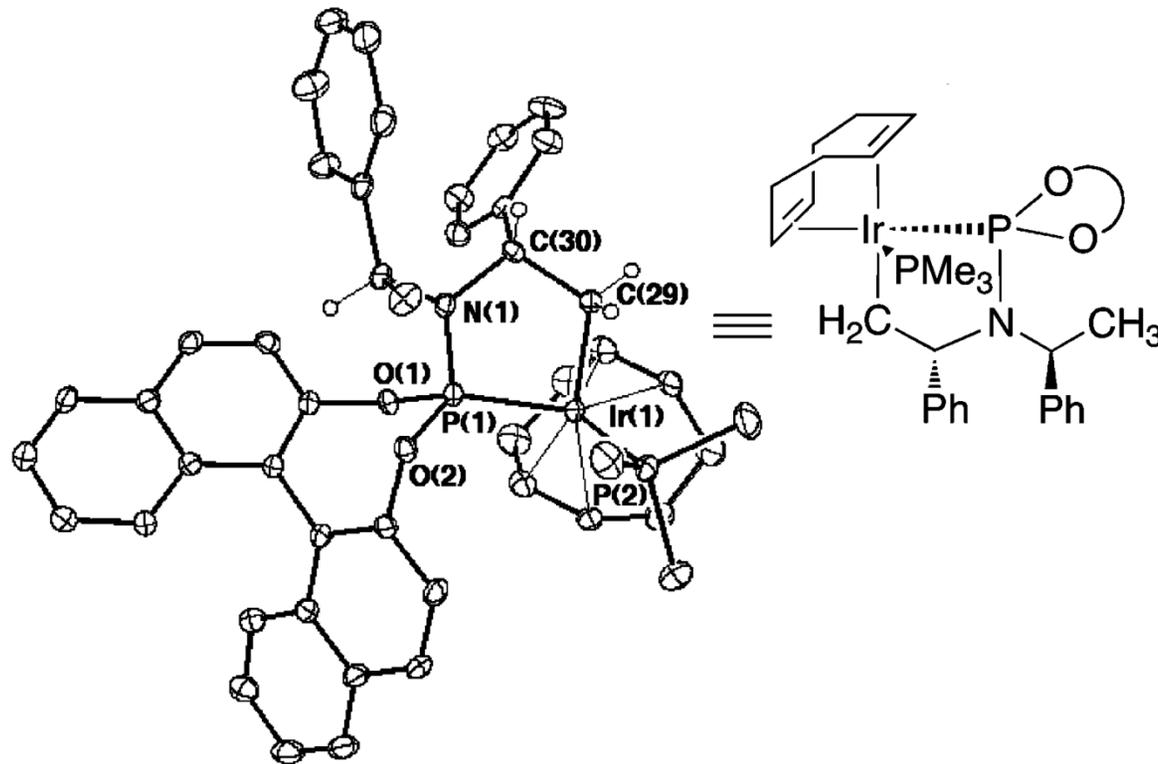
- Upon further reacting, new 5-coordinate species was formed



5-coordinate species

19

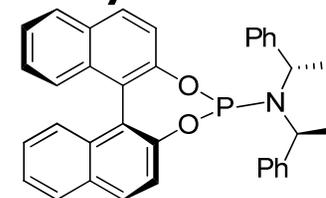
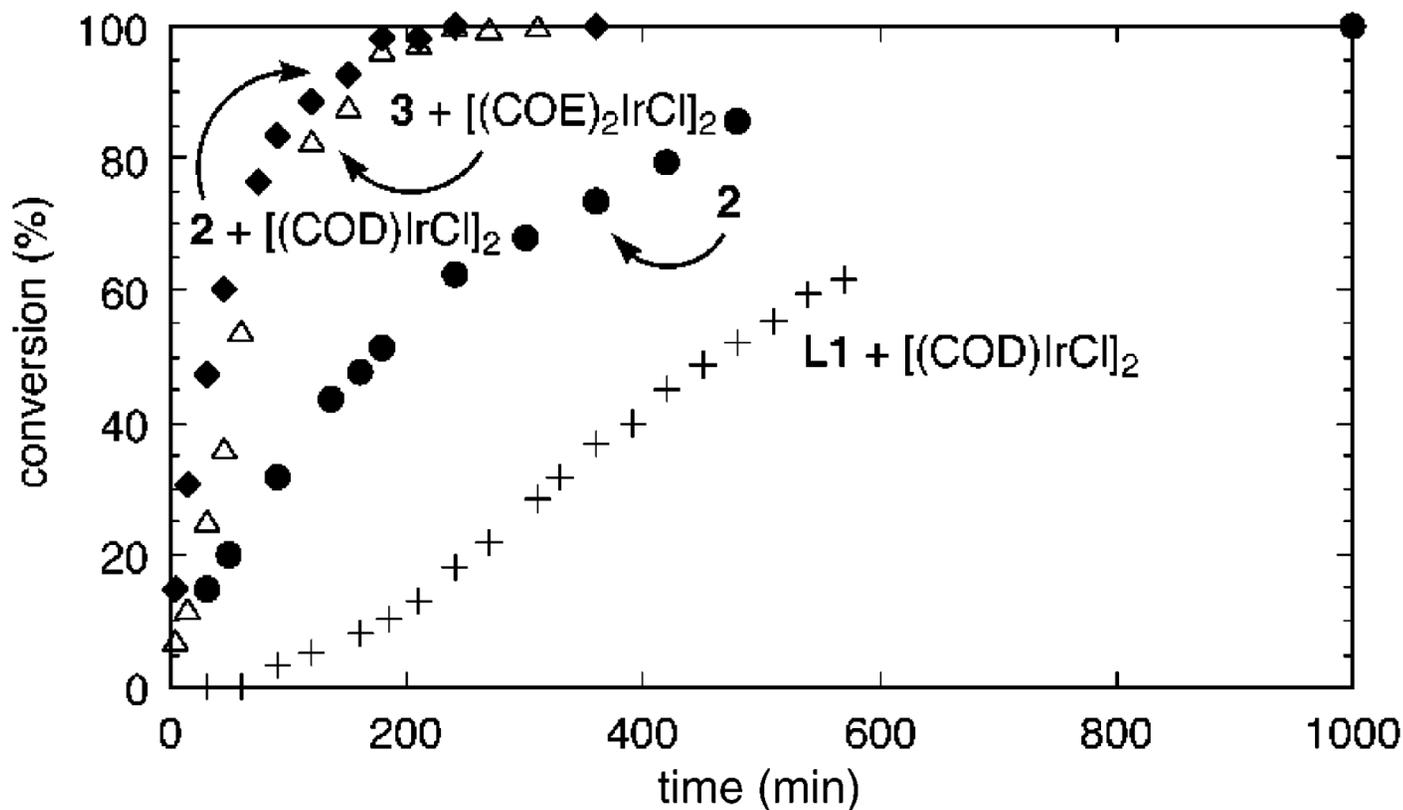
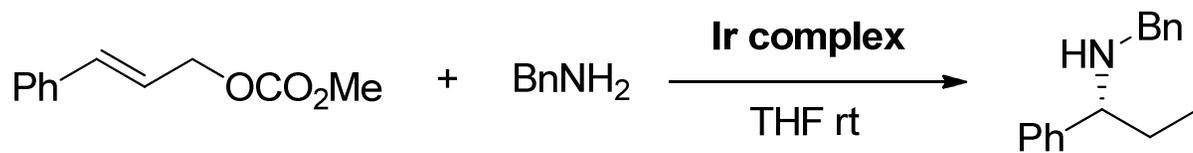
- Reaction of species with PMe_3 led to obtaining of crystal structure



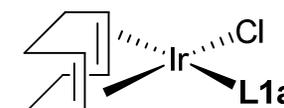
But is it active?

20

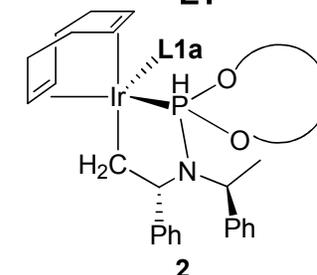
Comparison of compounds for catalytic activity



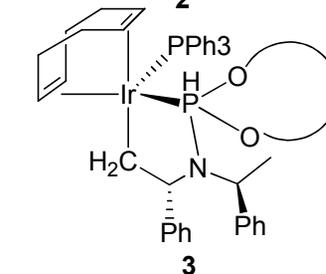
L1a-(S,S,S)



L1



2

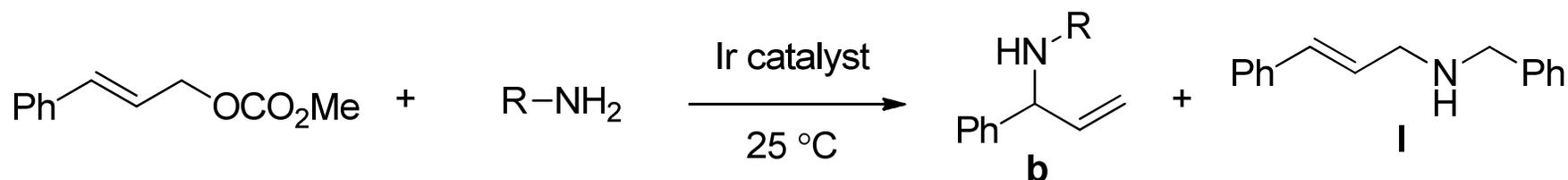


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Using New Species

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Comparison to original catalyst system

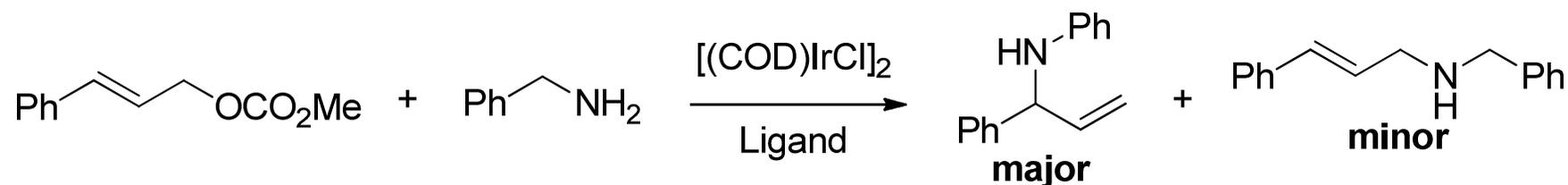


| Entry | Product | Catalyst | Time (h) | b / l | yield ^a | ee |
|-------|---------|---|----------|-------|--------------------|-----|
| 1 | | 1% 2 + [Ir(COD)Cl] ₂ | 2 | 98/2 | 81% | 97% |
| 2 | | 2% L1 + [Ir(COD)Cl] ₂ | 12 | 98/2 | 84% | 95% |
| 3 | | 1% 2 + [Ir(COD)Cl] ₂ | 10 | 97/3 | 85% | 98% |
| 4 | | 2% L1 + [Ir(COD)Cl] ₂ | 10 | – | 11% ^b | – |
| 5 | | 0.1% 2 + [Ir(COD)Cl] ₂ | 10 | 99/1 | 81% | 98% |
| 6 | | 0.2% L1 + [Ir(COD)Cl] ₂ | 16 | 99/1 | 64% | 97% |
| 7 | | 1% 2 + [Ir(COD)Cl] ₂ | 2 | 99/1 | 81% | 97% |
| 8 | | 2% L1 + [Ir(COD)Cl] ₂ | 24 | – | <1% | – |

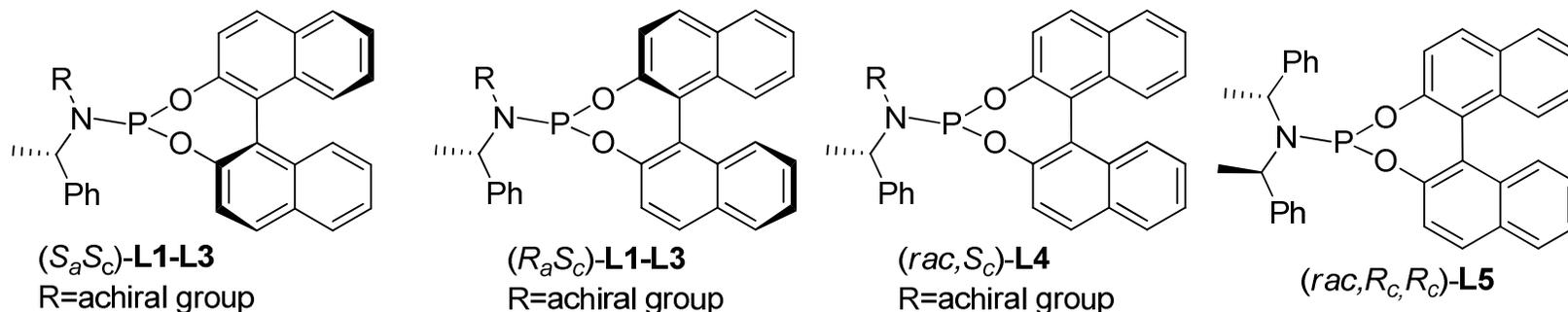
Phosphoramidite Catalyst Stereochemistry

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□ Catalytic allylic amination reaction

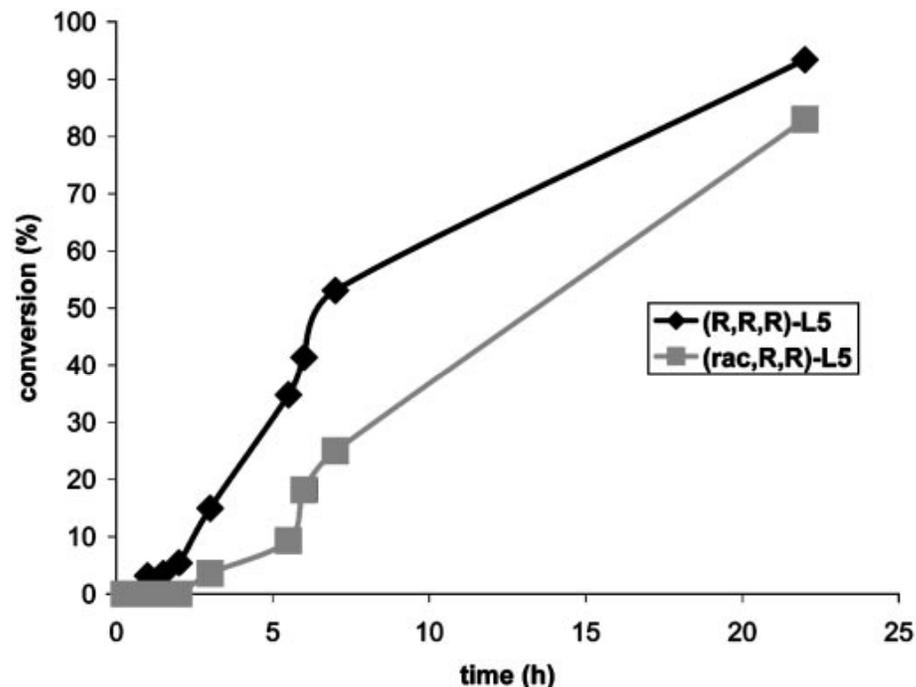
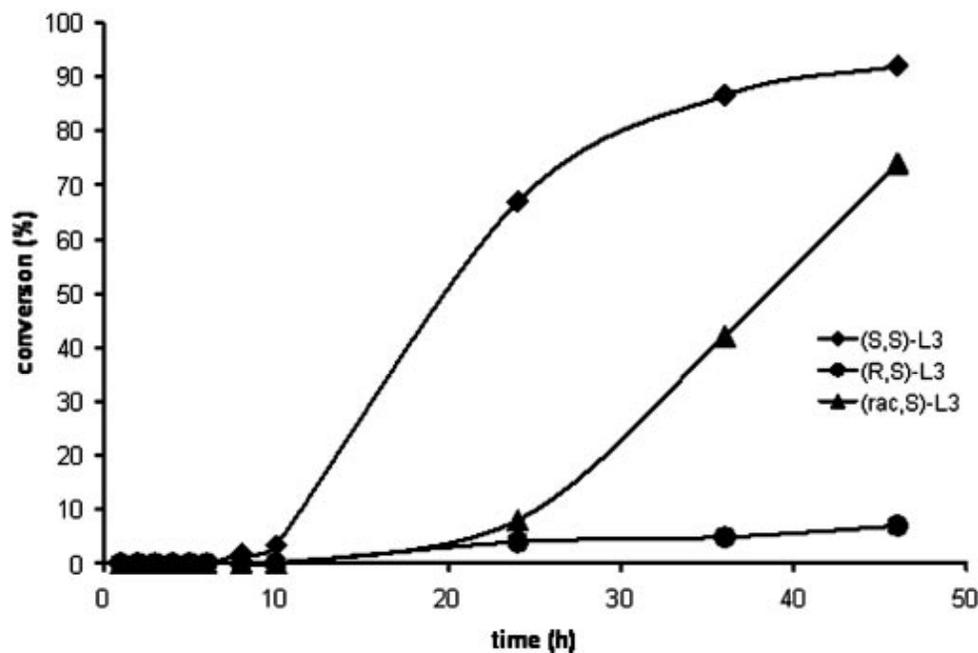


□ Investigation of phosphoramidite diastereomers



Phosphoramidite Catalyst Stereochemistry

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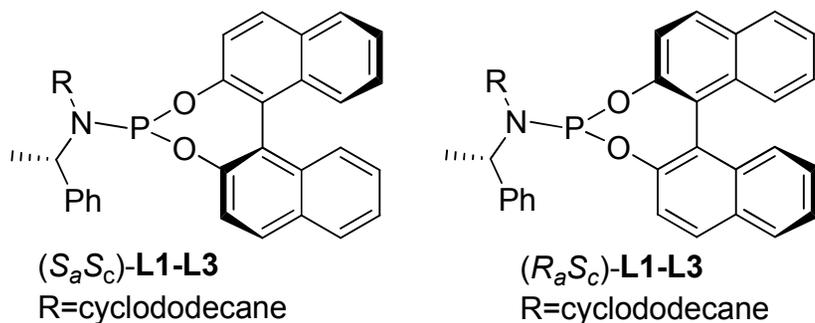


- Shows that only matched case is an active catalyst
- Again reinforced existence of a single active diastereomer

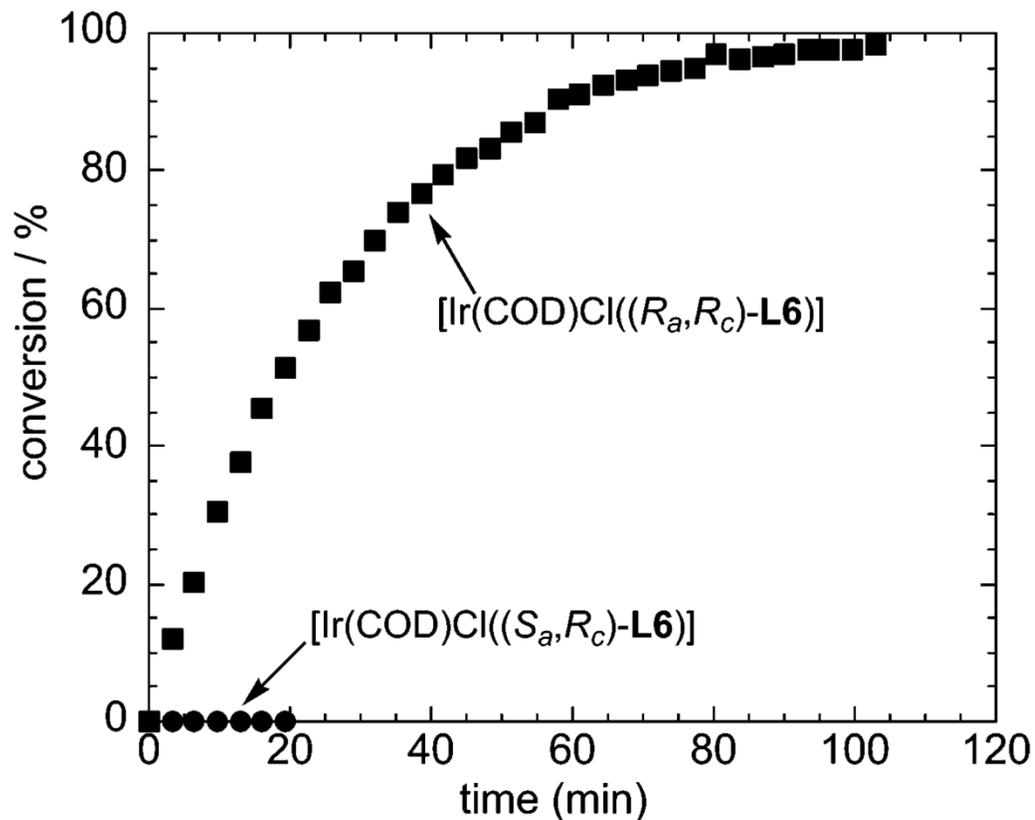
Relative Rates of Cyclometalation

24

- Comparison of matched and mismatched diastereomers for cyclometalation



- Rate indeed faster for matched case

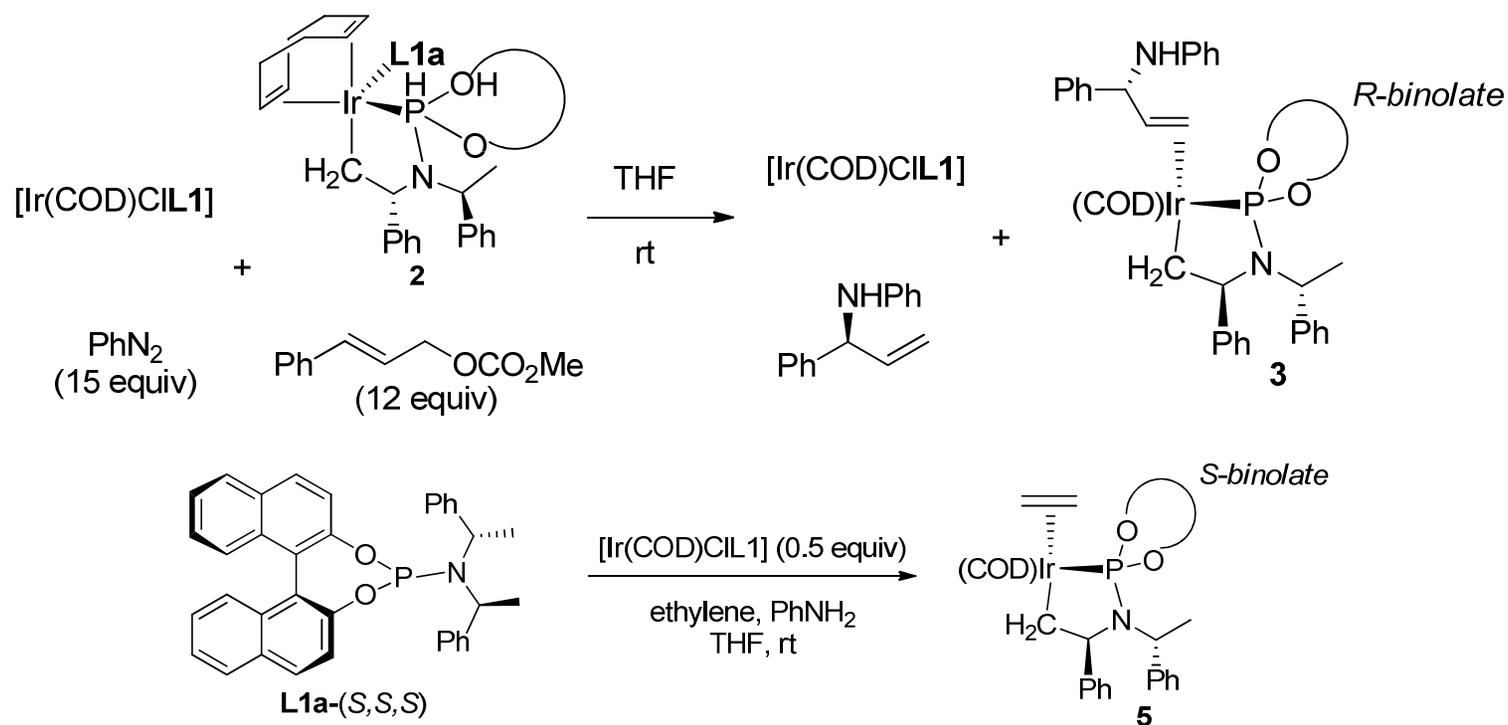


Hartwig, J. F. et al *J. Am. Chem. Soc.* **2005**, *127*, 15506.

Catalyst Resting State

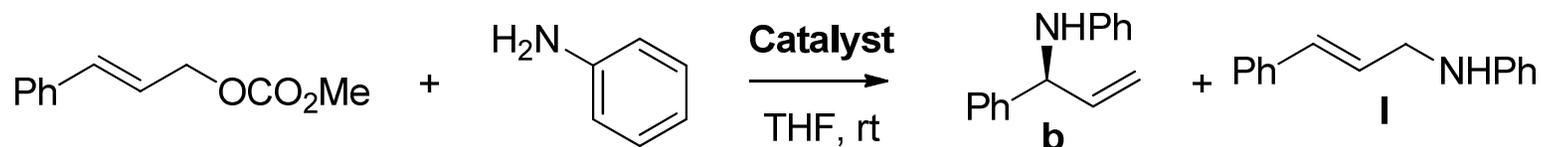
25

- Reaction monitored via ^{31}P NMR and discovered a singlet that was variable upon the amine

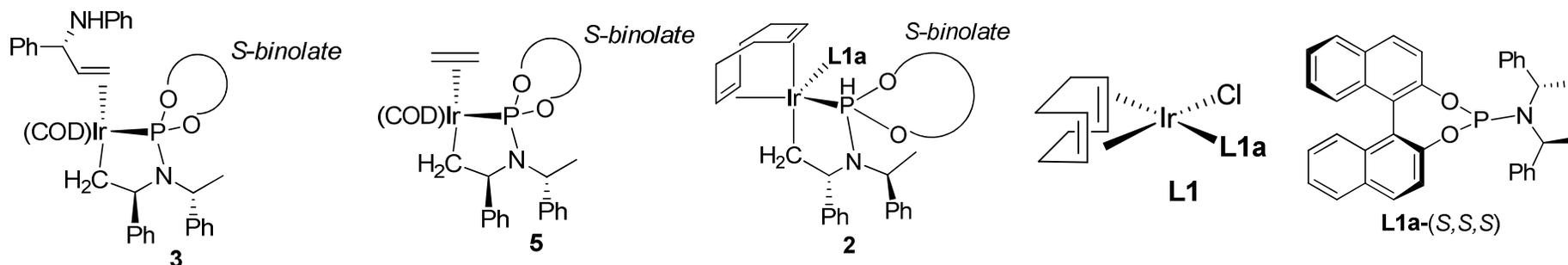


Reactivity of Resting State

26



| Entry | Catalyst | Yield (%) | e.r. | b:l |
|-------|--------------------------------------|-----------|--------|--------|
| 1 | 3 | 79 | 98 : 2 | 99 : 1 |
| 2 | 5 | 82 | 98 : 2 | 99 : 1 |
| 3 | 2 / [Ir(COD)Cl] ₂ | 80 | 98 : 2 | 99 : 1 |
| 4 | [Ir(COD)Cl] ₂ / L1 | 77 | 98 : 2 | 99 : 1 |



□ Both new states shown to be catalytically competent

Kinetic Equation

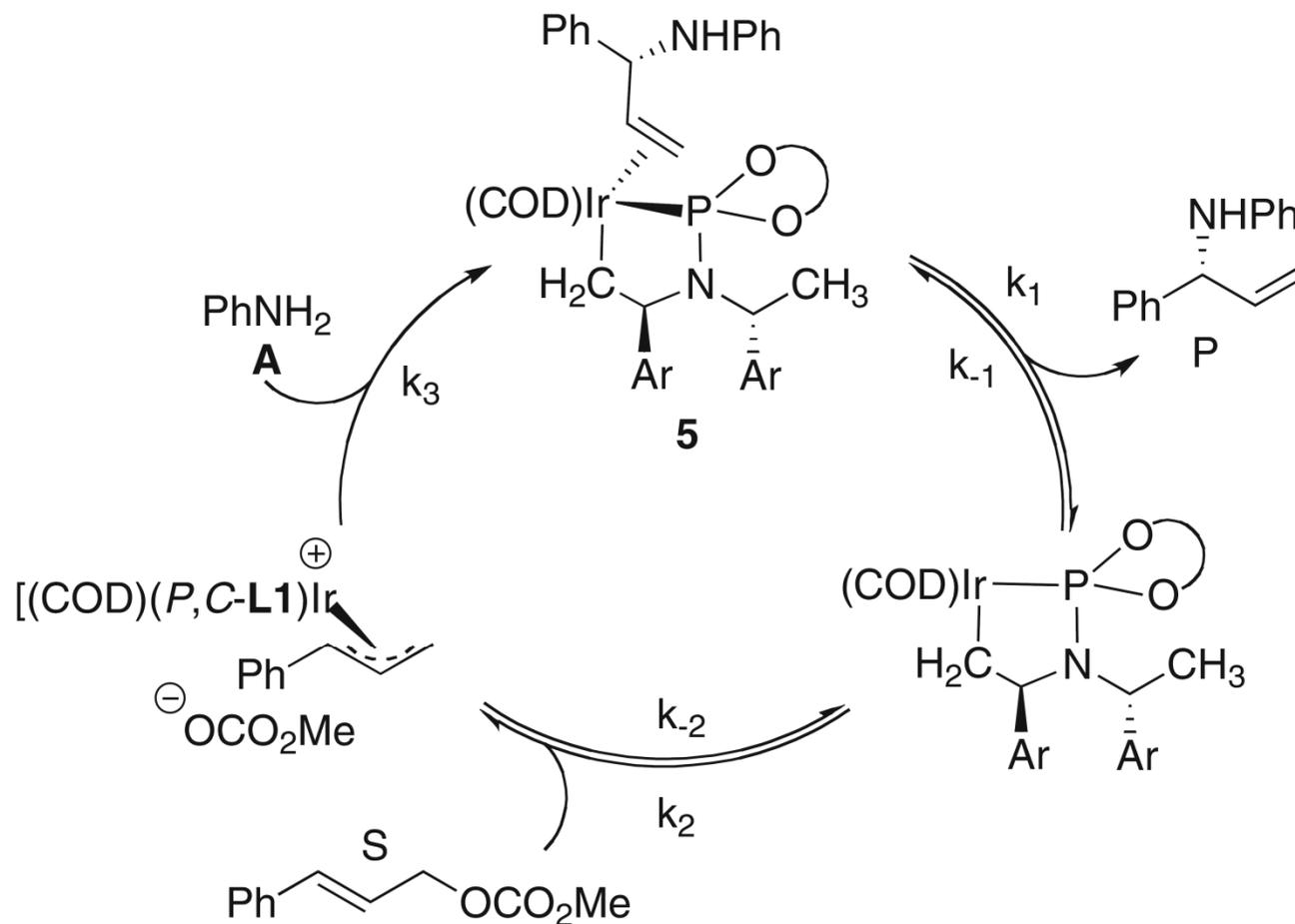
27

$$rate = \frac{d[P]}{dt} = \frac{K_1 K_2 k_3 [S][A][Ir]_{tot}}{[P]}$$

- Reaction is:
 - First order in allylic carbonate
 - First order in catalyst
 - First order in aniline
 - Inverse first order in allylamine product

Catalytic Cycle

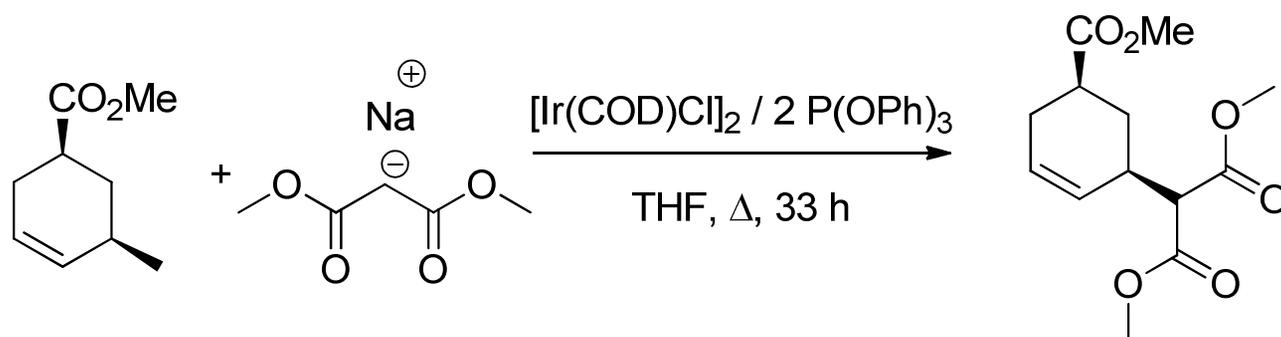
28



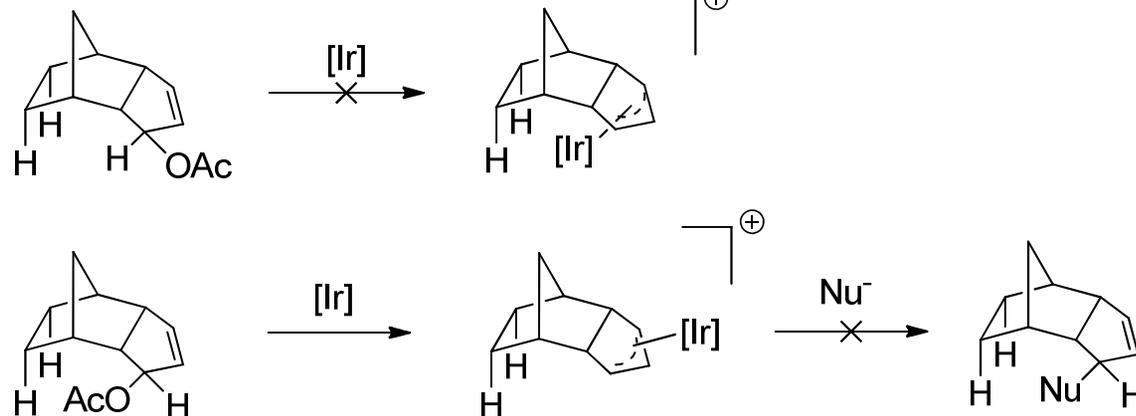
Stereochemical Investigation of Configuration – Steric Control

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- Investigation for erosion of enantiomeric purity



- Use of a sterically hindered substrates that do not allow for inversion

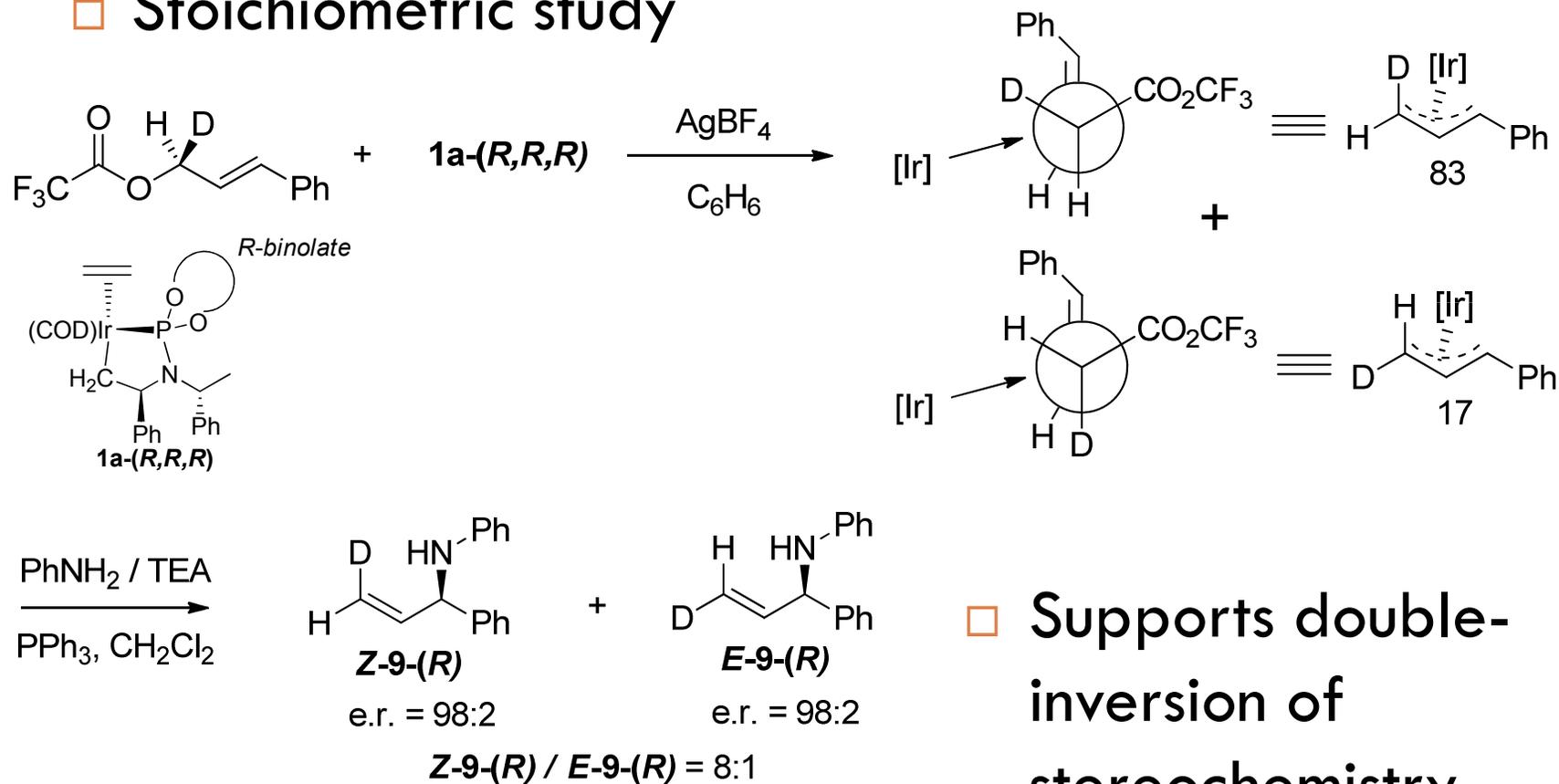


Takeuchi, R. et al *Angew Chem Int Ed* **1997**, 36, 263.
Helmchen, G. et al *Eur. J. Inorg. Chem*, **2002**, 2569.

Stereochemical Investigation of Configuration – Deuterium Labeling (Stoichiometric)

30

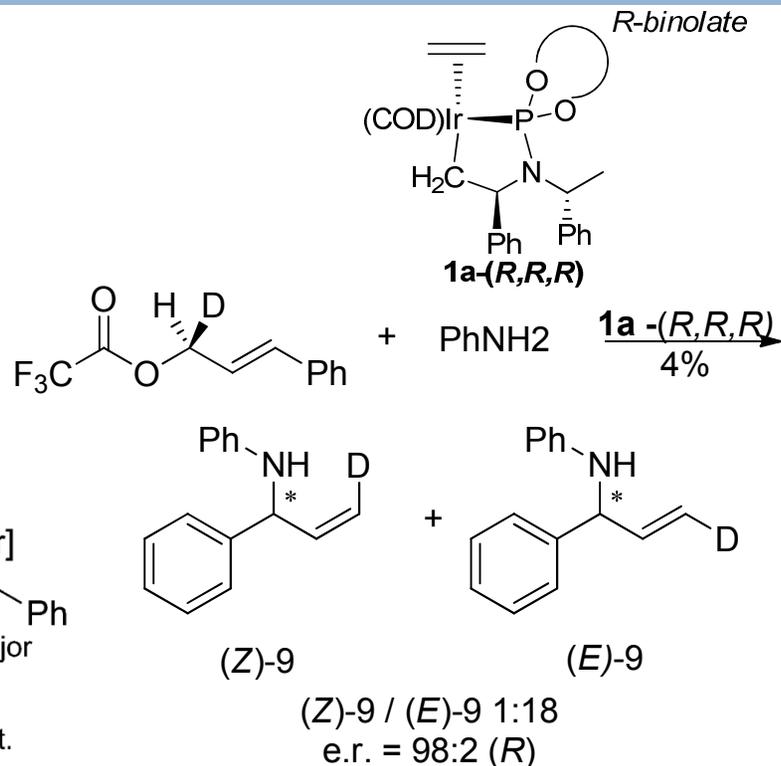
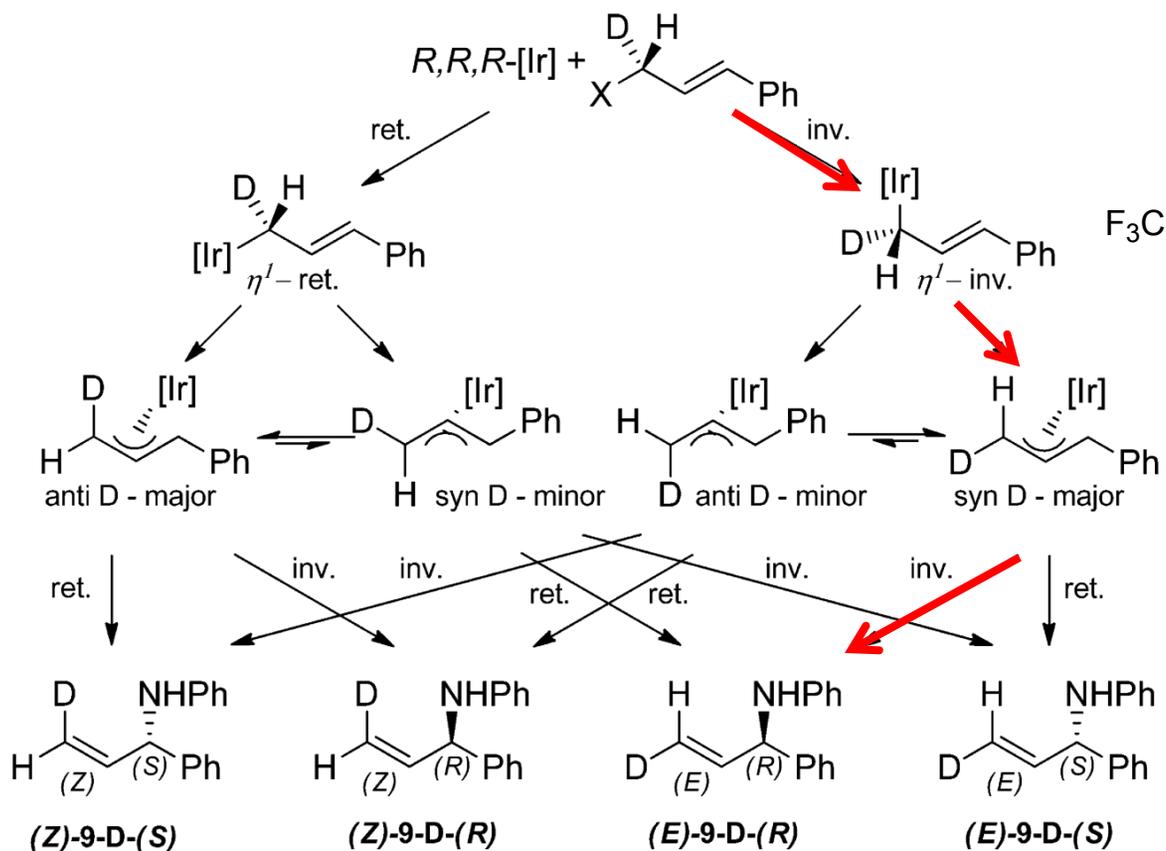
□ Stoichiometric study



Stereochemical Investigation of Configuration – Deuterium Labeling (Catalytic)

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Catalytic study

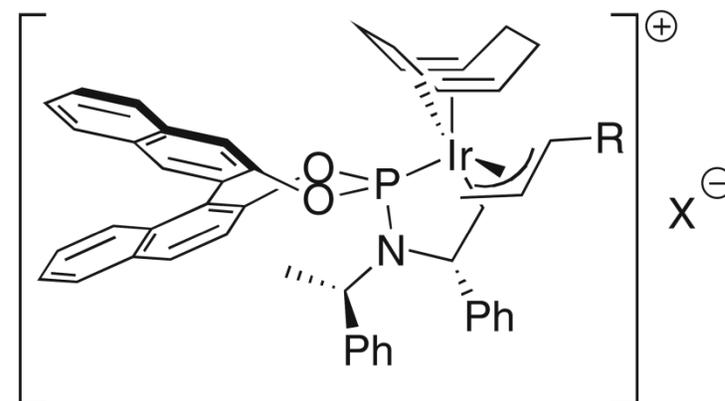
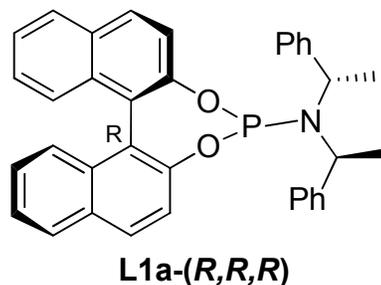


Further support of double inversion

Isolation of π -allyliridium Intermediates

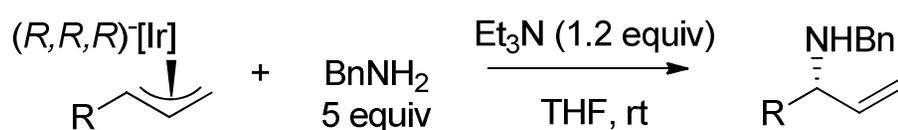
32

- Previous isolations, while catalytically competent, are fleeting in cycle



R = H, X = OTf (**6b**)

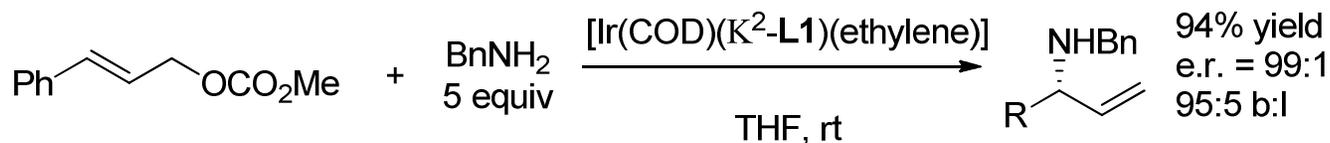
R = Me, X = SbF₆ (**6b**)



6a: R = H, 100% yield

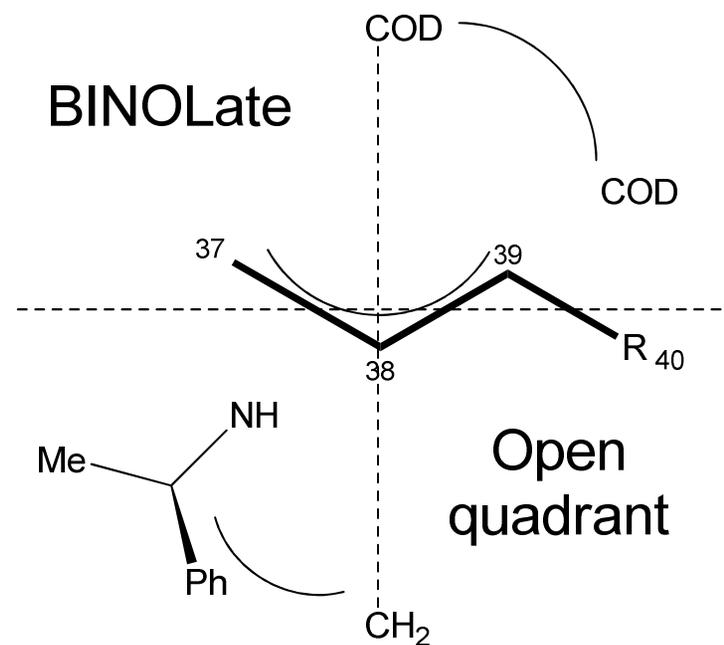
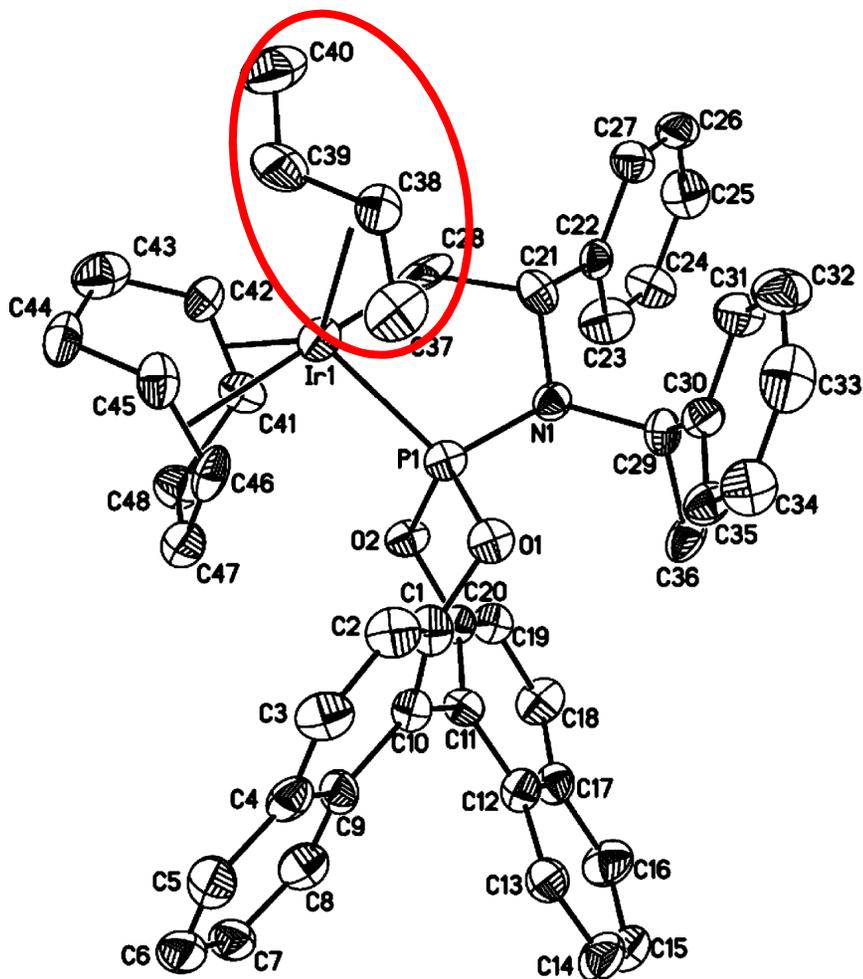
6b: R = Me, 100% yield

e.r. = >99:1, 97:3 b:l



Substrate Binding Quadrants

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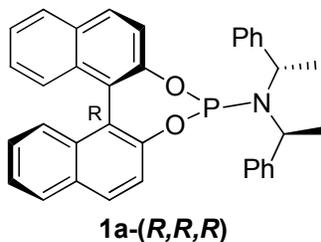
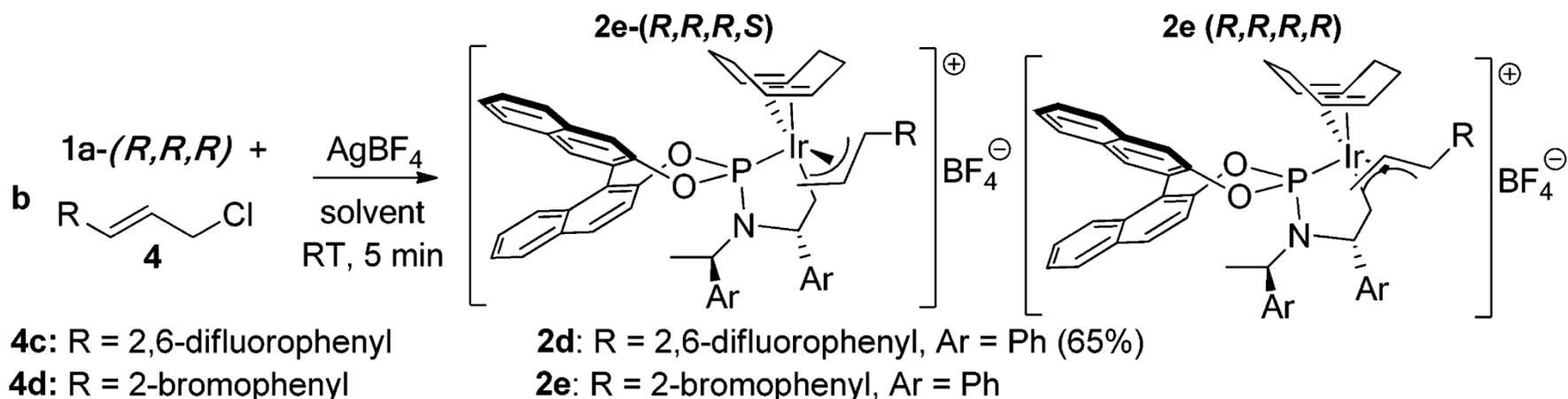


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Discreet π -allyliridium Diastereomer

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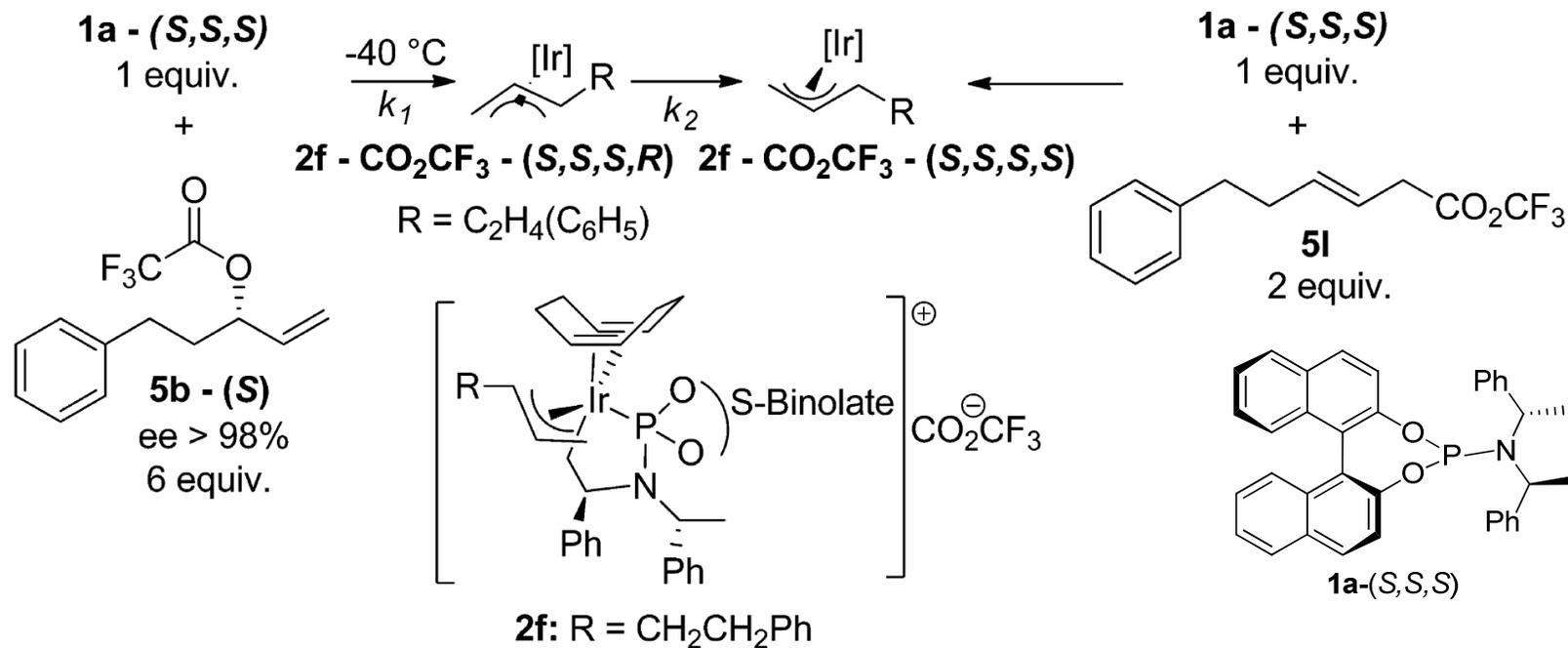
- Attempt to trap the intermediate diastereomers



- Formed in a 60:40 ratio (in benzene), 80:20 (THF), 90:10 (CH_2Cl_2)
- $2e-(R,R,R,R)$ is more stable diastereomer

Conversion of Diastereomers

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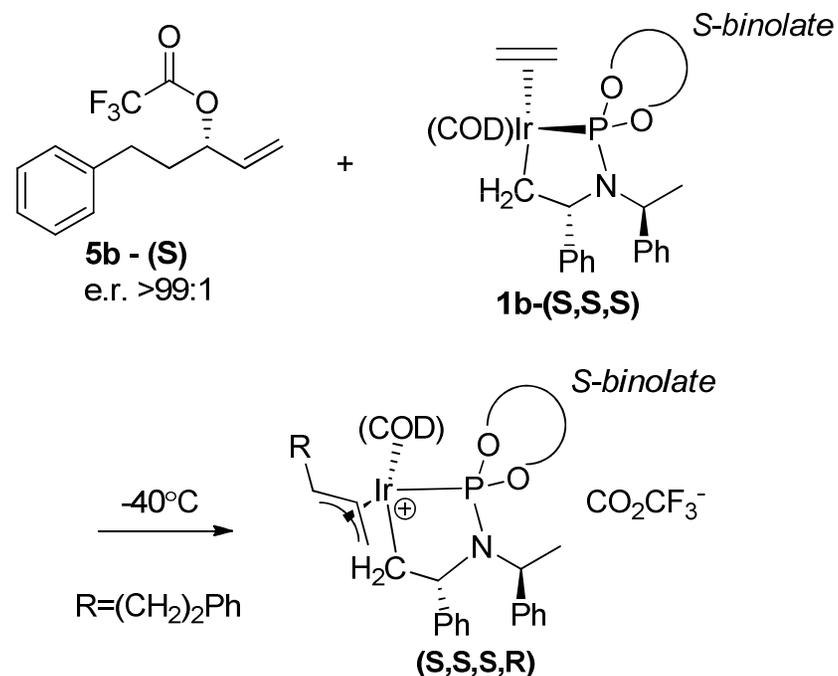
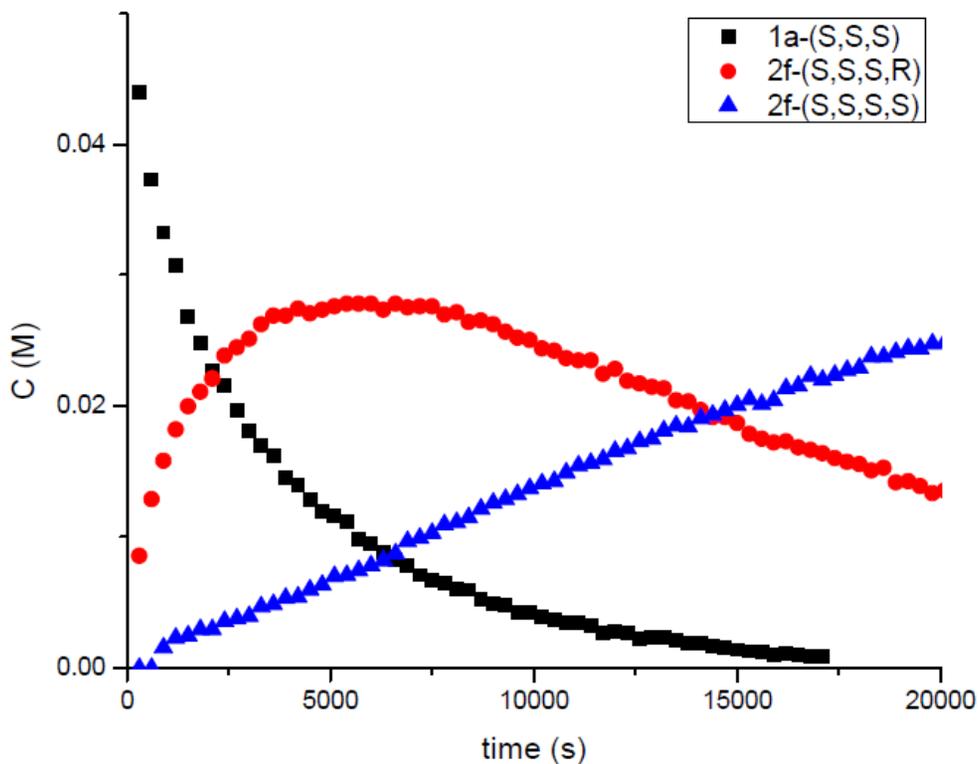


- Initial reaction of **5b** with **1a** gave **2f-(S,S,S,R)**, but converted to **2f-(S,S,S,S)** at -40°C over several hours
- Same reaction at 25°C gave solely **2f-(S,S,S,S)** product

Determination of Epimerization Rate

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- “Epimerization of the allyl intermediate ... occurs slowly, even at room temperature”

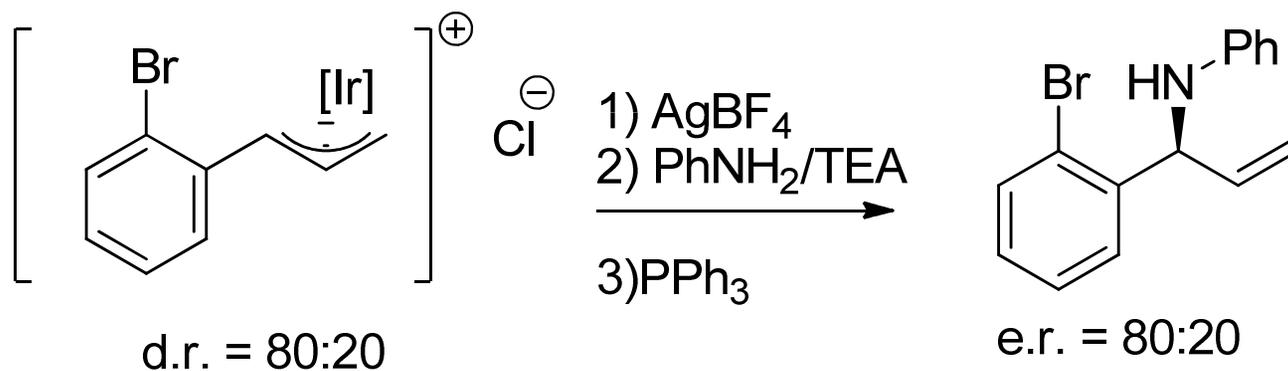


Rate constant: $5.4 \times 10^{-5} \text{ s}^{-1}$

Comparison of Nucleophile Attack to Interconversion

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- “Diastereomeric complexes ... react with the nucleophiles faster than they interconvert”

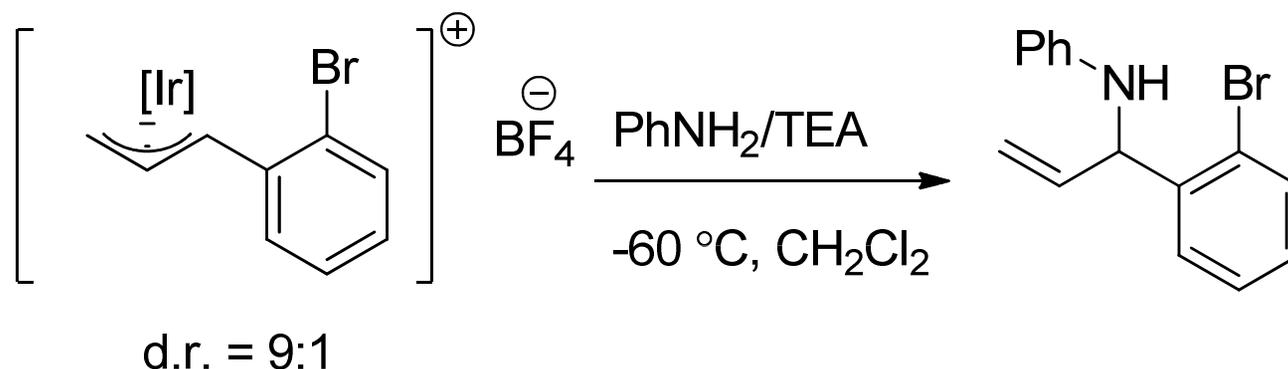


- [Ir] = (S,S,S,S) as shown
- d.r. is directly related to e.r.

Rate Differentiation of Diastereomers

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□ Low e.r. compound

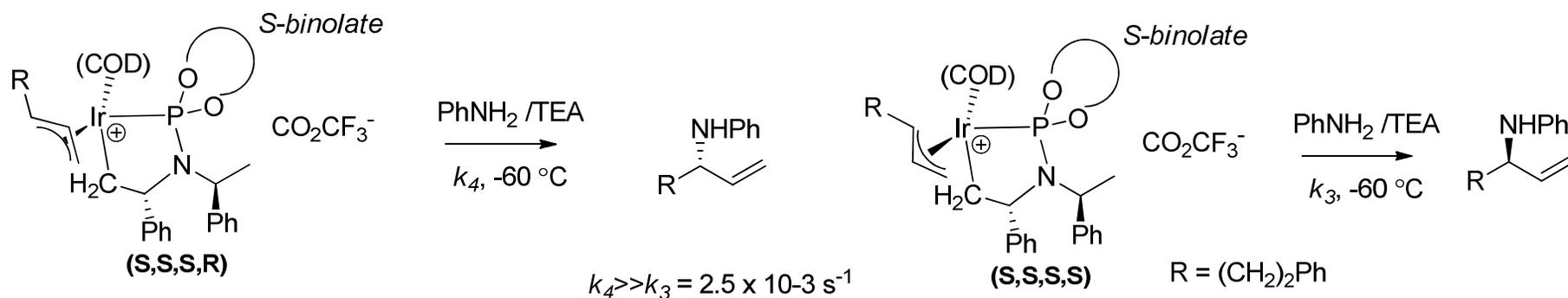


- Minor diastereomer rate constant = $2 \times 10^{-4} \text{ s}^{-1}$
- Major diastereomer rate constant = $1.2 \times 10^{-4} \text{ s}^{-1}$
- Based on initial rates, minor more reactive

Rate Differentiation of Diastereomers

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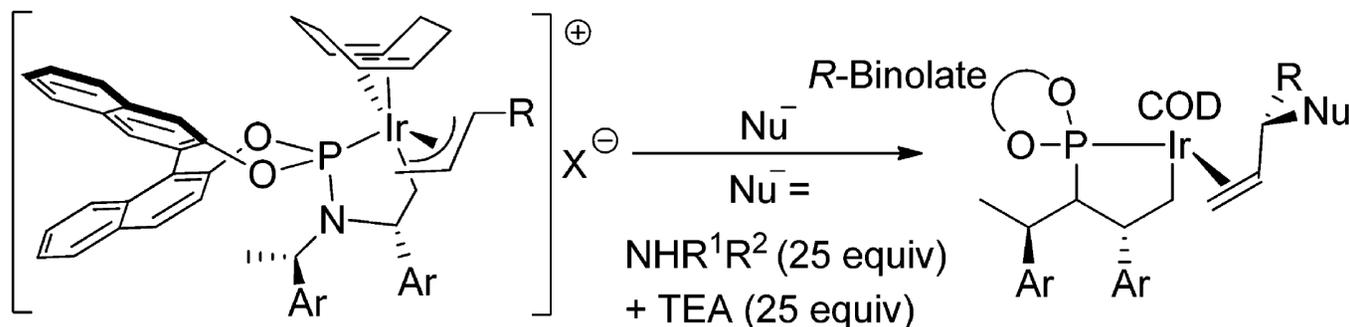
- “Reaction of the more stable diastereomer is slower than reaction of the (less stable) diastereomer”
- 1:1 ratio of (S,S,S,R) and (S,S,S,S)



- Attack on less stable (S,S,S,R) faster than more stable diastereomer (complete conv. in 3 min vs only 5%)

Rate Determination for Nucleophilic Attack

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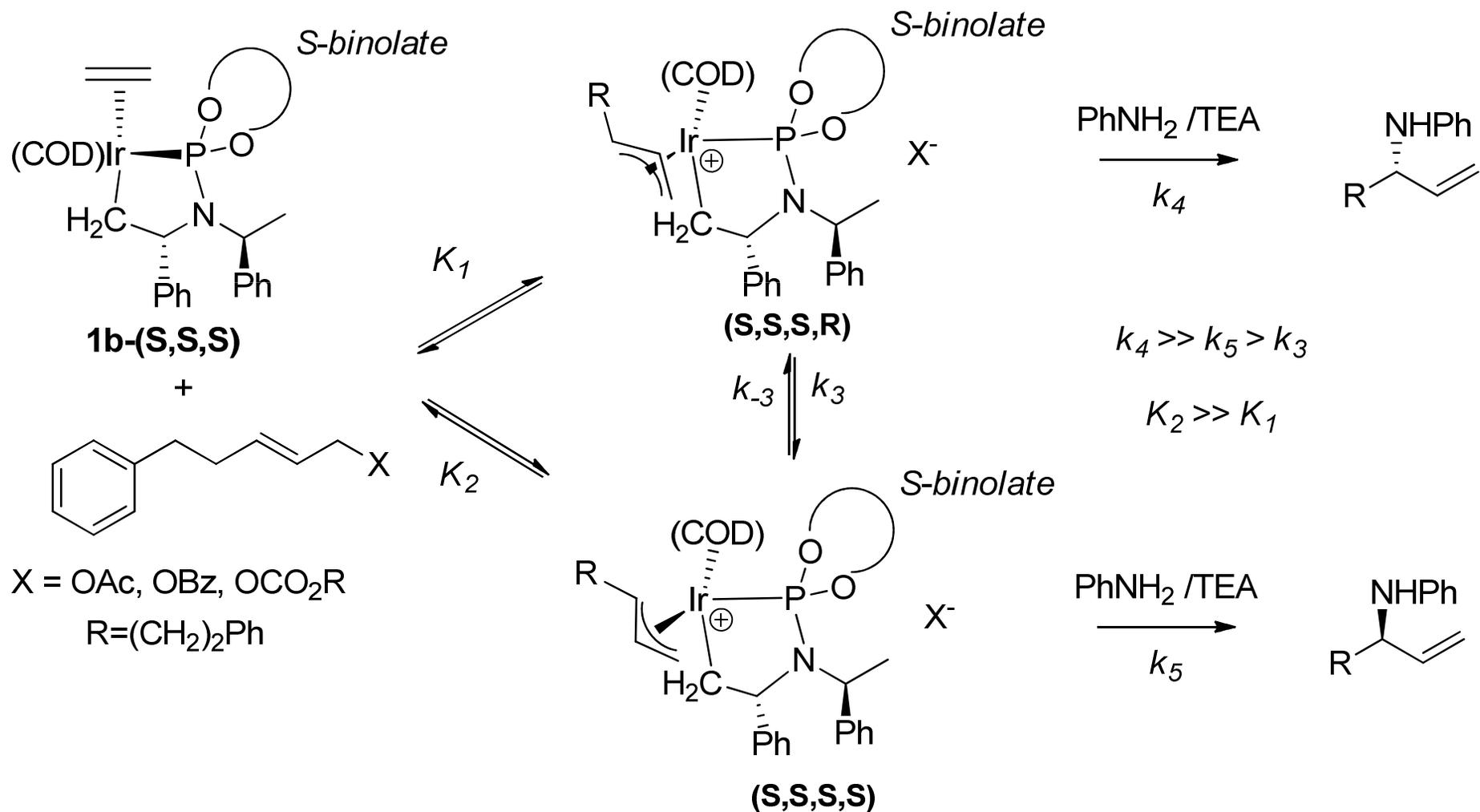


| Entry | Complex | R ¹ (R ²) | Solvent | (M) | T, °C | k_{obs} , s ⁻¹ |
|-------|---------------|----------------------------------|---------------------------------|-------|-------|------------------------------------|
| 1 | 2c | H (Ph) | CH ₂ Cl ₂ | 0.030 | -30 | 6.0 x 10 ⁻⁴ |
| 2 | 2c | H (Ph) | THF | 0.043 | -40 | 3.4 x 10 ⁻³ |
| 3 | 2c | H (Ph) | THF | 0.030 | -60 | Too fast |
| 4 | 2c | TBAOAc | THF | 0.030 | -60 | Too fast |
| 5 | 2d | H (Ph) | CH ₂ Cl ₂ | 0.030 | -30 | 2.8 x 10 ⁻⁴ |
| 6 | 2d | Me (Ph) | CH ₂ Cl ₂ | 0.043 | -30 | 2.0 x 10 ⁻⁴ |
| 7 | 3b | H (Ph) | THF | 0.030 | -40 | 9.9 x 10 ⁻⁴ |
| 8 | 2f-TFA | H (Ph) | THF | 0.046 | -40 | 2.5 x 10 ⁻³ |

Hartwig, J. F. *et al* *J. Am. Chem. Soc.* **2012**, *134*, 8136.

Big Picture

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Enantioselectivity Big Picture

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- Nucleophilic attack on minor diastereomer faster than major diastereomer
- Nucleophilic attack on diastereomers faster than interconversion of diastereomers
- More stable diastereomer leads to major enantiomer

- Therefore: oxidative addition **MUST** be highly selective

Conclusions

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- Ir-catalyzed allylic substitution reactions can lead to highly enantioenriched products of O-, N-, and C-nucleophiles at the branched position
- Proceeds via a double inversion pathway
- Cyclometalation step key in formation of active catalyst species with lower loadings
- High enantioselectivity depends on selective oxidative addition step
- Oxidative addition is a reversible process

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