Tsuji-Trost Reaction: Selectivity in Palladium-Catalyzed Allylic Substitution

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April 10th 2021

Outline

- **Introduction**
- **Selectivity of π-Allyl Intermediate**
  Isomerization
  Regioselectivity for Soft Nu
  Regioselectivity for Hard Nu
- **Enantioselectivity Tsuji-Trost Reaction**
  Asymmetric Allylic Alkylation
  Kinetic Resolution
- **Summary**
- **Acknowledgement**

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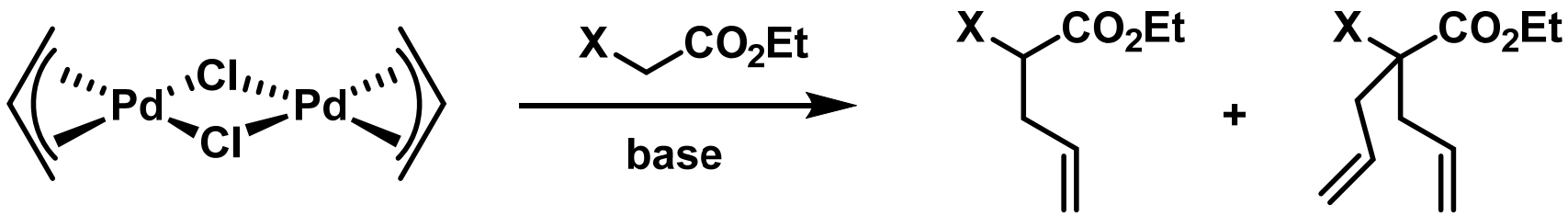
Introduction of Tsuji-Trost Reaction

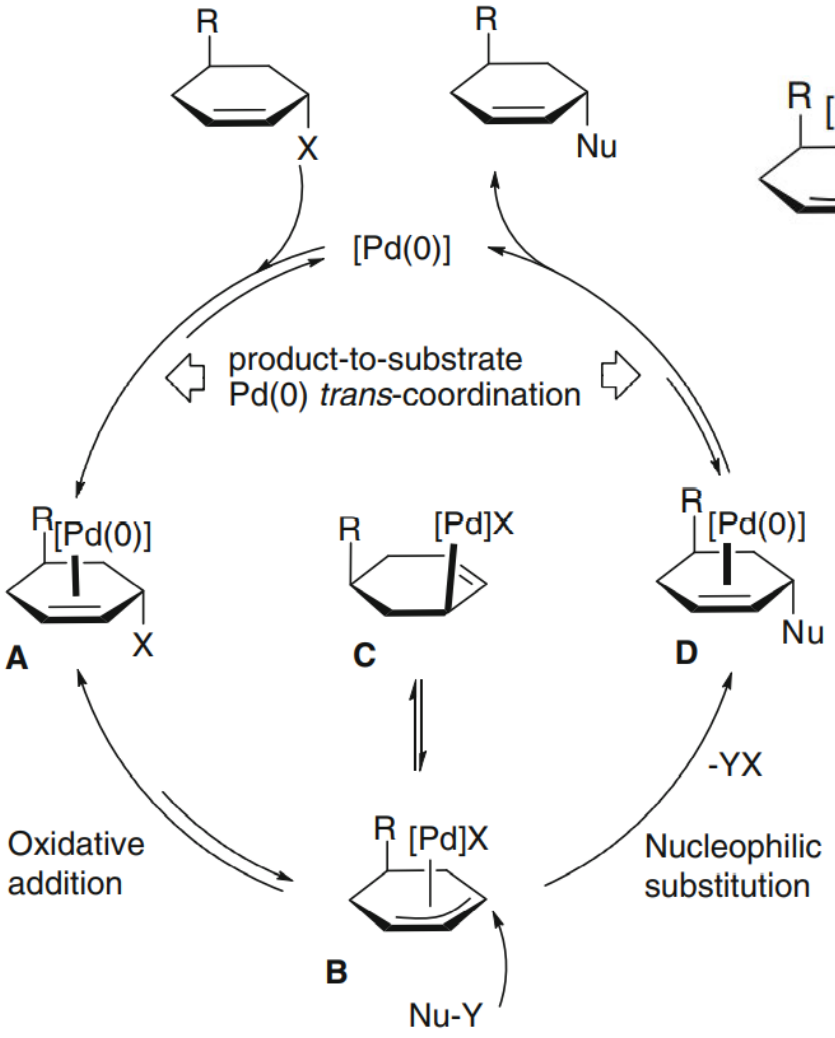
- In 1965, J. Tsuji discovered that C–C bond formation can be achieved by the reaction of π-allylpalladium complexes with C-nucleophiles, typically stabilized carbanions such as malonates.

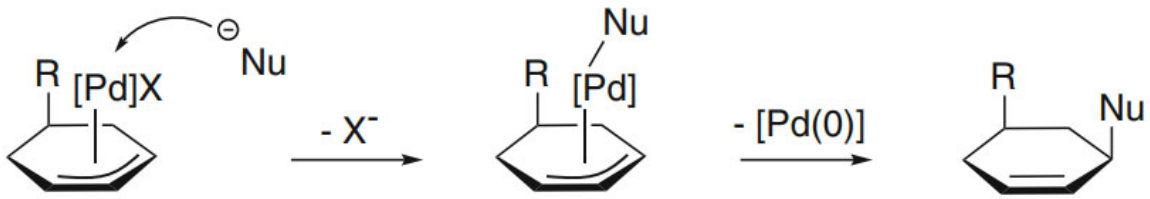


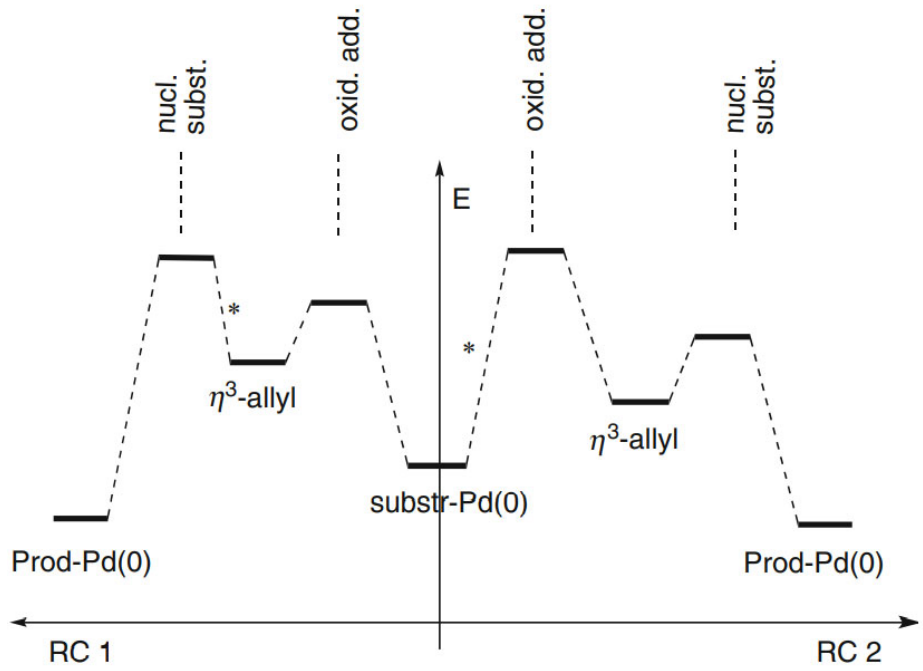
- Later on, catalytic and enantioselective versions were developed mainly by B. M. Trost and his group.

Tsuji, J et al. *Tetrahedron lett.* **1965**, *6*, 4387.

Typical Mechanism

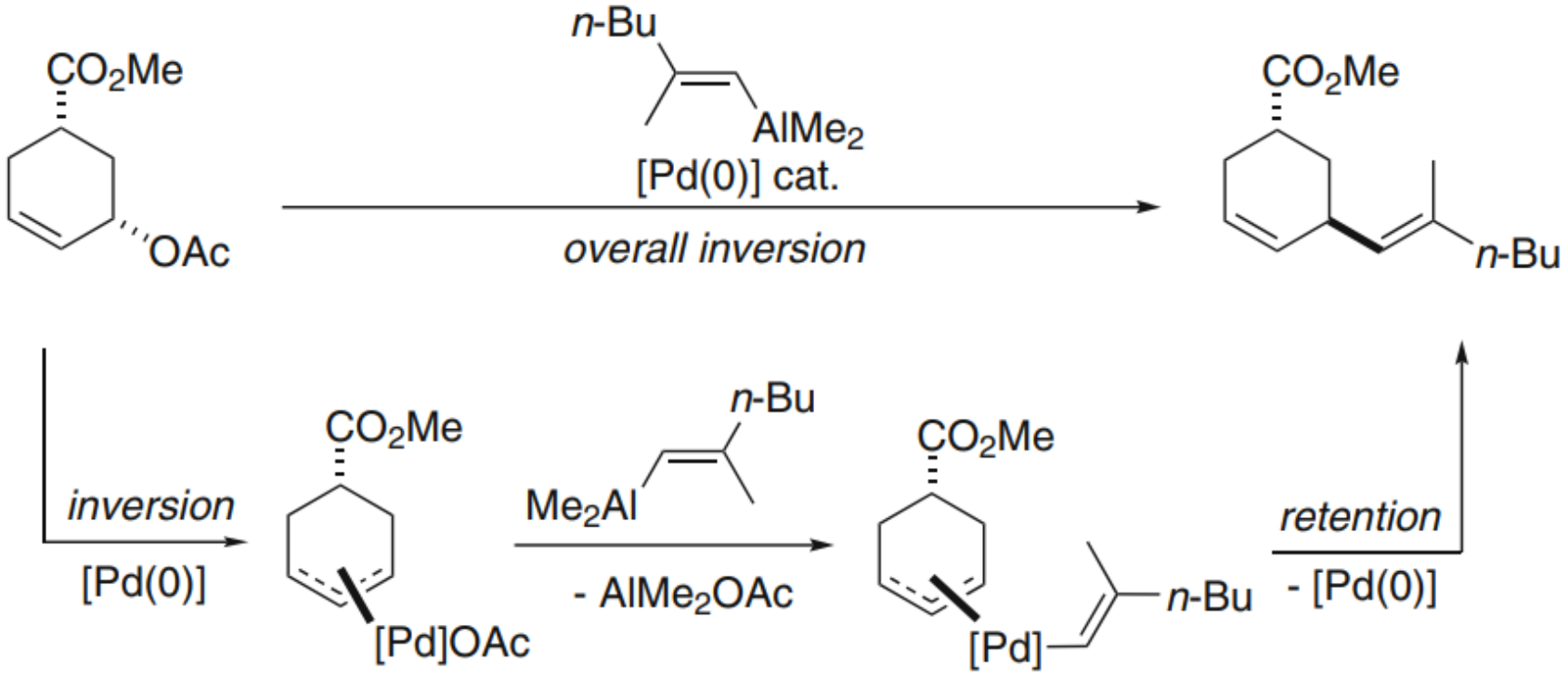




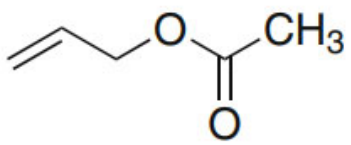


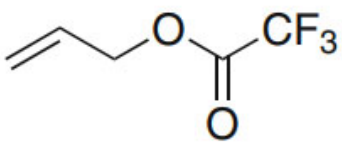
Soft & Hard Nucleophiles

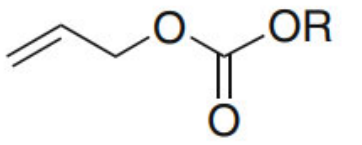
- Normally, "Soft" nucleophiles' conjugate acids have p*K*a < 25 and "Hard" nucleophiles' conjugate acids have p*K*a > 25.



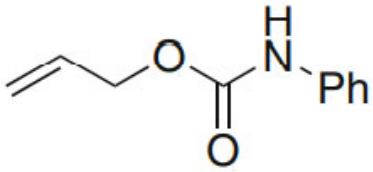
Classical Electrophiles

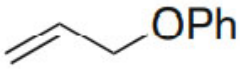


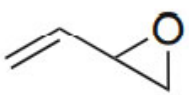


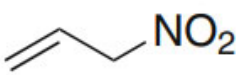


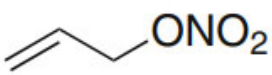
R = Me, CH_2CCl_3

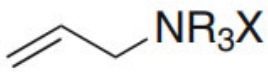


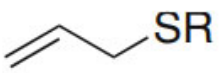


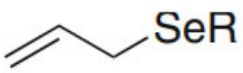


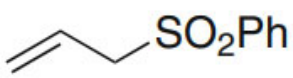


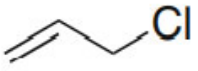


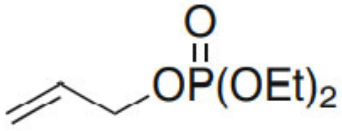












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  Kinetic Resolution
- **Summary**
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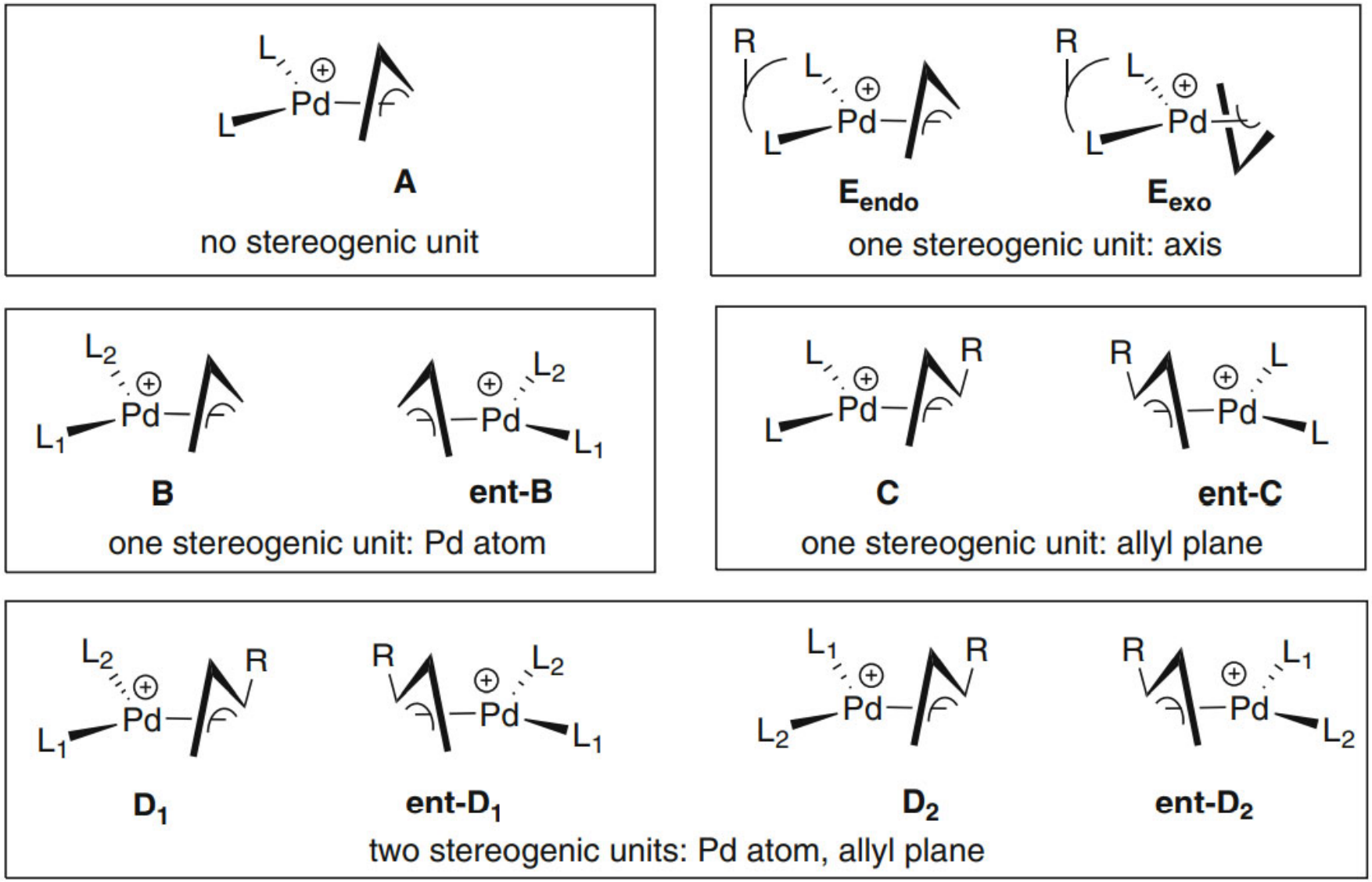
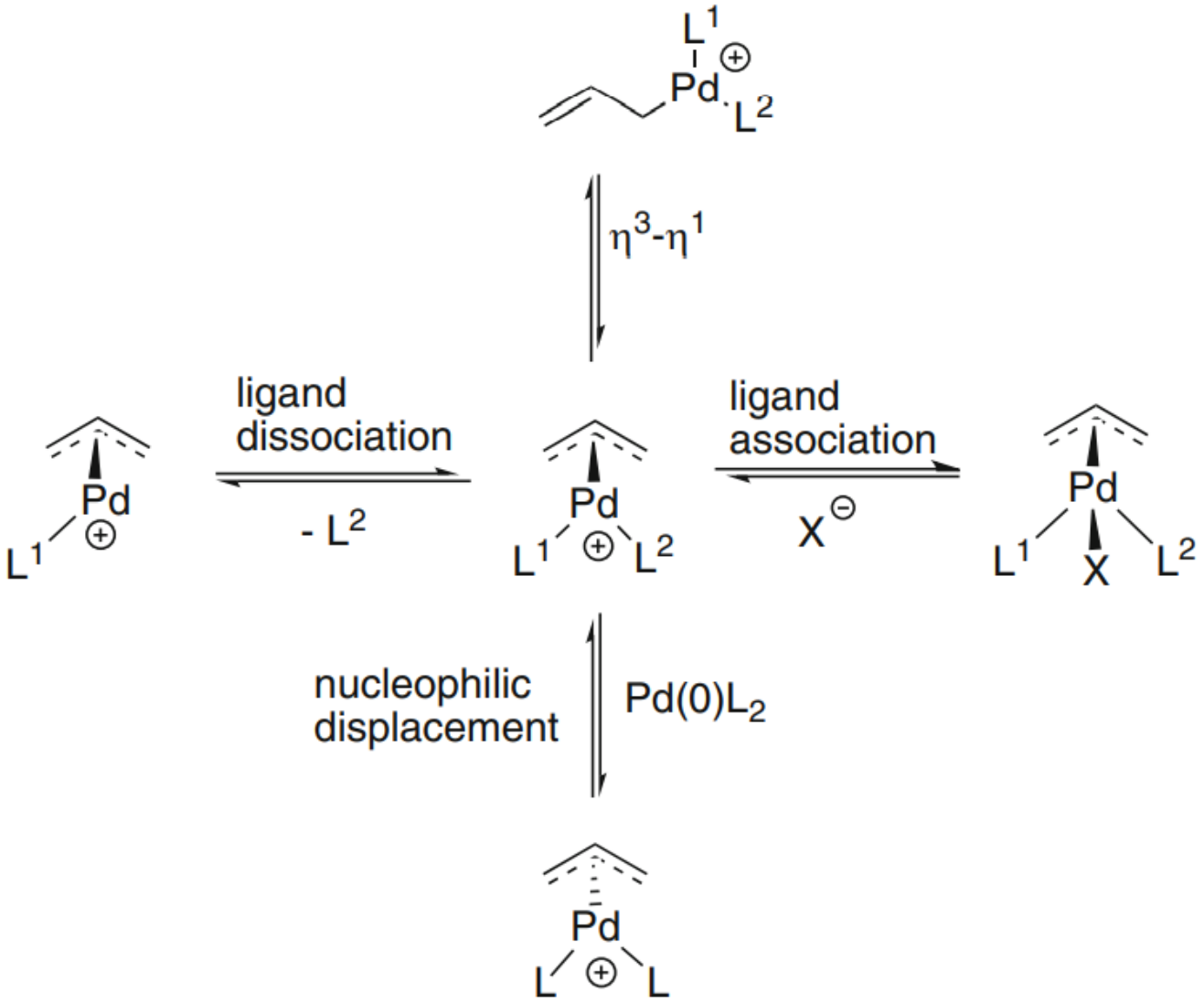
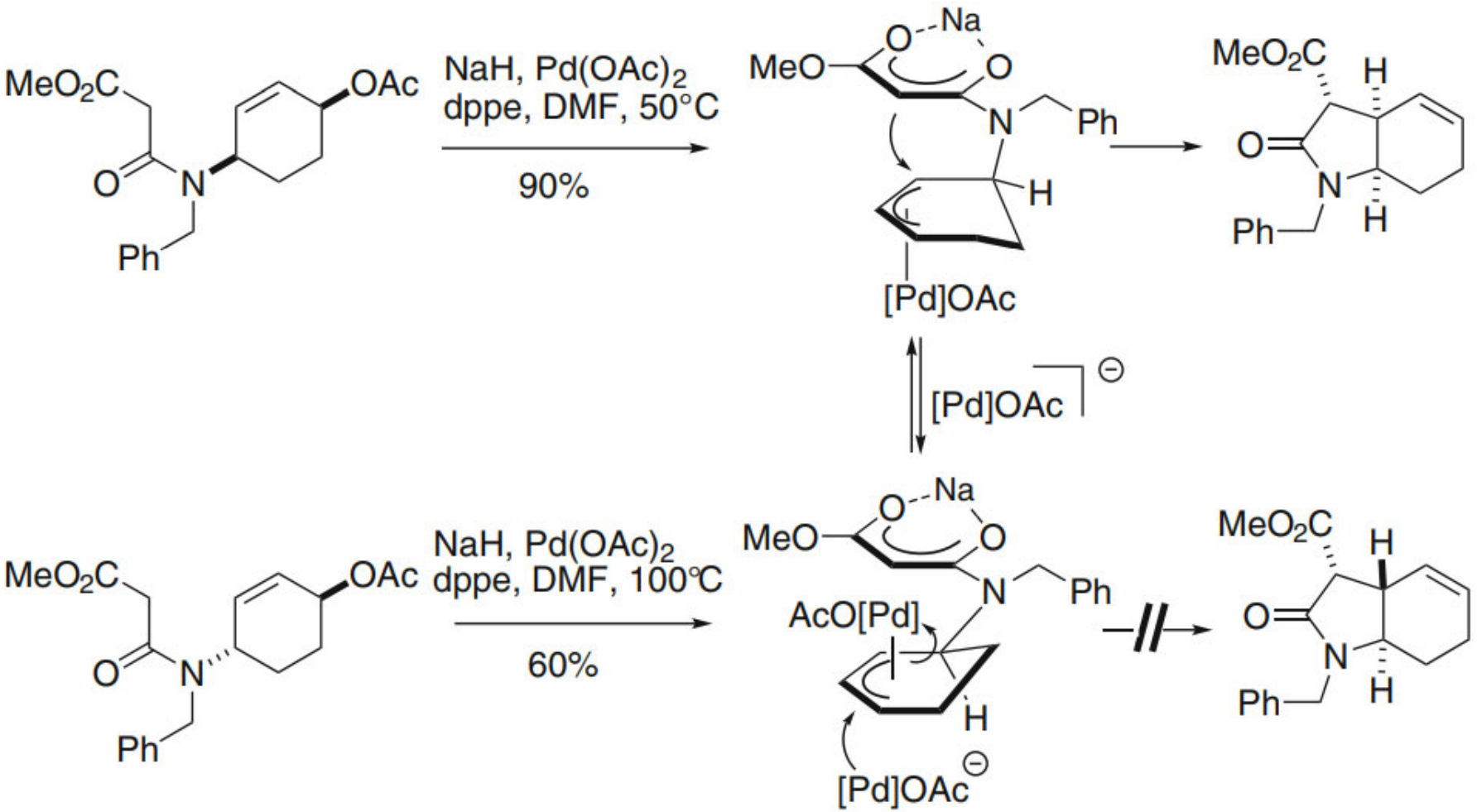
Possible Isomers



Possible Equilibria

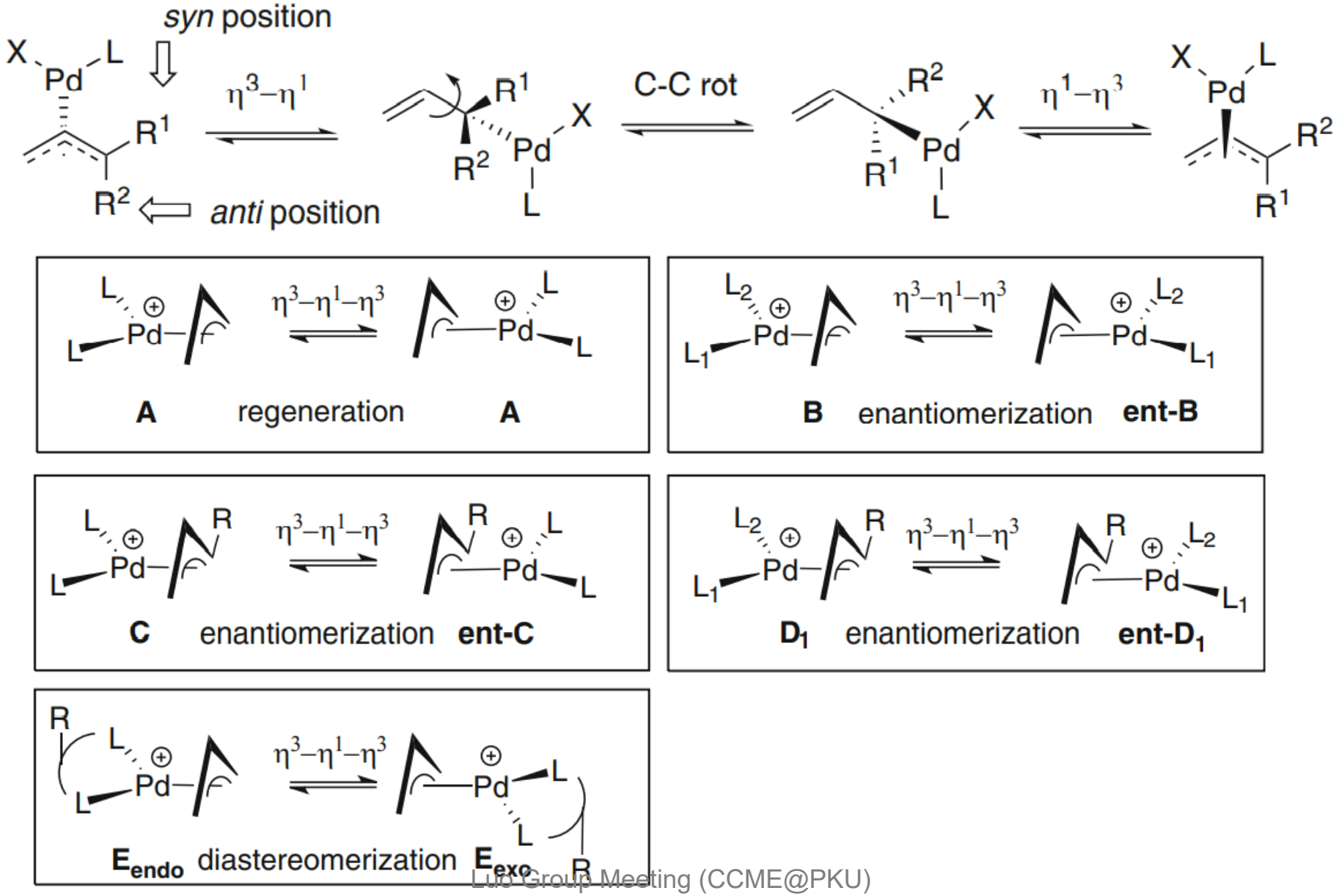


Allyl Exchange: High Pd Concentration



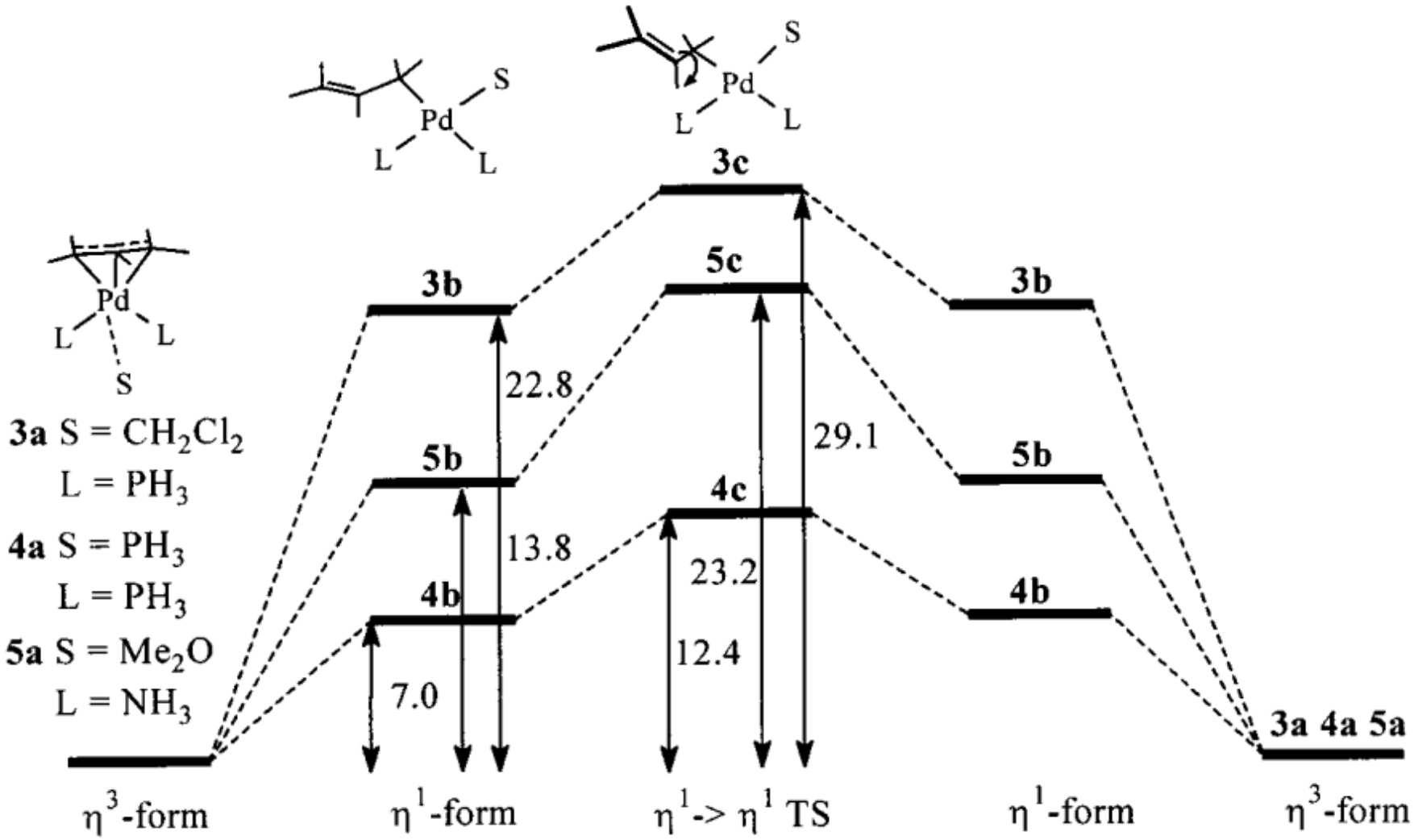
Poli, G et al. *Eur. J. Org. Chem.* **2004**, *13*, 2840.

Syn-Anti Exchange: Normally Fast



Syn-Anti: Solvent Effect

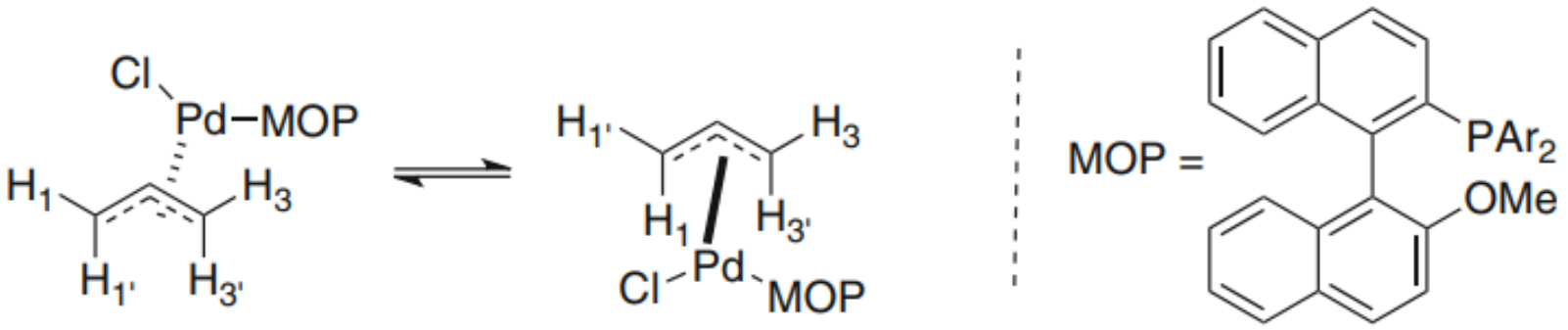
- More efficient in **Me_2O** than in **CH_2Cl_2** by 6.8 kcal/mol



Niclas, S et al. *Organometallics* **2001**, *20*, 5464.

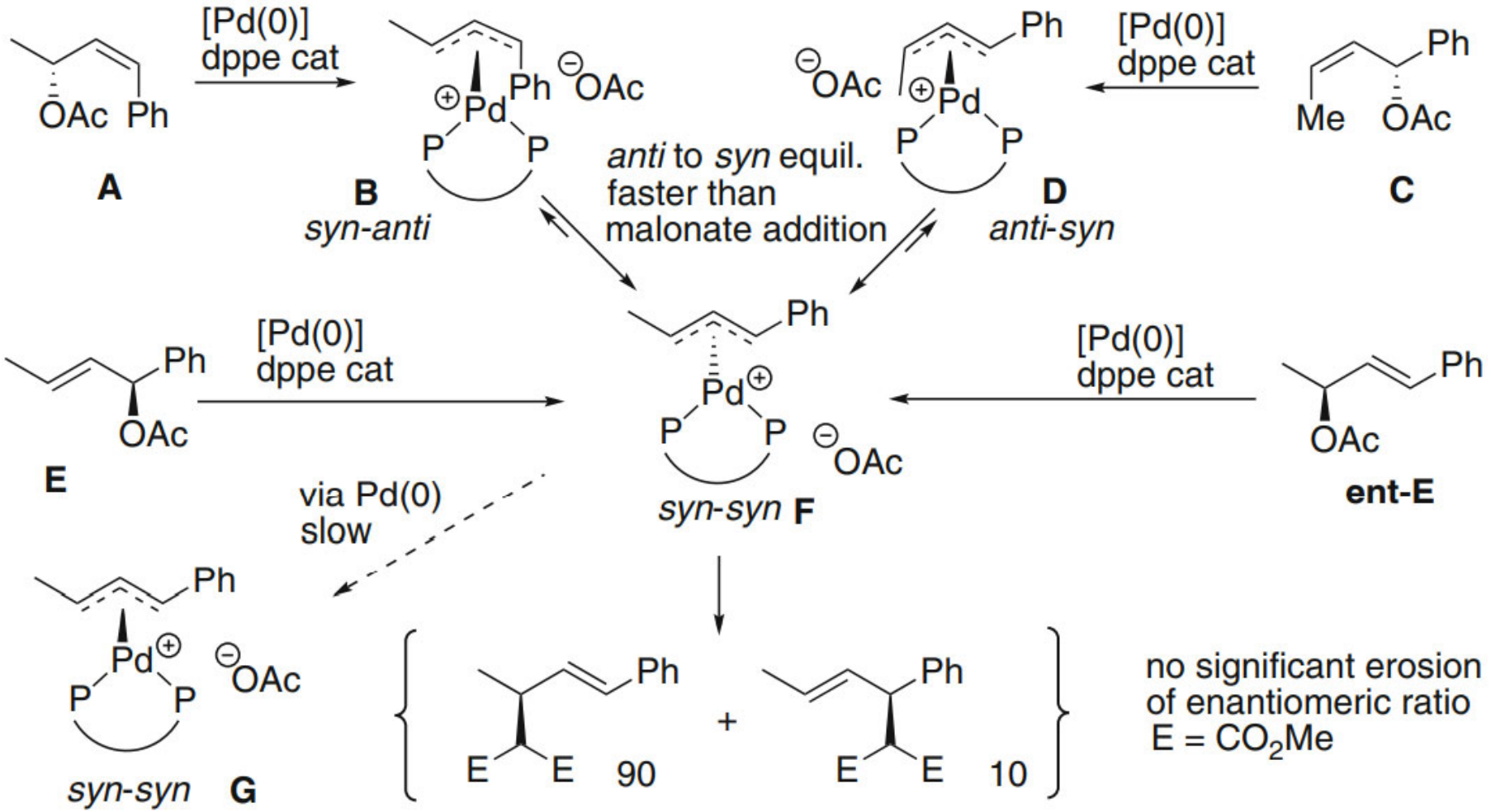
Syn-Anti: Ligand Effect

- ERG attached to phosphorus is beneficial for fast SAE.



Entry	Ar	k (s^{-1})
1	3-$CF_3C_6H_4$	1.7
2	Ph	0.4
3	4-$MeOC_6H_4$	0.08

Syn-Prefer: Z-Selectivity is Hard



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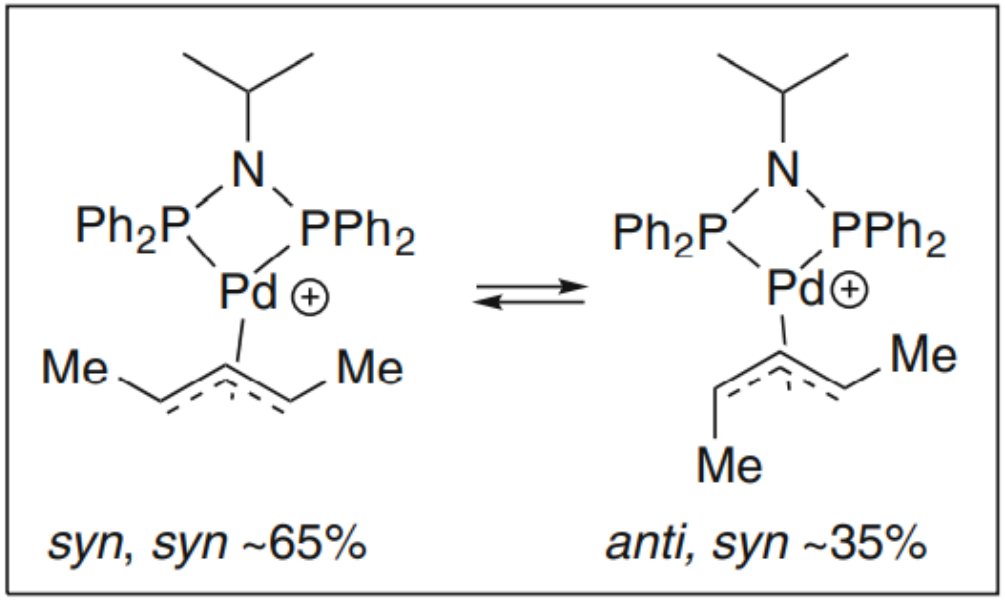
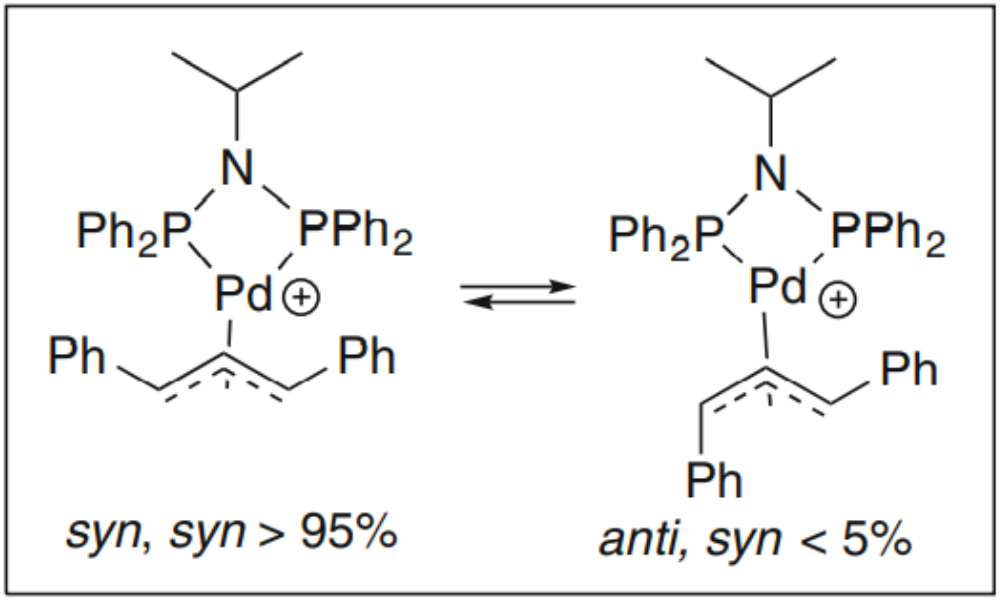
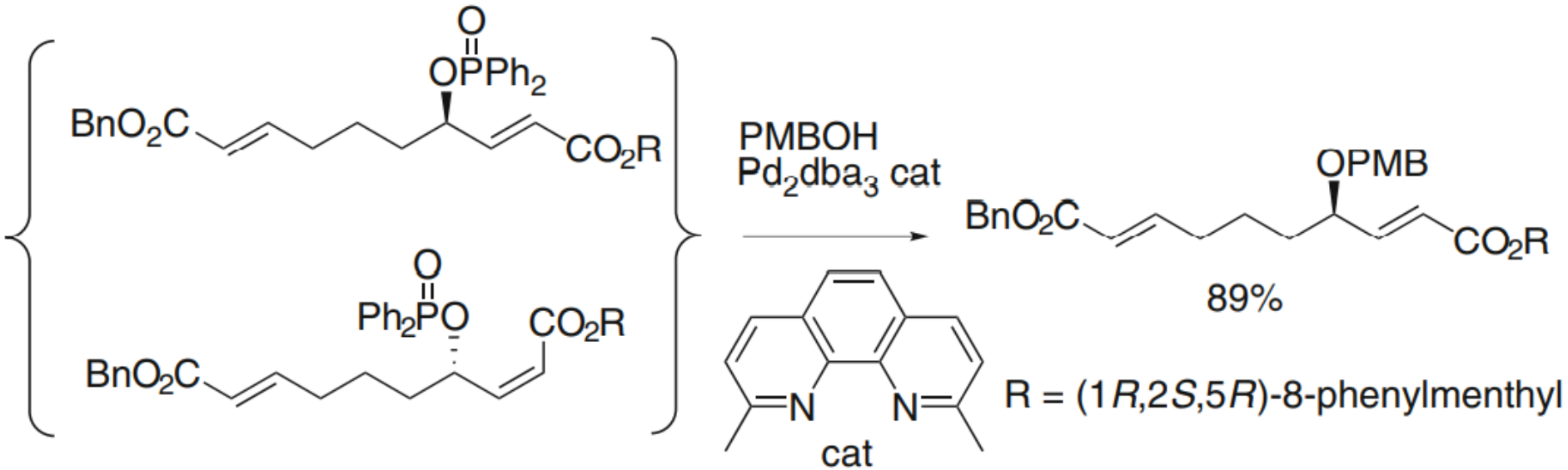


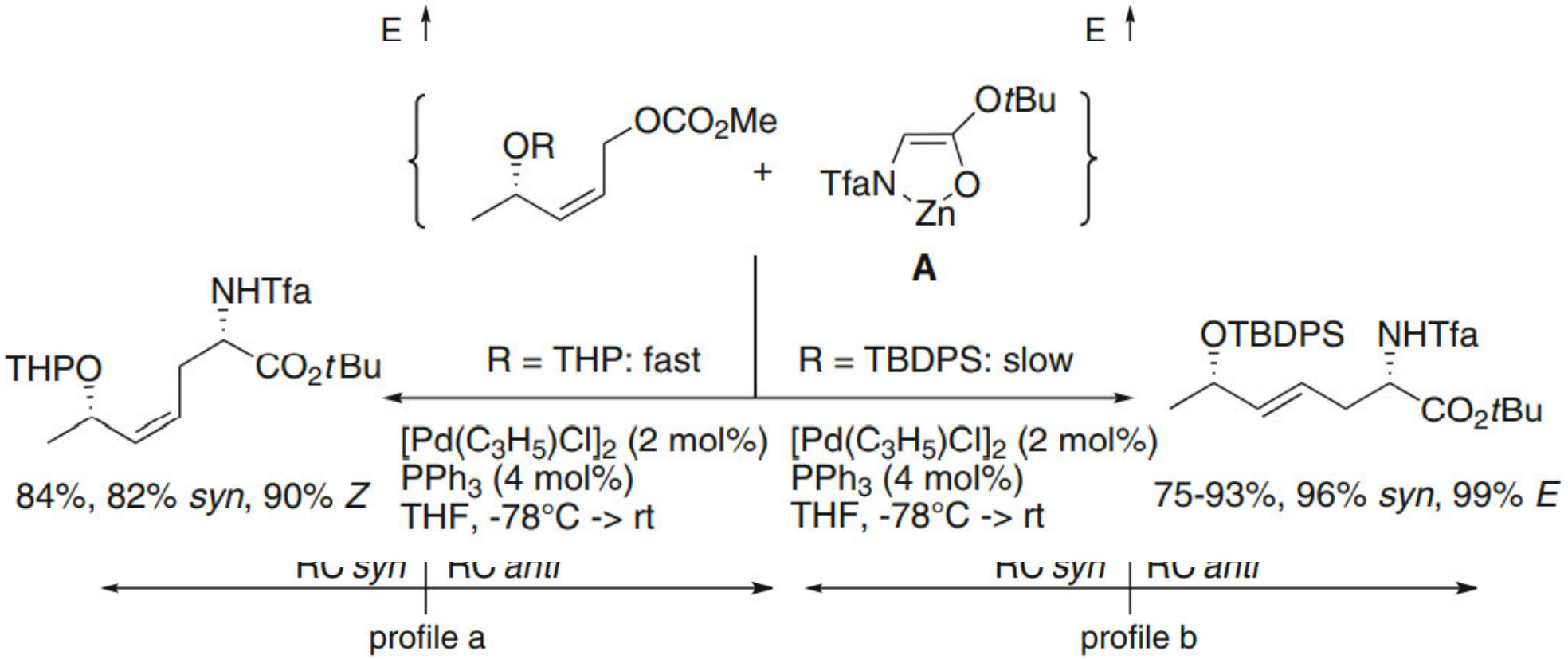




Mandal, S et al. *J. Organomet. Chem.* **2003**, *676*, 22; Pedersen, T et al. *J. Am. Chem. Soc.* **2001**, *123*, 9738.

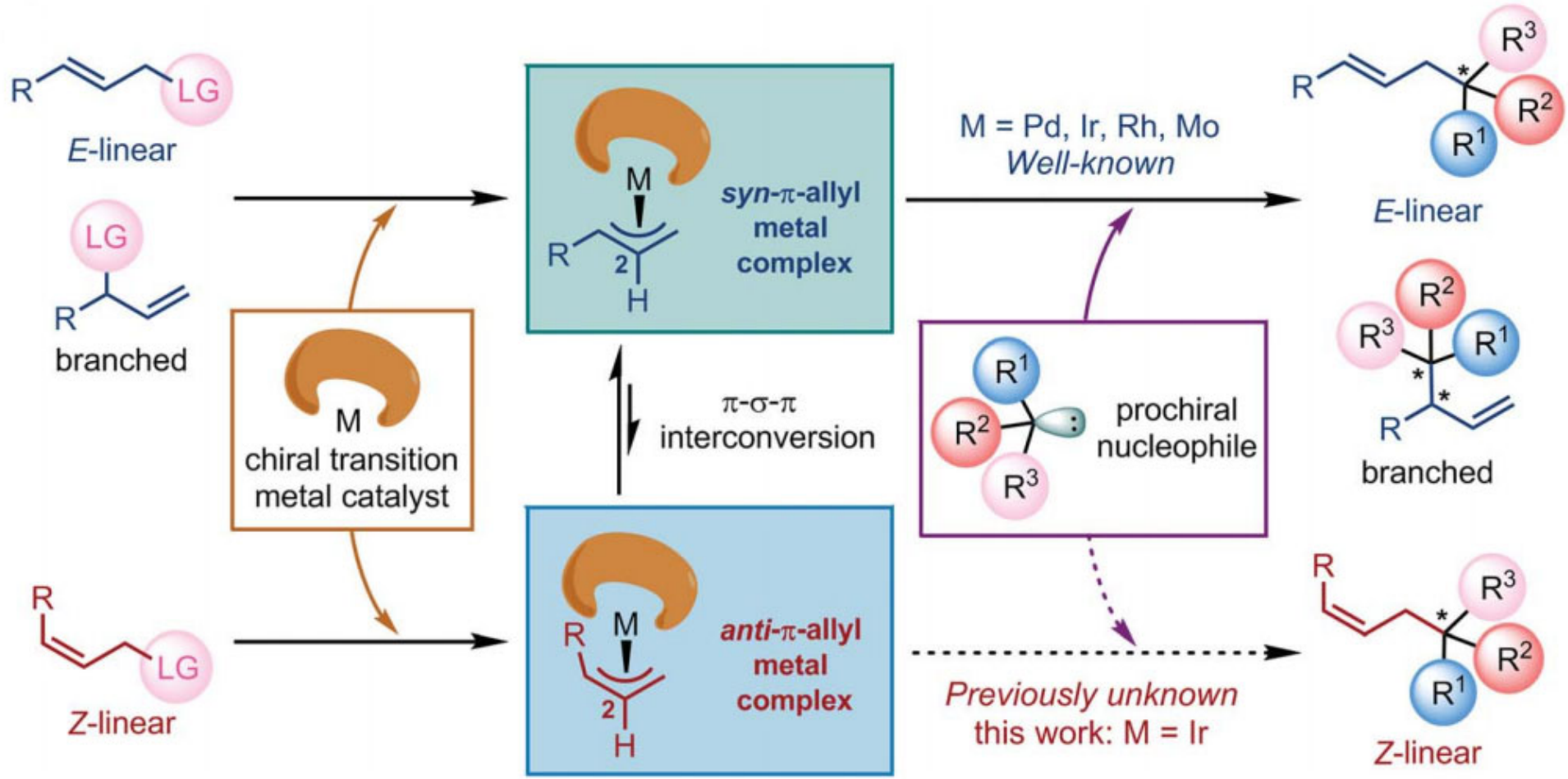
How to Make Z-Selectivity Possible?

- Two paths: Slow down SAE or Speed up Attack.



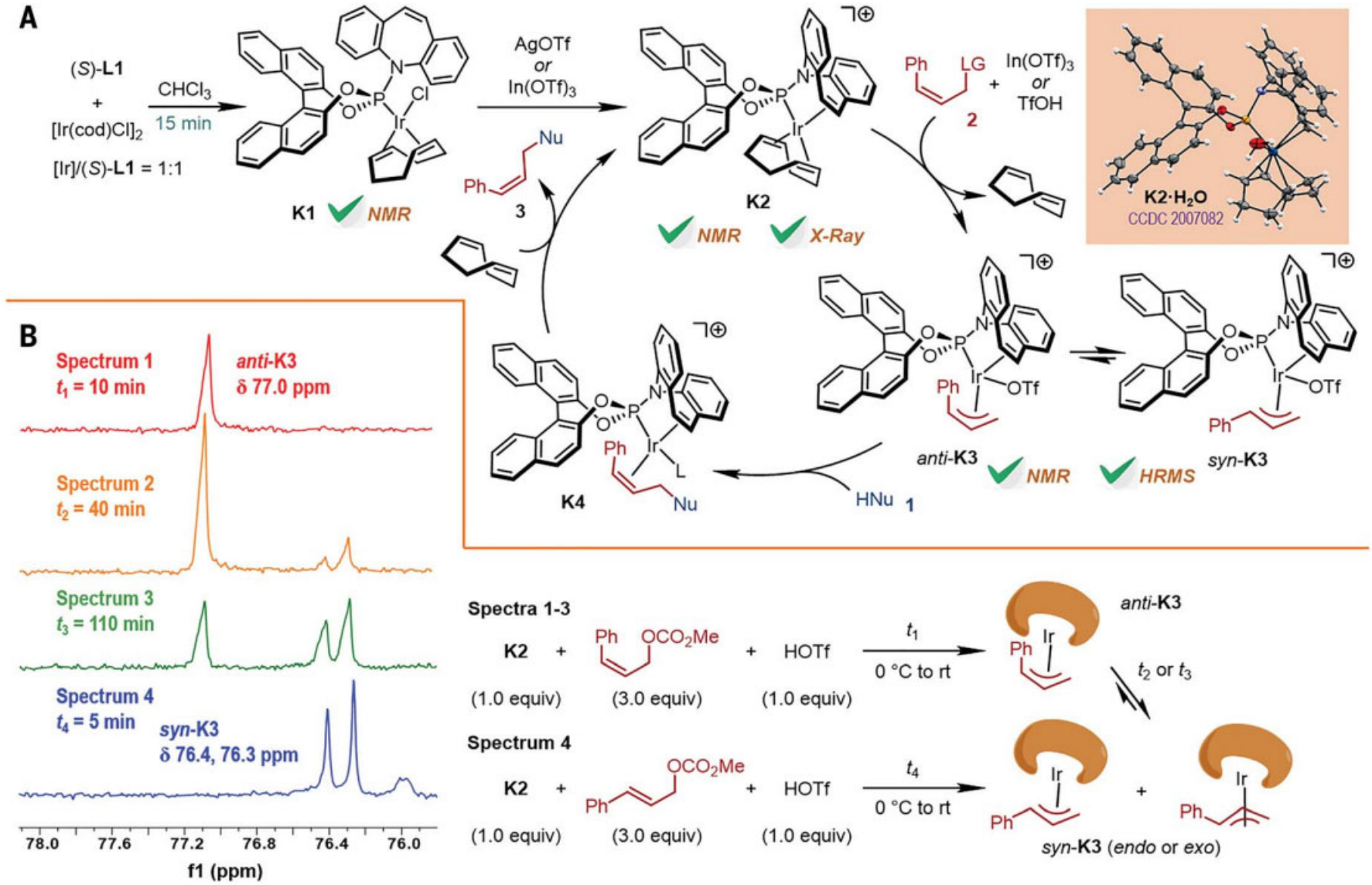
Kramer, K et al. *J. Org. Chem.* **2006**, *71*, 8950.

Ir-Catalyzed Z-Retentive: A Solution



You, S et al. *Science.* **2021**, *371*, 380.

Iridium & Ligand: Isomerization Slower



You, S et al. *Science.* **2021**, *371*, 380.

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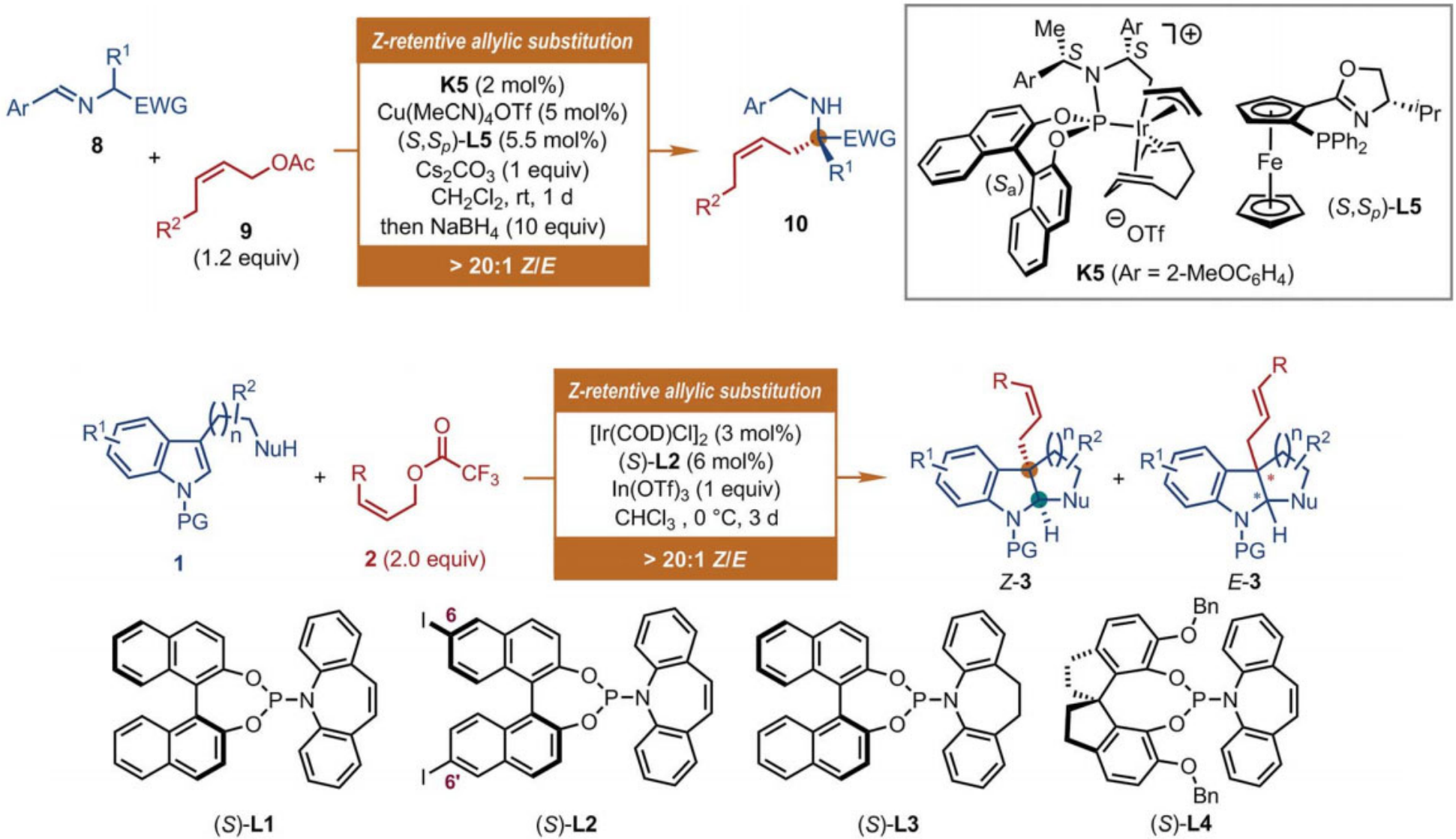
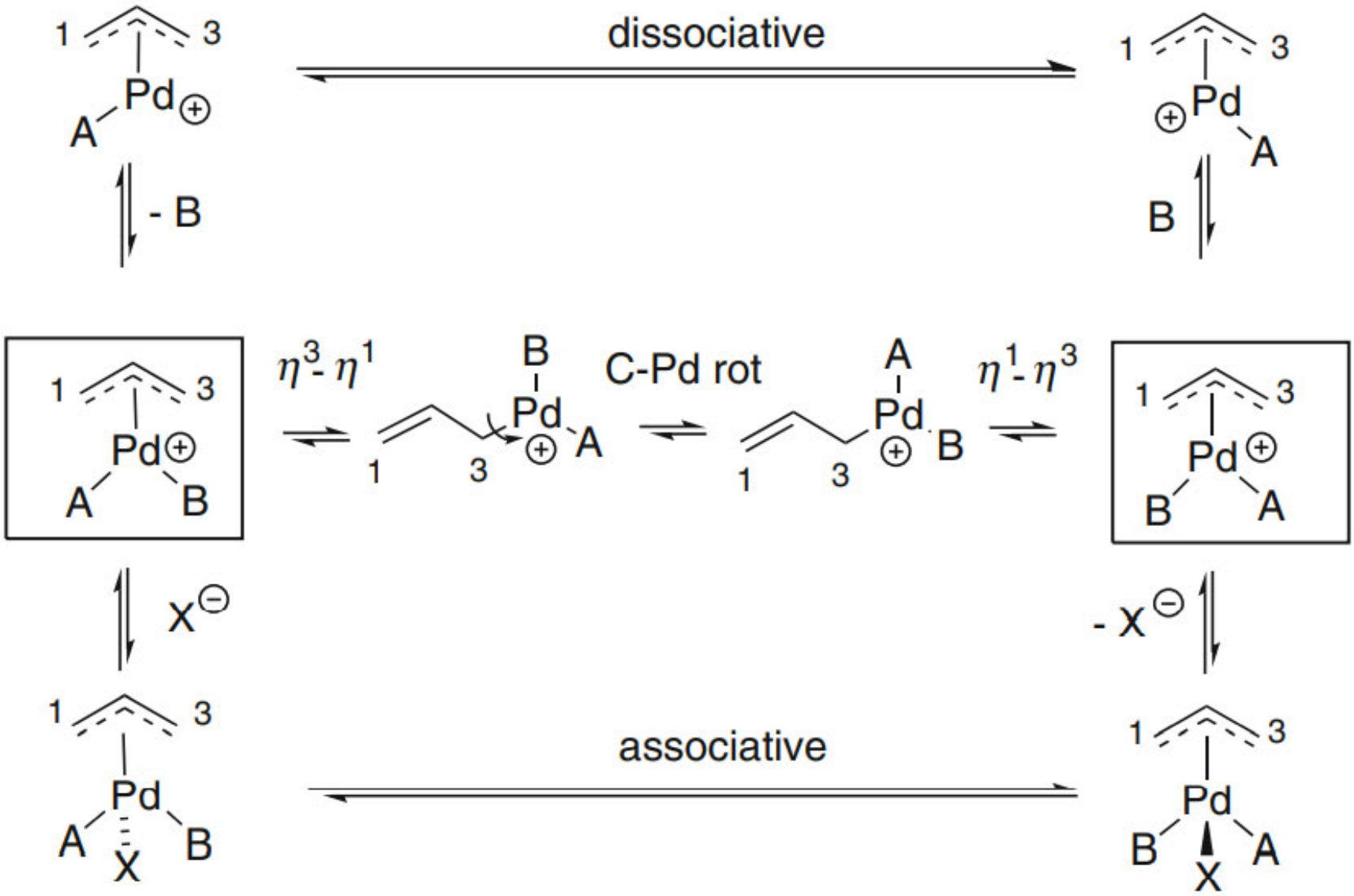


Apparent Allyl Rotation: Pathways

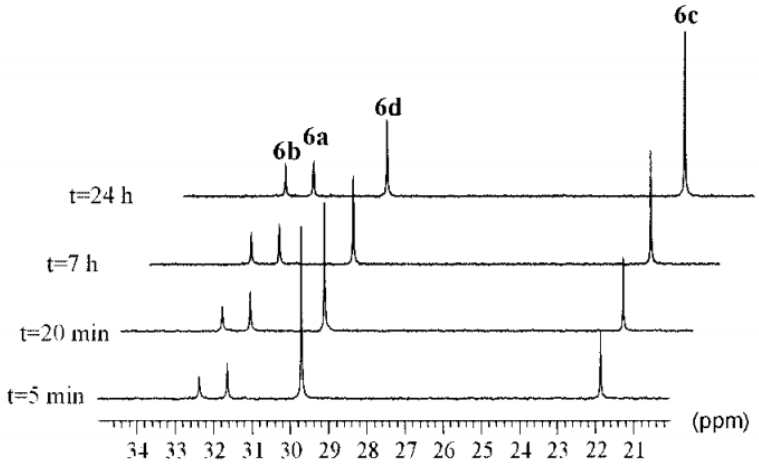


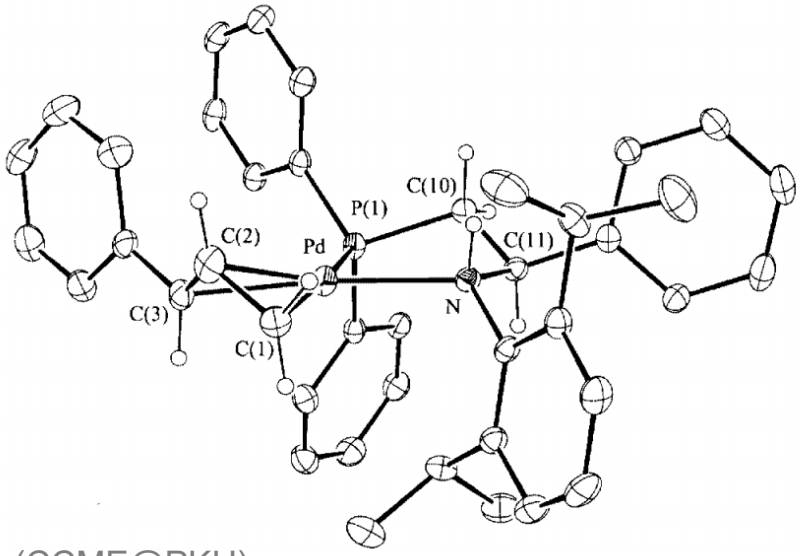
AAR & SAE: Share Bliss?

	endo/exo syn trans-P (**a/b** or **b/a**)	*endo/exo syn cis*-P (**c/d** or **d/c**)
3	53/30	11/6
4	78/9	9/4
5	55/22	12/11
6	9/7	62/22

$[(\eta^3\text{-}C_3H_4R)Pd(P\frown N)^+,PF_6^-]$

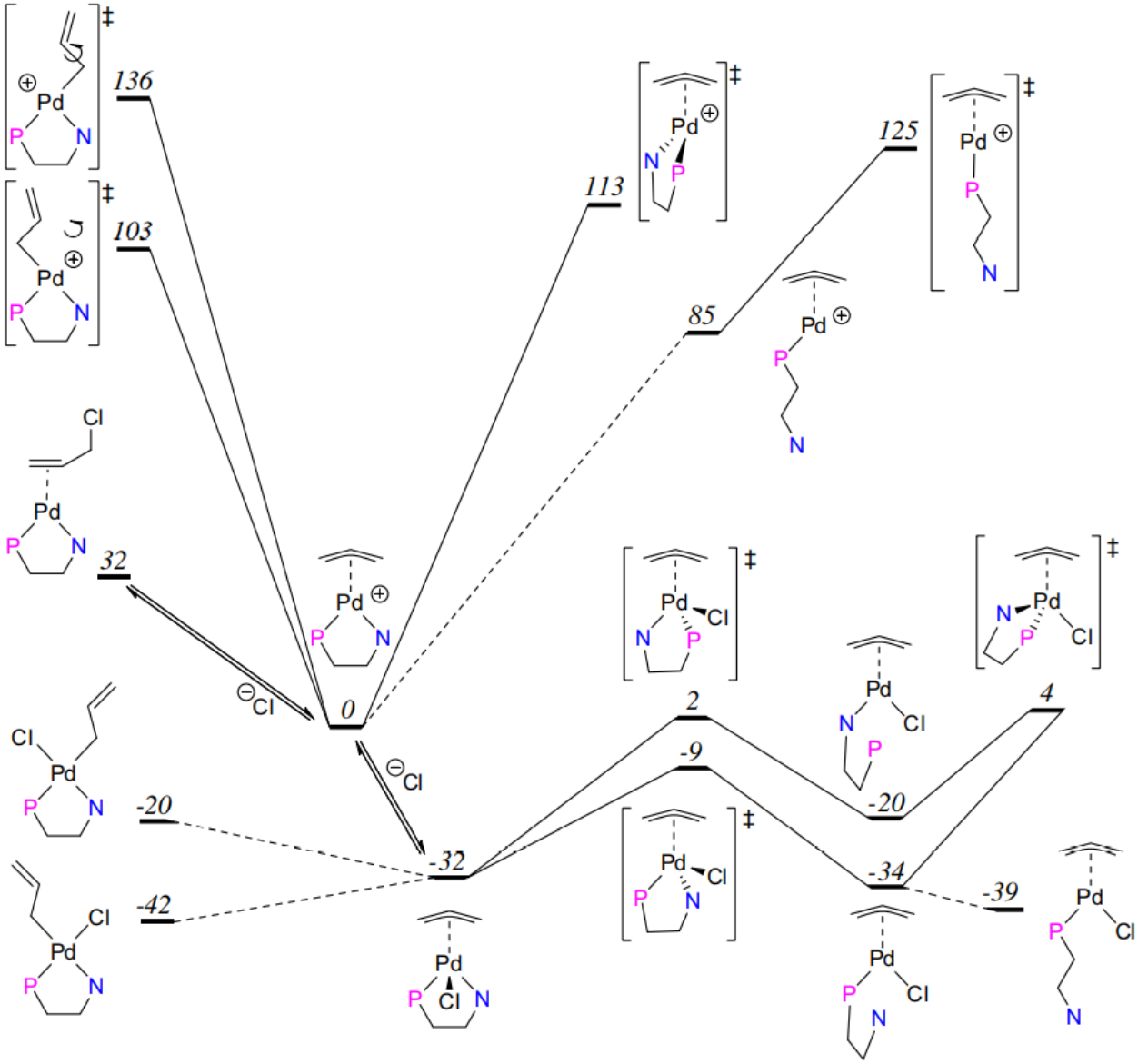
1, R = H, Ar = Ph
2, R = H, Ar = 2,6-$C_6H_3i\text{Pr}_2$
3, R = Me, Ar = Ph
4, R = Me, Ar = 2,6-$C_6H_3i\text{Pr}_2$
5, R = Ph, Ar = Ph
6, R = Ph, Ar = 2,6-$C_6H_3i\text{Pr}_2$



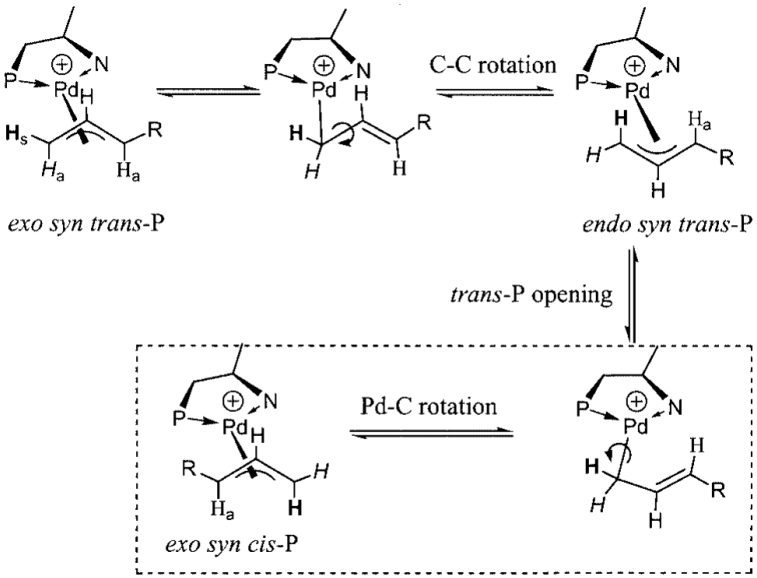


Rinaldo, P et al. *Eur. J. Inorg. Chem.* **2004**, 1081.

AAR vs SAE: Possible Paths



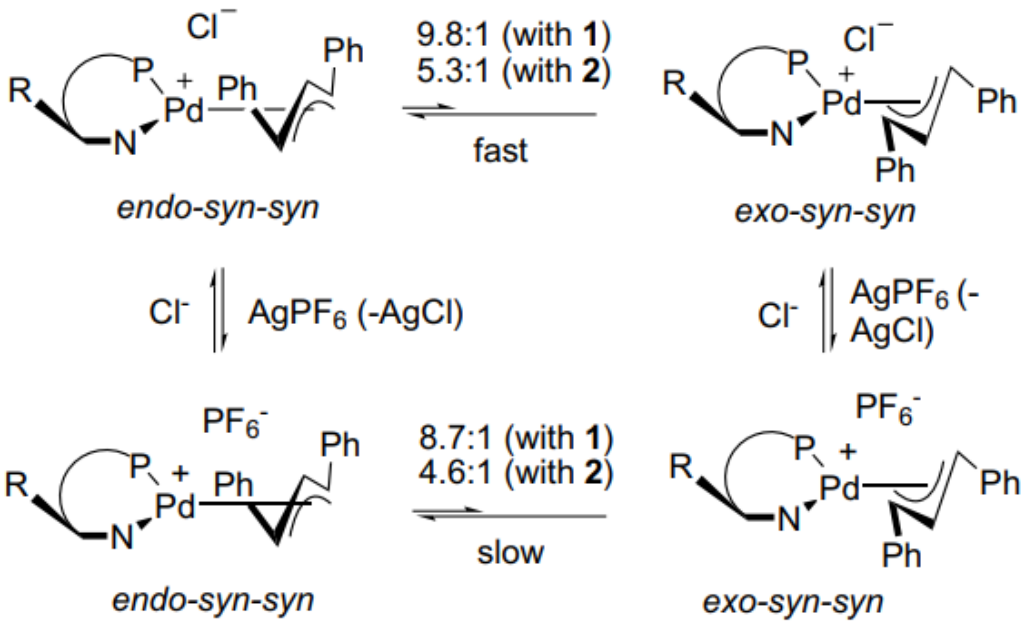
- Pd-C is harder to rotate than C-C
- Larger steric barrier in Pd-C rotation

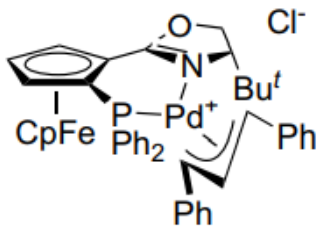


Cho, C et al. *Tetrahedron:* Asymmetry **2006**, *17*, 2240.

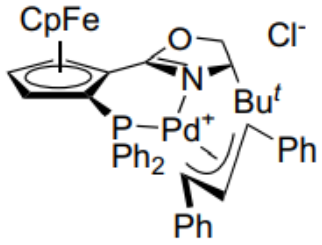
AAR vs SAE: Relationship

- Normally, direct AAR (lowest energy barrier is 27kcal/mol) is slower than SAE.
- Coordination solvents or additives accelerate AAR.
- Positive Pd-center prefer AAR when additives exist.





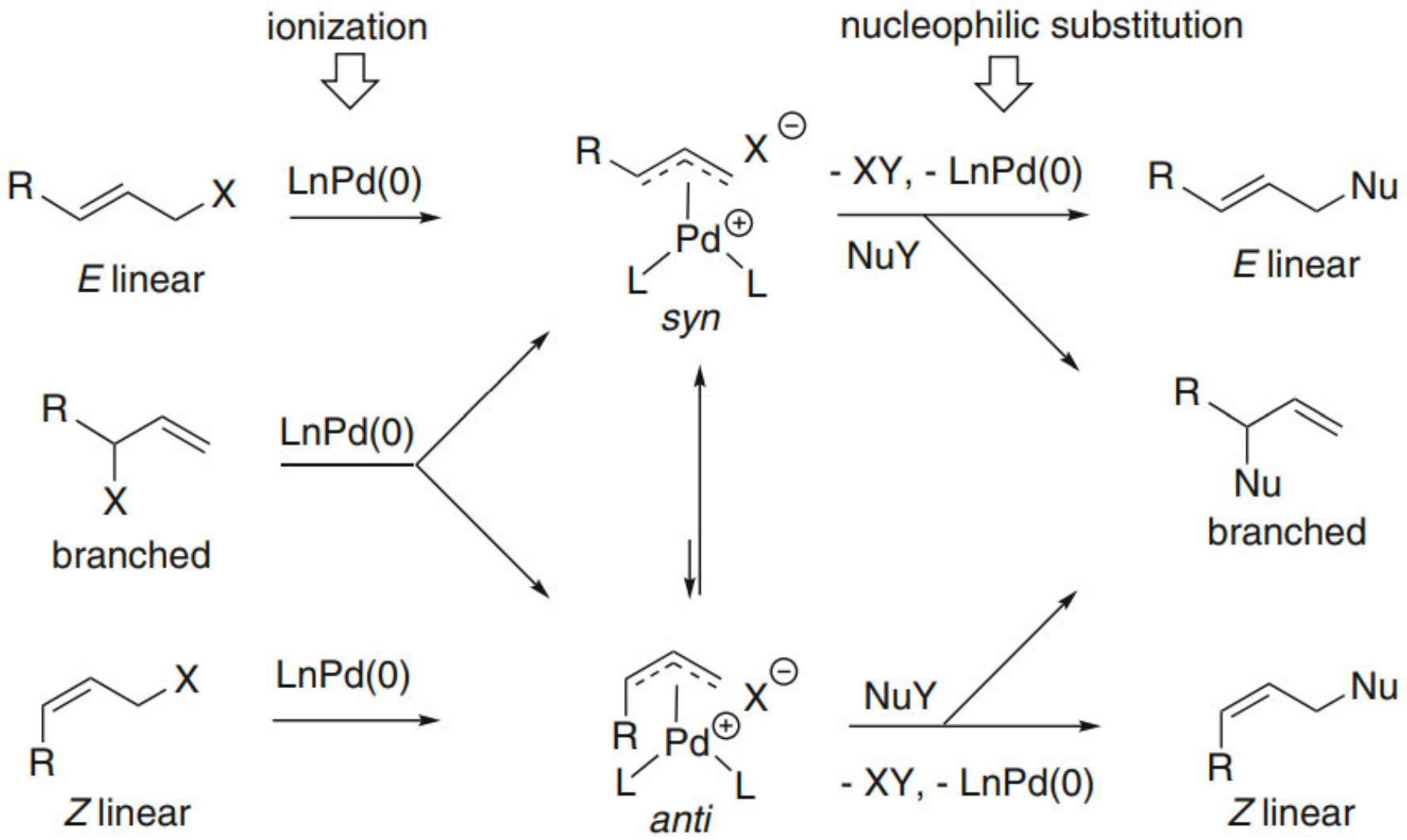
1n



2n

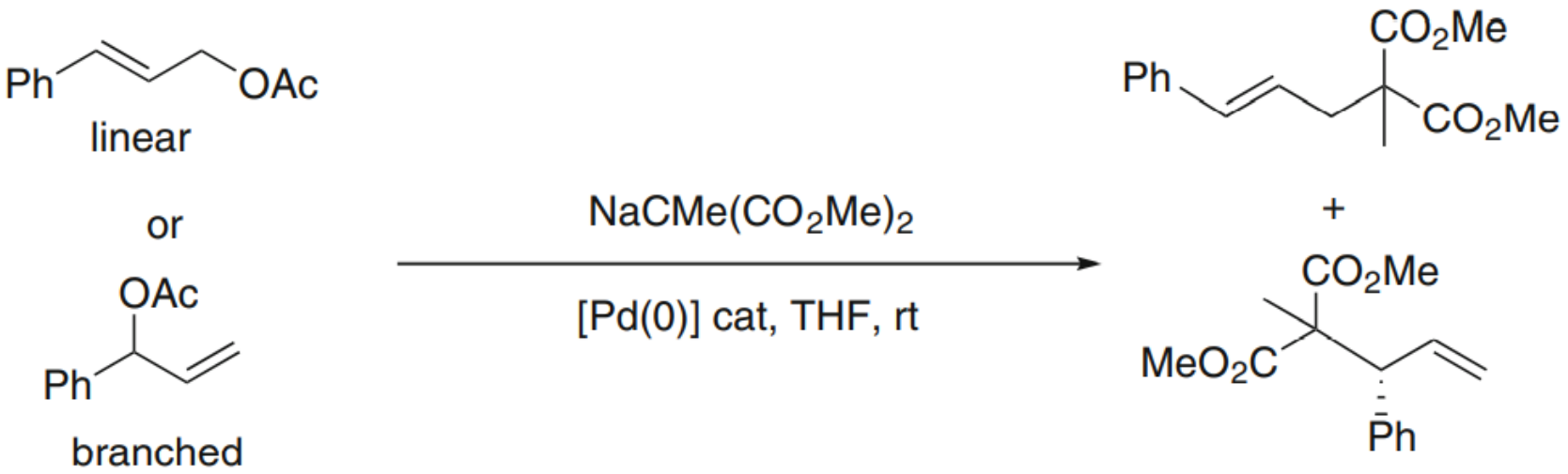
Cho, C et al. *Tetrahedron:* Asymmetry **2006**, *17*, 2240.

Soft Nu: Terminal or Branch



Structural Detail: Allyl Groups

- Terminal carbanion is more stable.
- For symmetric ligands: terminal is Steric favored and branch is Electronic favored.

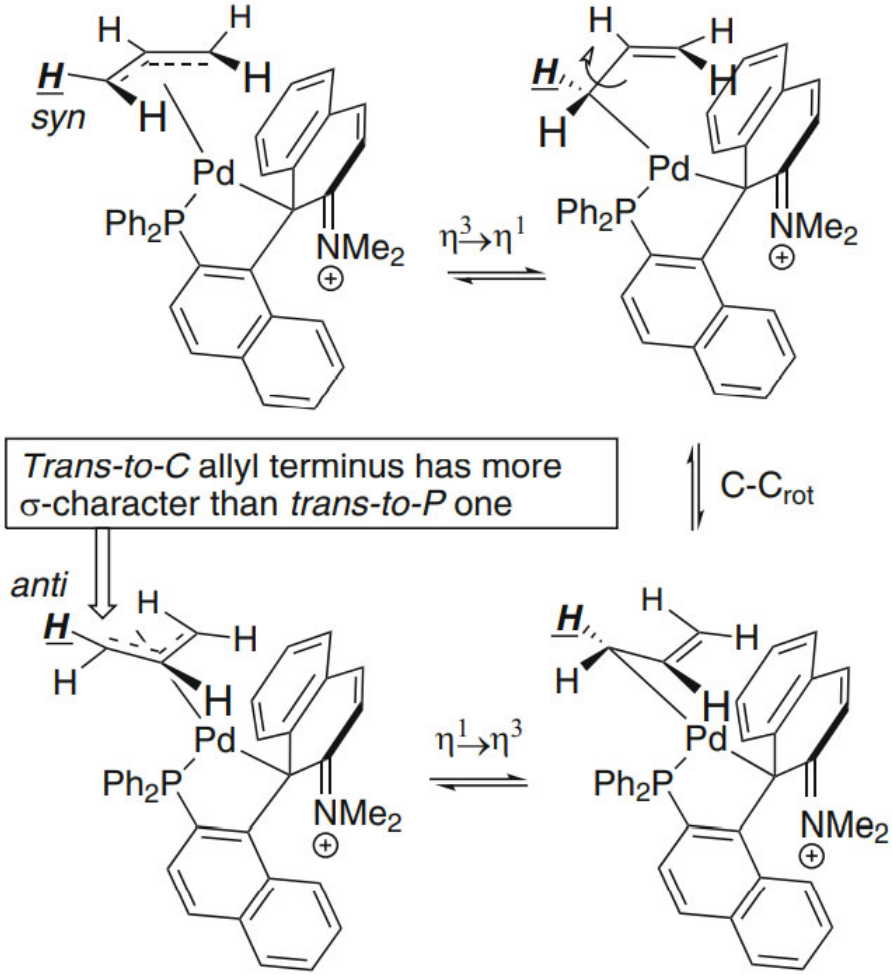


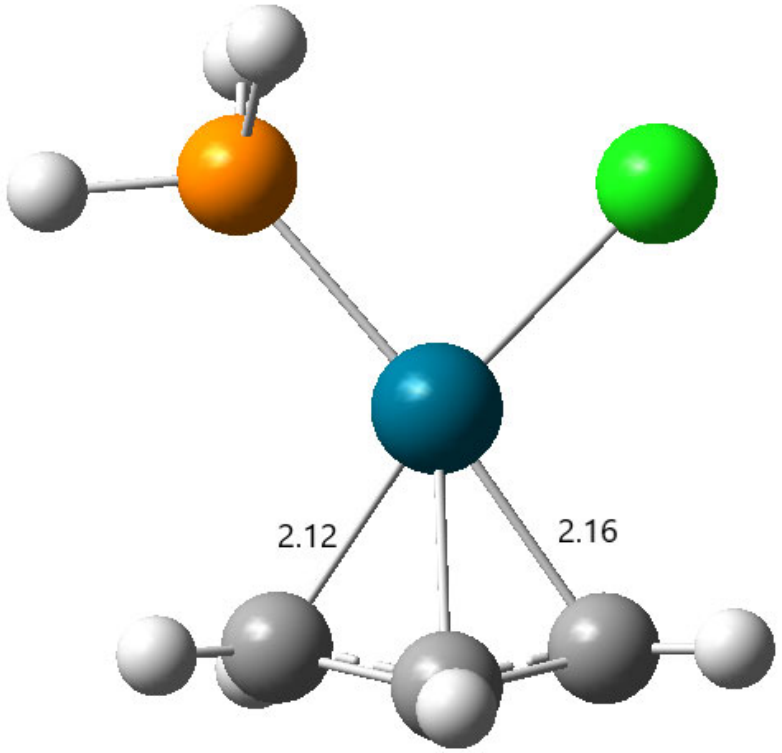
	Ligand	Substrate	Linear		Branched	Ref
canonical (ionic)	PPh_3	linear	91	:	09	219
		branched	92	:	08	219

Thomas, R. *Organometallics* **1996**, *15*, 2836.

Structural Detail: Asymmetric Ligands

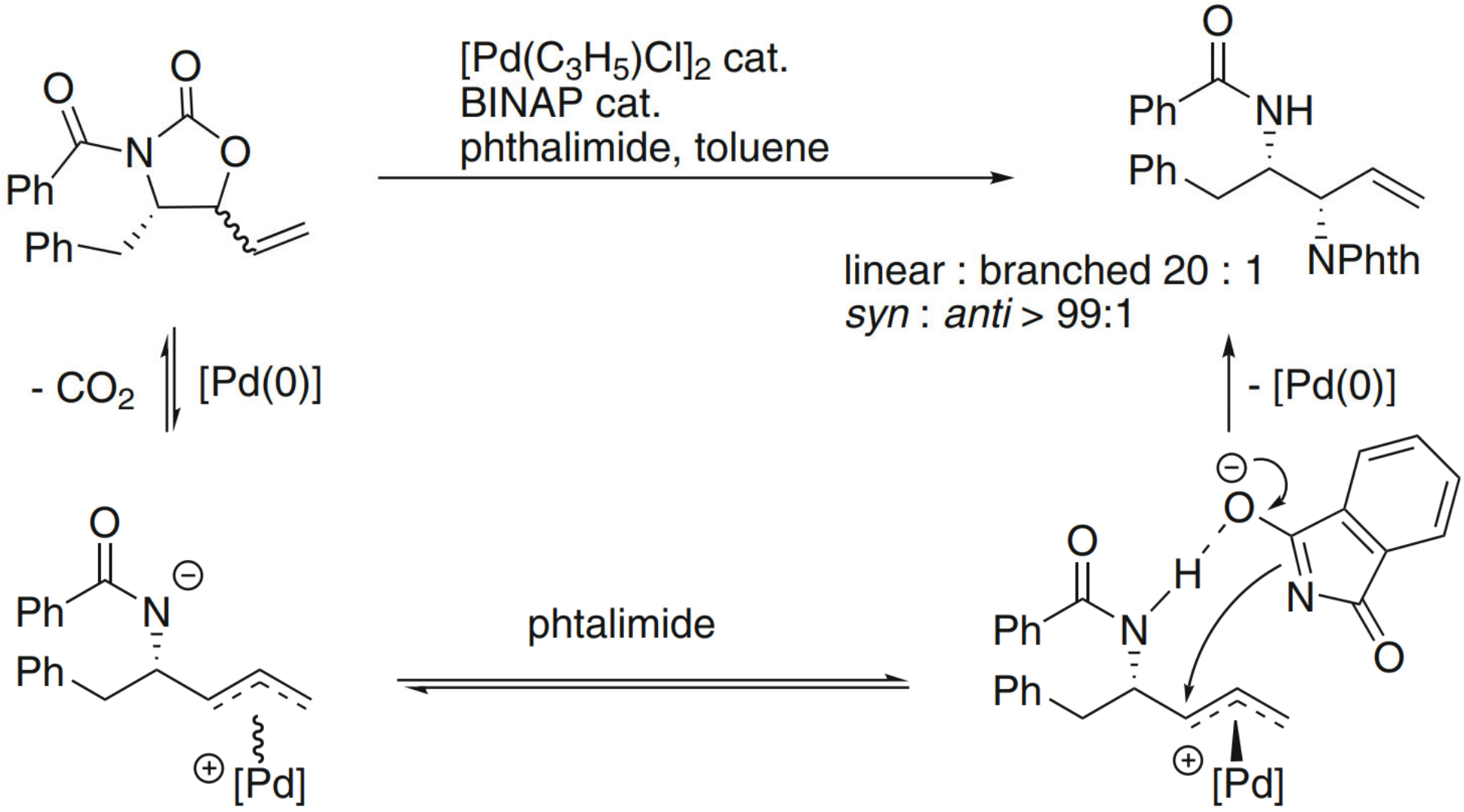
- *Trans*-P effect: *trans*-P is longer and easy to be attacked.





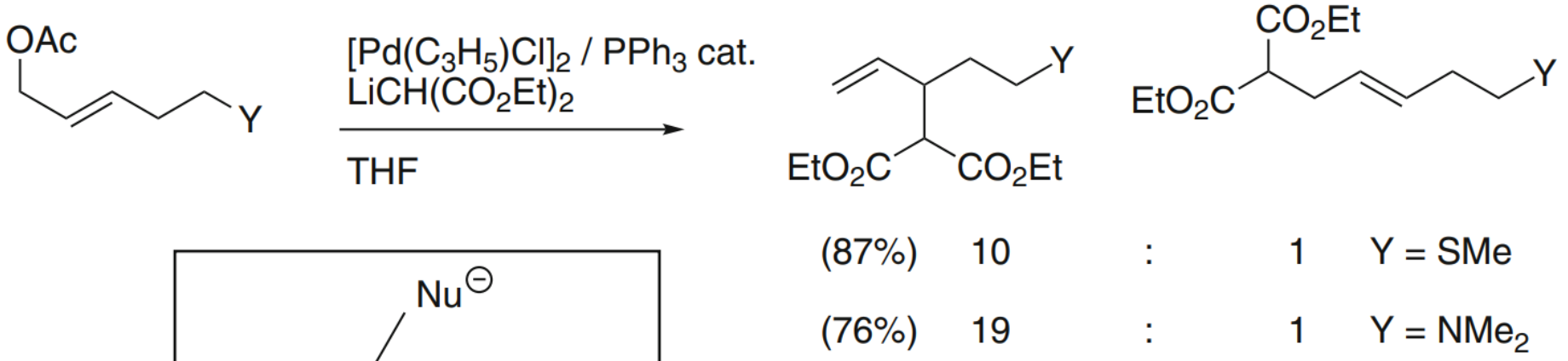
Lloyd-Jones, G et al. *Chem. Eur. J.* **2000**, *6*, 4348.

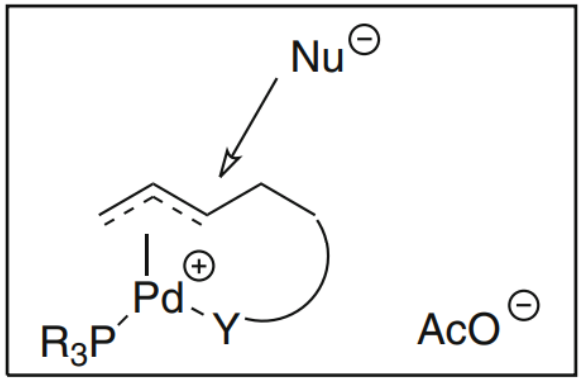
Substance Control: Hydrogen Bond

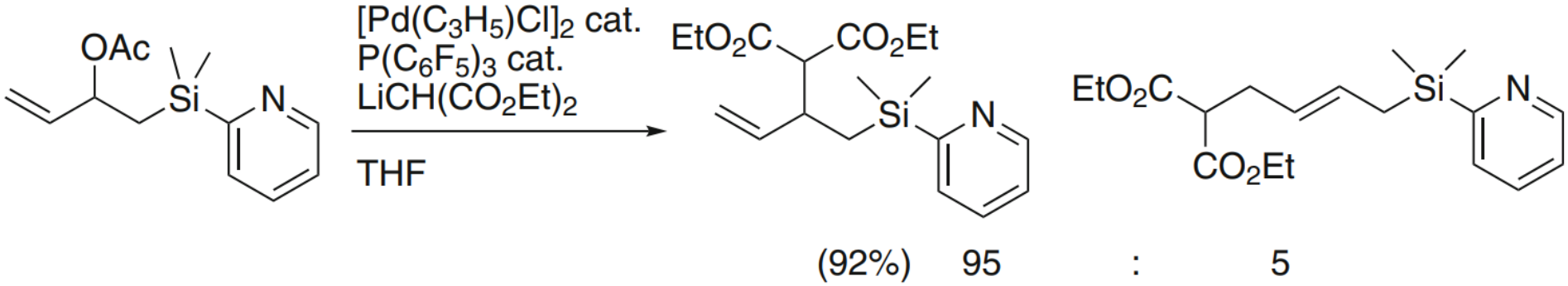


Cook, G et al. *J. Am. Chem. Soc.* **2003**, *125*, 5115.

Substance Control: Coordination

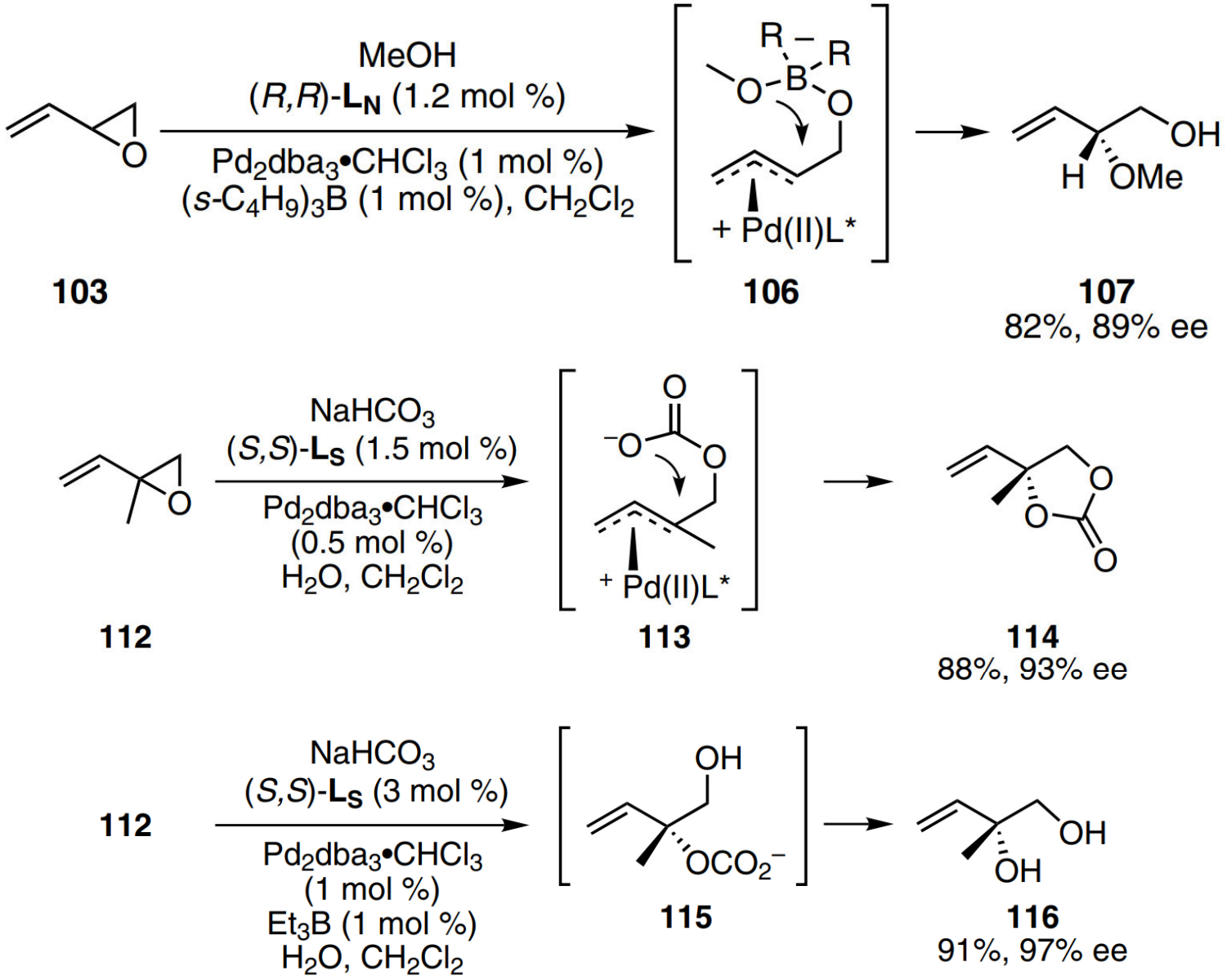






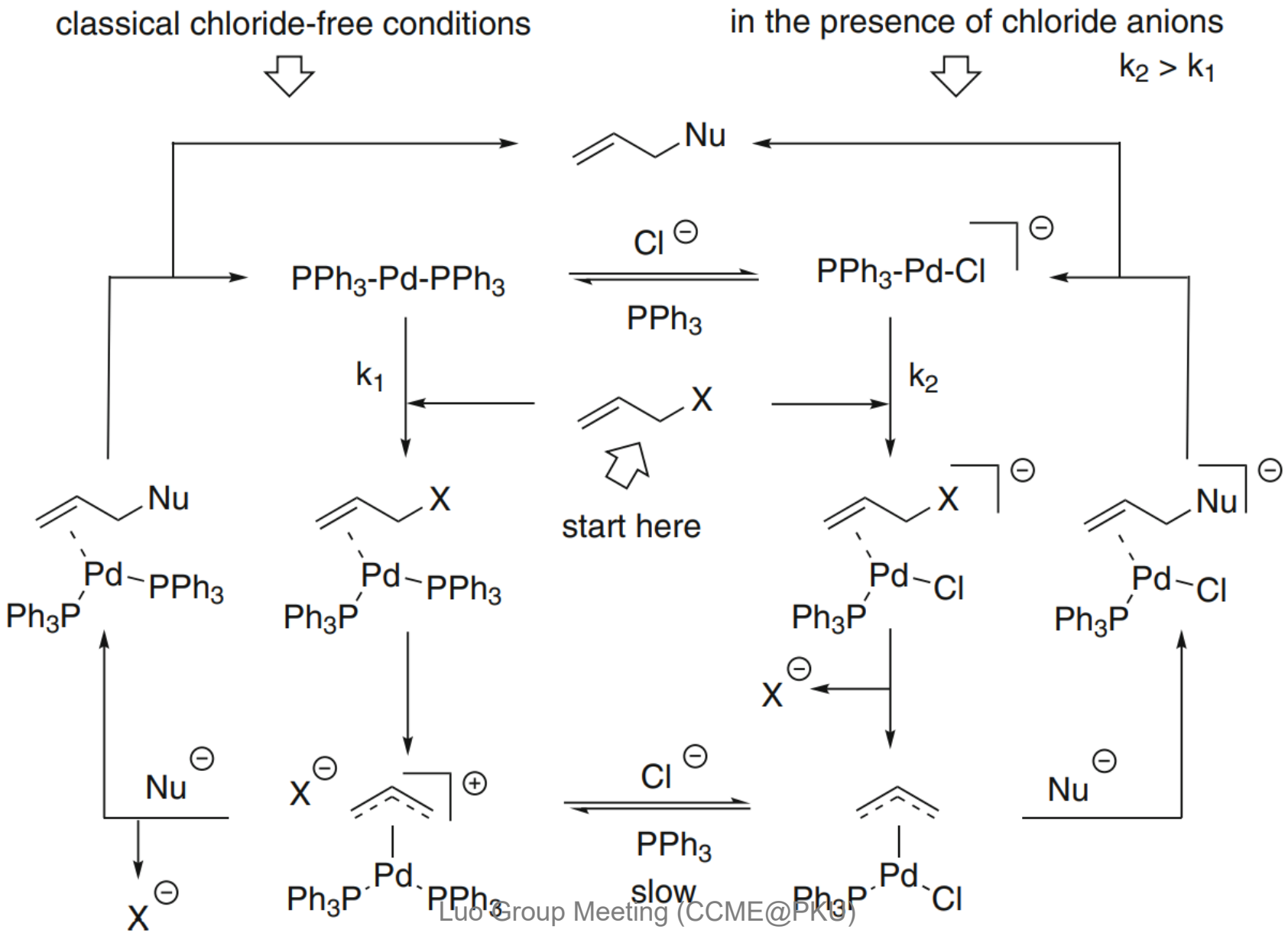
Itami, K et al. *J. Am. Chem. Soc.* **2001**, *12*, 6957.

Substance Control: Coordination

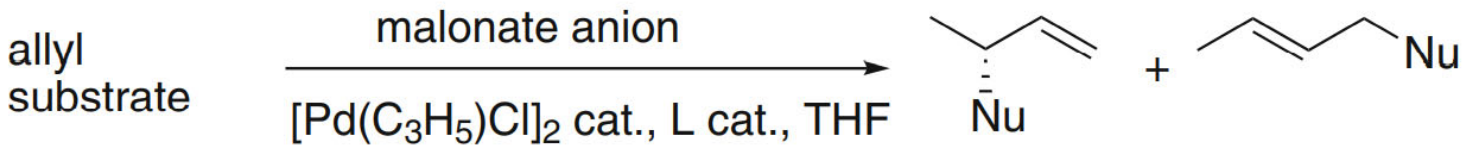


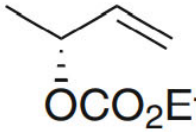
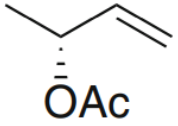
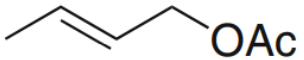
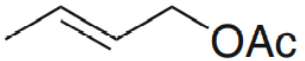
Trost, B et al. *J. Am. Chem. Soc.* **1999**, *121*, 8649; Trost, B et al. *J. Am. Chem. Soc.* **1998**, *120*, 12702.

Memory Effect



Memory Effect I: Asymmetric Ligands

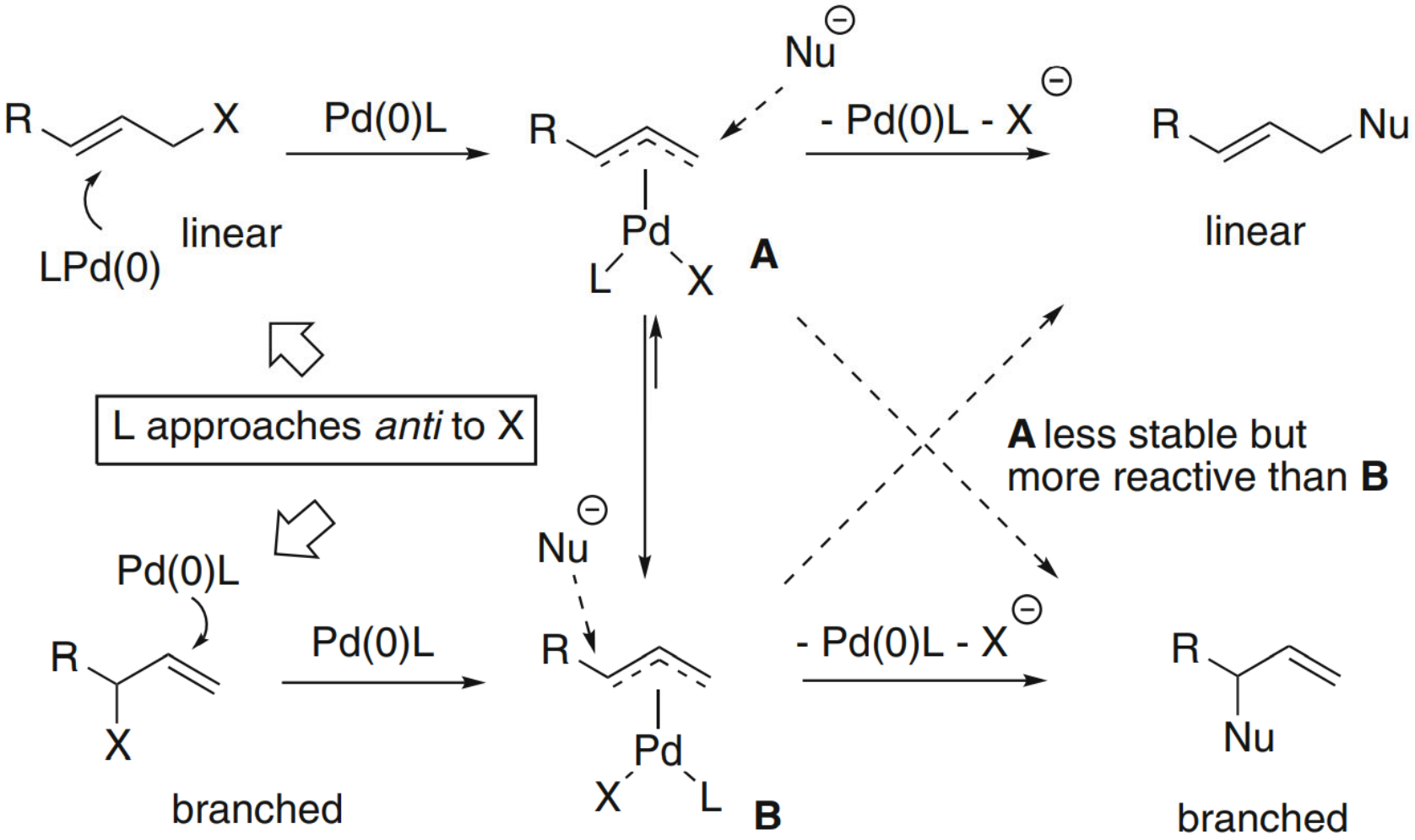


entry	allyl substrate[a]	malonate anion	L	branched	:	linear	Ref.
1		$NaHC(CO_2Me)_2$	PCy_3	87 (82% ee)	:	13	222
2		$NaHC(CO_2Me)_2$	PCy_3	94 (64% ee)	:	6	223
3		$NaHC(CO_2Me)_2$	PPh_3	50 (15% ee)	:	50	223
4		$NaHC(CO_2Me)_2$	PCy_3	57	:	43	223
5		$NaEtC(CO_2Et)_2$	PCy_3	8	:	92	223

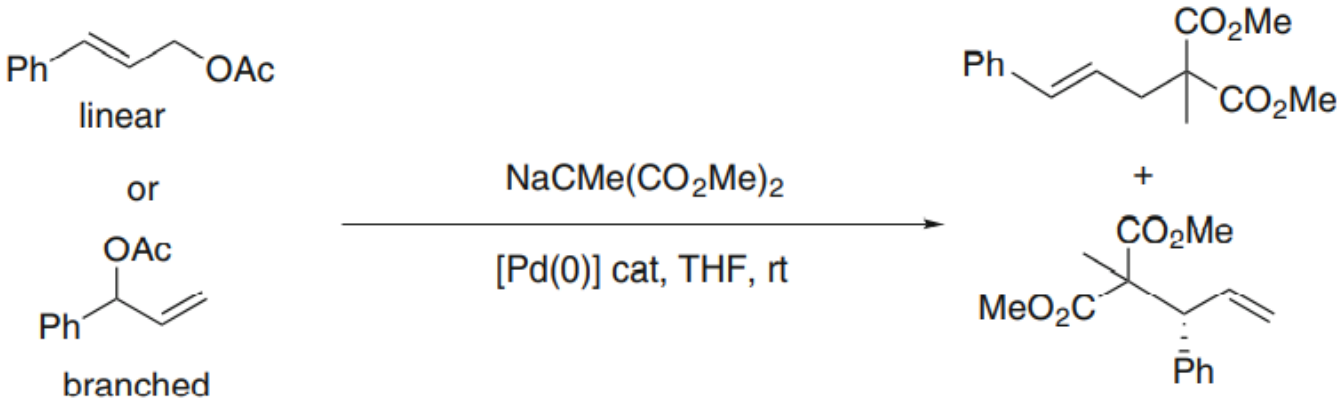
a) allyl carbonate: 91% ee

Blacker, A et al. *Org. Lett.* **1999**, *1*, 1969.

Memory Effect II: Tight Ion Pair



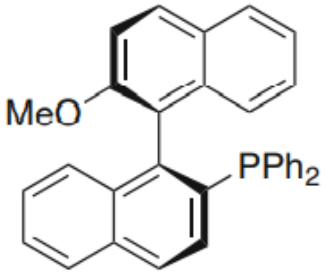
Memory Effect II: Tight Ion Pair



	Ligand	Substrate	Linear		Branched	Ref
canonical (ionic)	L1	linear	91	:	09	219
	L1	branched	92	:	08	219
memory effect	L2	linear	79	:	21	220
	L2	branched	23	:	77	220
	L3	linear	97	:	03	80
	L3	branched	33	:	67	80
chloride effect	L3 + Cl^-	linear	99	:	01	80
	L3 + Cl^-	branched	84	:	16	80

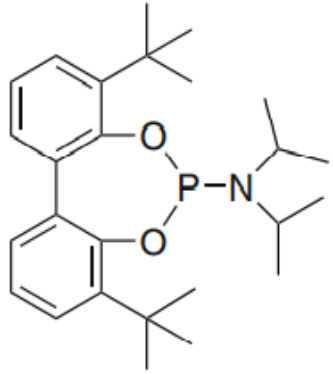
L1: PPh_3

L2:



(*R*)-MeO-MOP

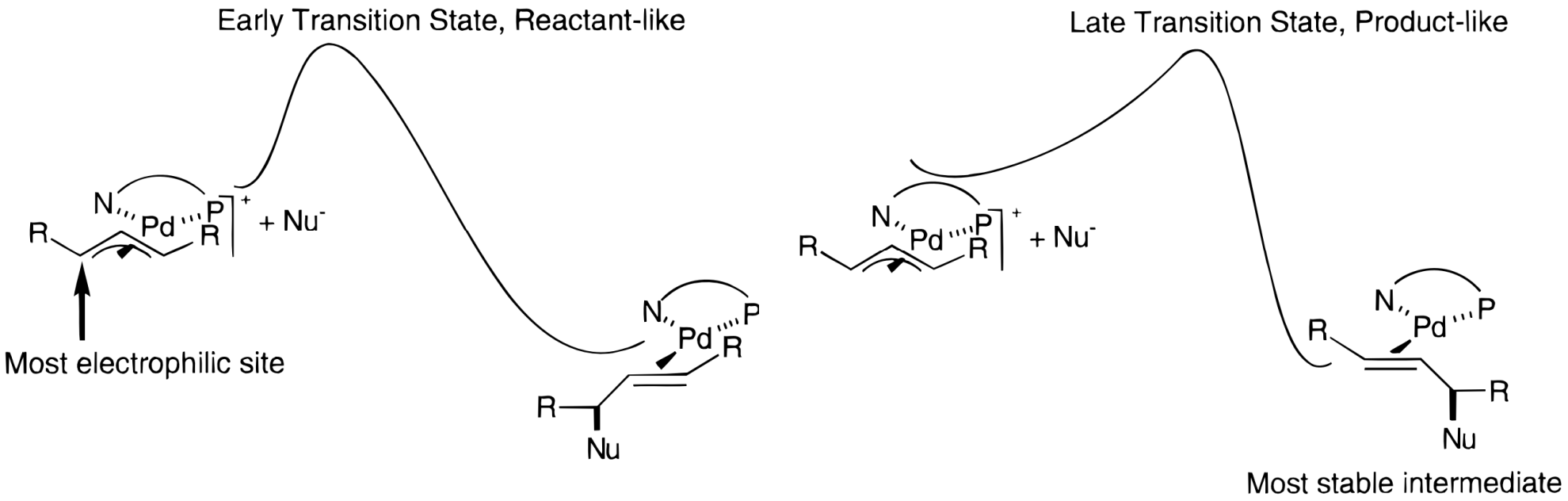
L3:



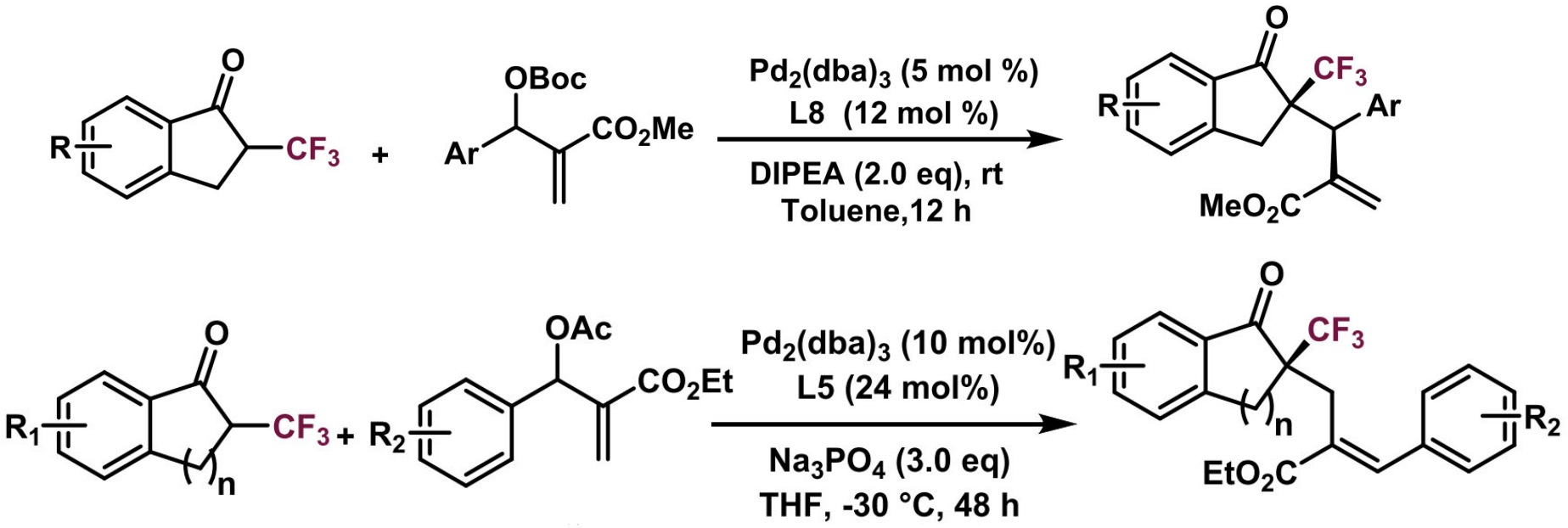
Boele, M et al. *Chem. Eur. J.* **2004**, *10*, 6232.

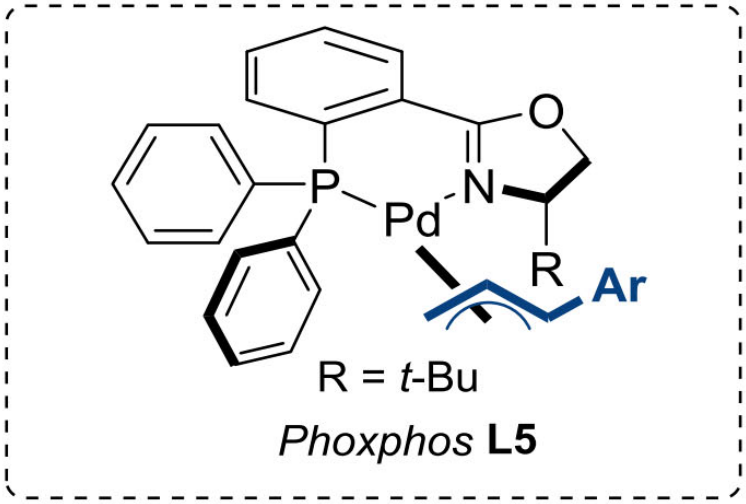
Memory Effect Missing

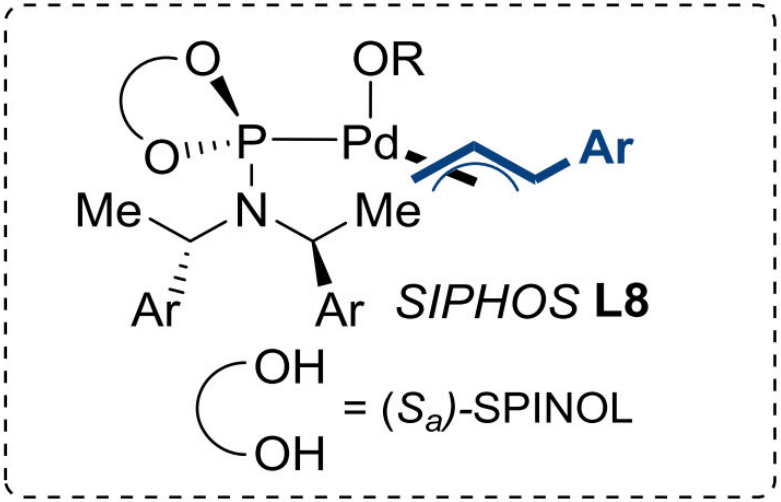
- Complexes formation: Memory vs Steric.
- Complexes Equilibria: SAE and AAR.
- Nucleophilic reagent: **Early** or **Late** TS.



Equilibria vs Memory: B-H Type



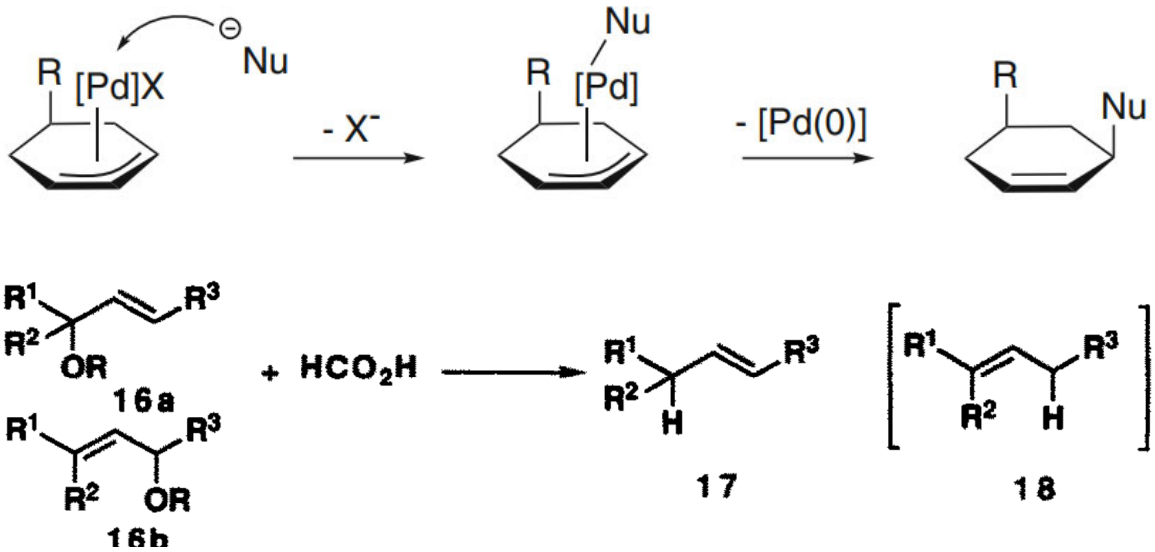


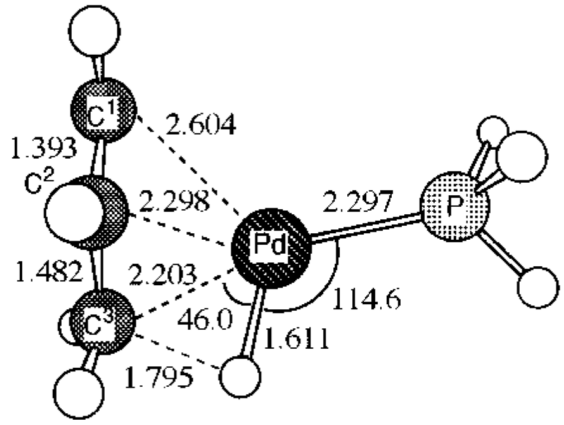


Pan, Y et al. *Org. Lett.* ***2021***, ASAP.

Hard Nu: Reductive Elimination

- Hard Nu is usually more Unstable than Soft Nu
- For HCOOH, H-M, R-M? Any differences between them?





	Pd	
	E_a	ΔE^a
HF	9.3	−40.5
MP2	6.1	−24.8
MP3	9.4	−27.4
MP4DQ	7.2	−28.1
MP4SDQ	5.4	−29.4
SD-CI(D)[b]	8.4	−29.7
SD-CI(DS)[c]	8.3	−26.5
SD-CI(P)[d]	8.3	−27.3
CCD	8.1	−28.2
CCD(ST4)	5.6	−27.9

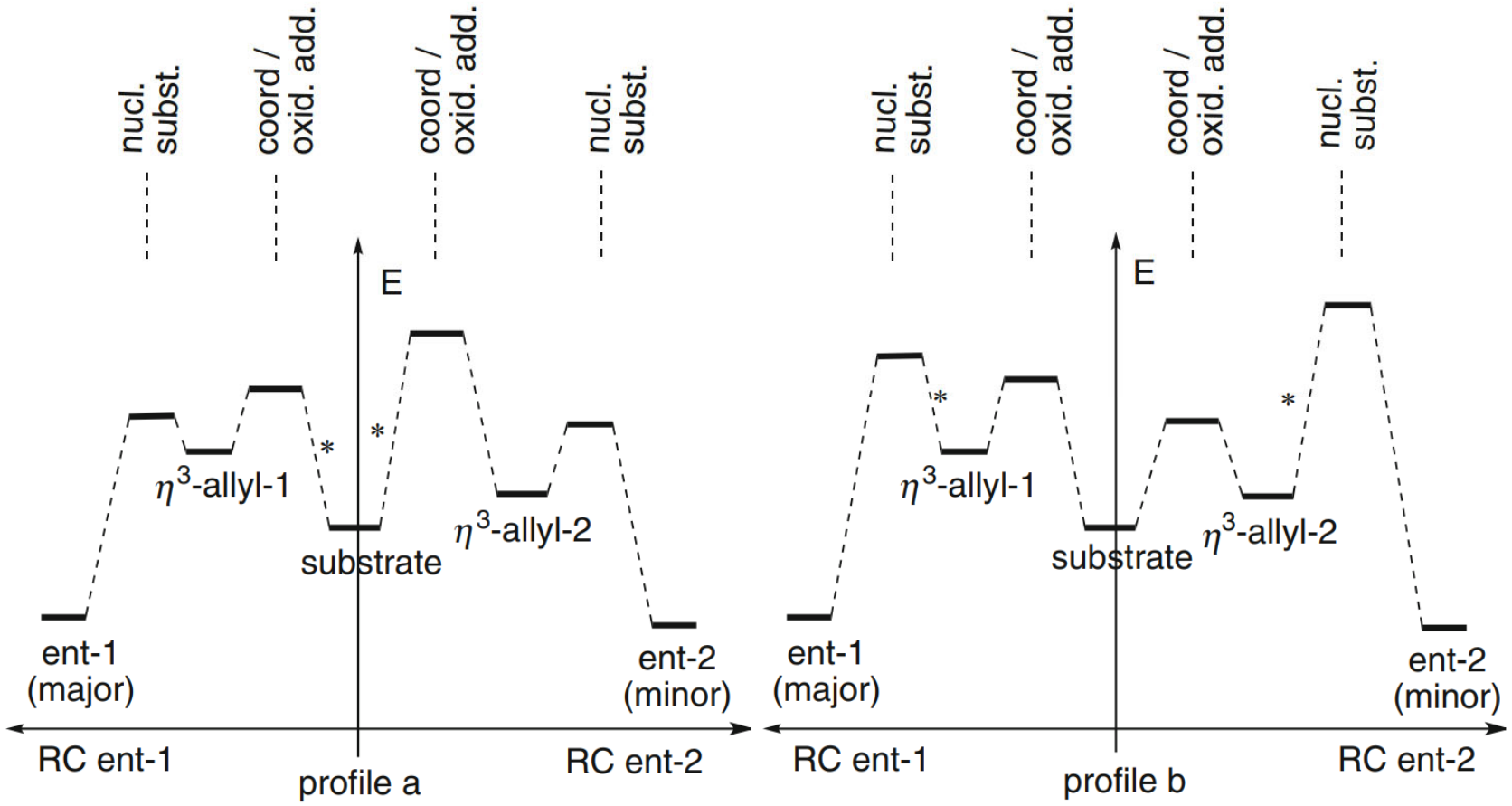
Ujino, K et al. *Organometallics* **1996**, *15*, 1713; Tsuji, J et al. *Tetrahedron* **1994**, *2*, 475.

Outline

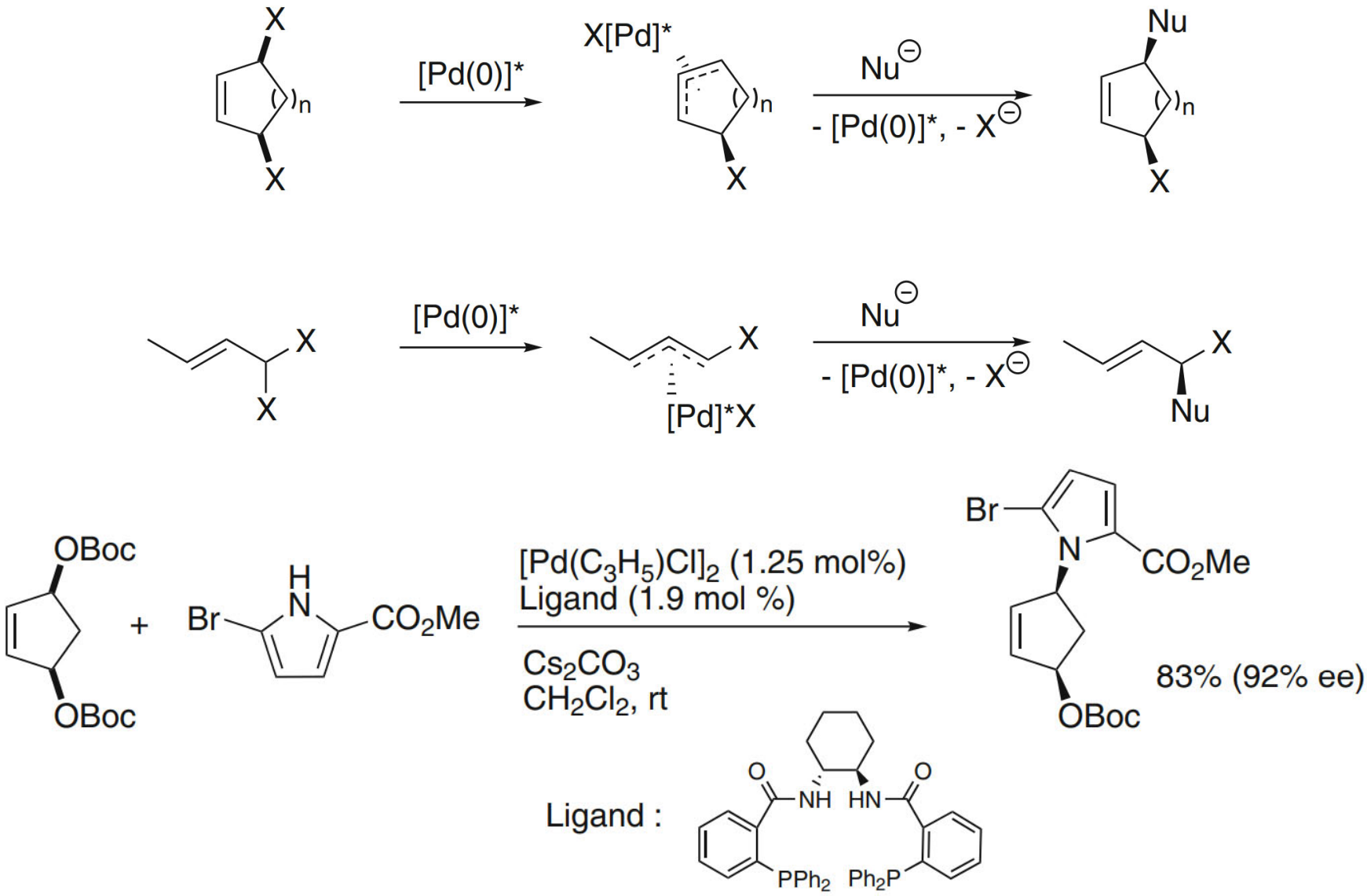
- **Introduction**
- **Selectivity of π-Allyl Intermediate**
  Isomerization
  Regioselectivity for Soft Nu
  Regioselectivity for Hard Nu
- **Enantioselectivity Tsuji-Trost Reaction**
  Asymmetric Allylic Alkylation
  Kinetic Resolution
- **Summary**
- **Acknowledgement**

Asymmetric Allylic Alkylation

- Two different types: *Enantiodiscriminating* Step?

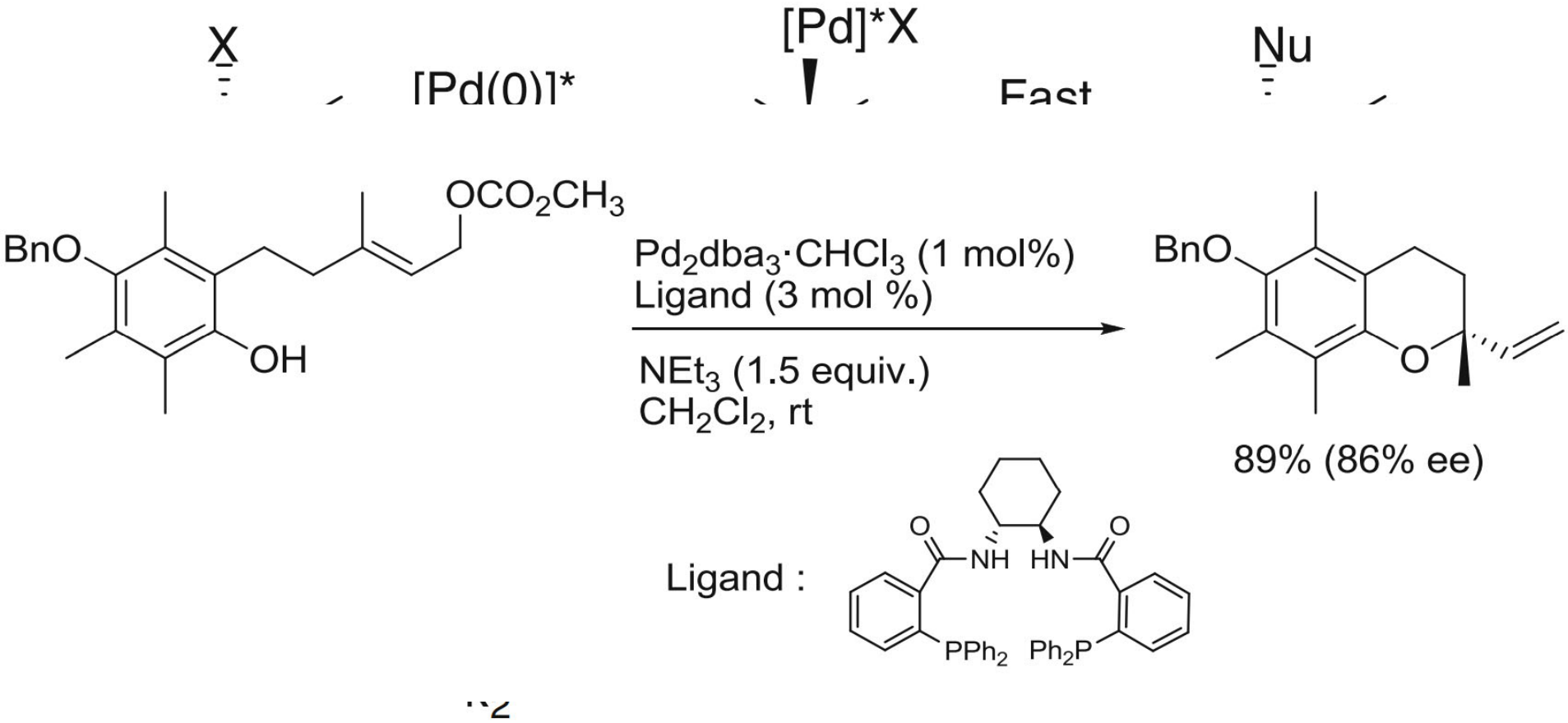


OA is *Enantiodiscriminating* Step



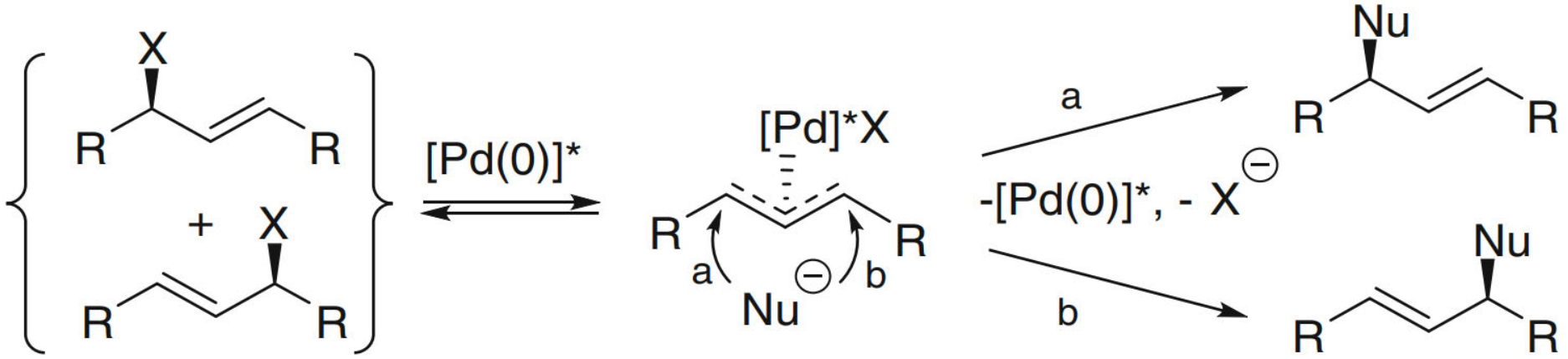
Trost, B et al. *J. Am. Chem. Soc.* **2006**, *128*, 6054.

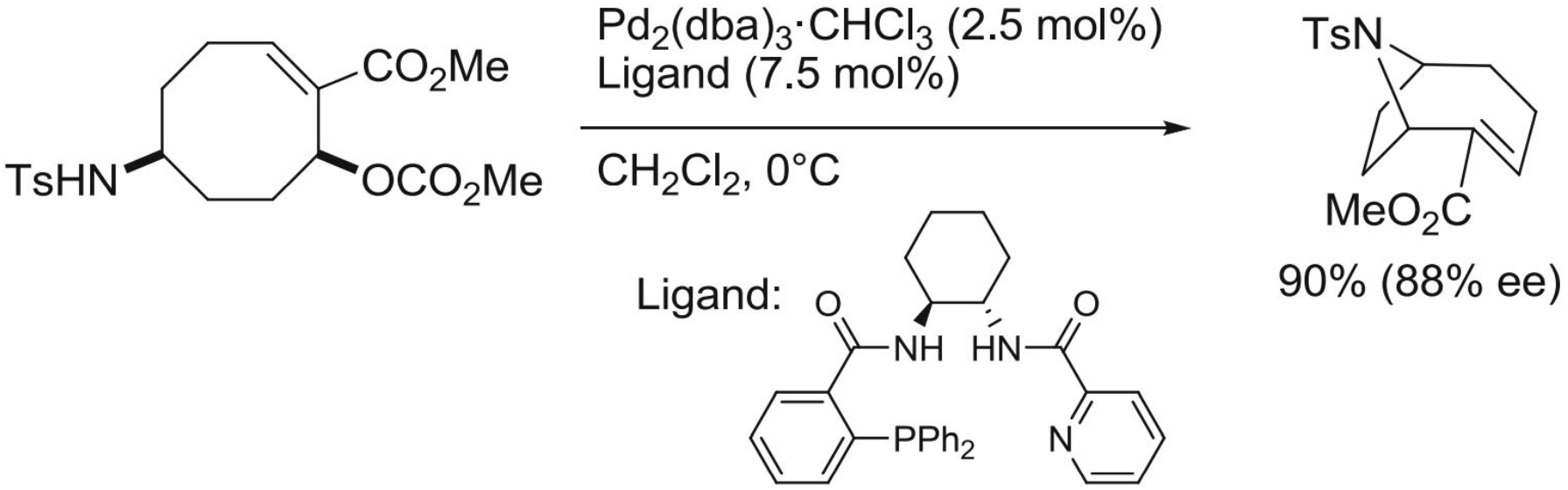
OA Determining: SAE is Undesirable



Trost, B et al. *Synthesis* **1999**, 1491.

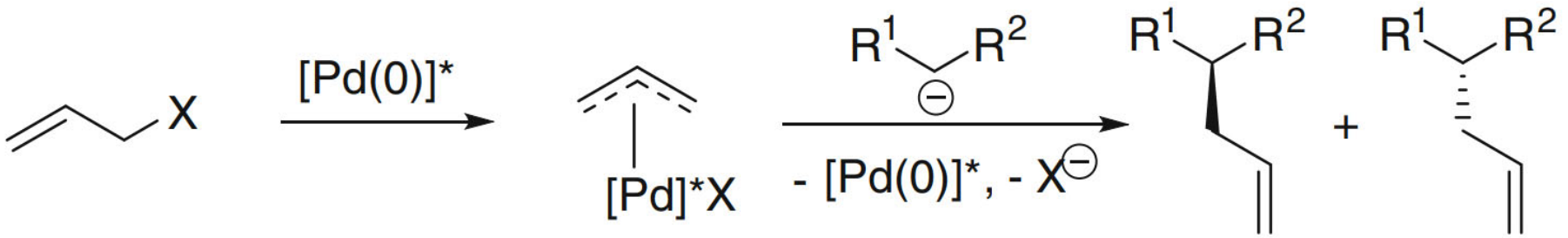
Attack Determining: Symmetry Allyl

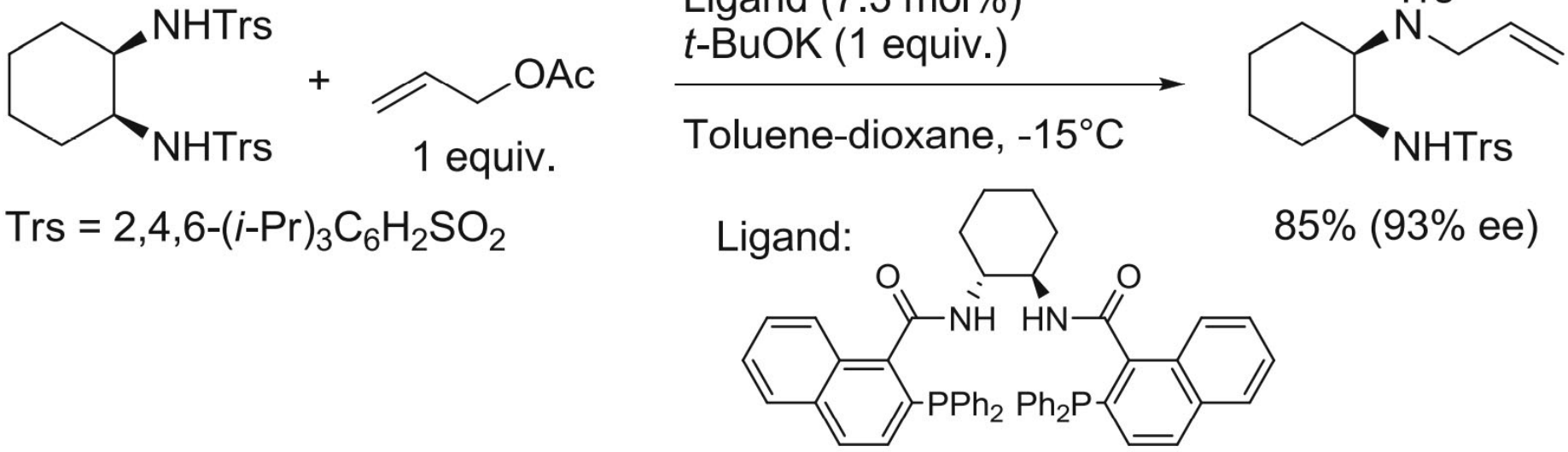




Trost, B et al. *J. Am. Chem. Soc.* **1999**, *121*, 3057.

Attack Determining: Symmetry Allyl

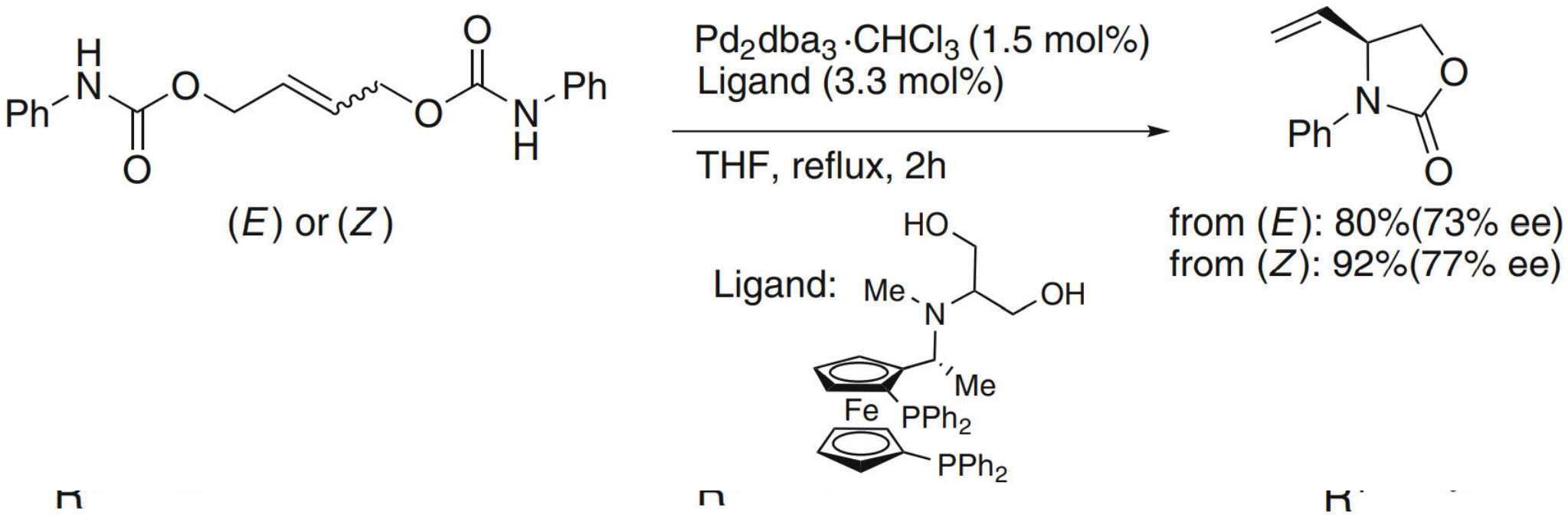




Trs = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$SO$_2$

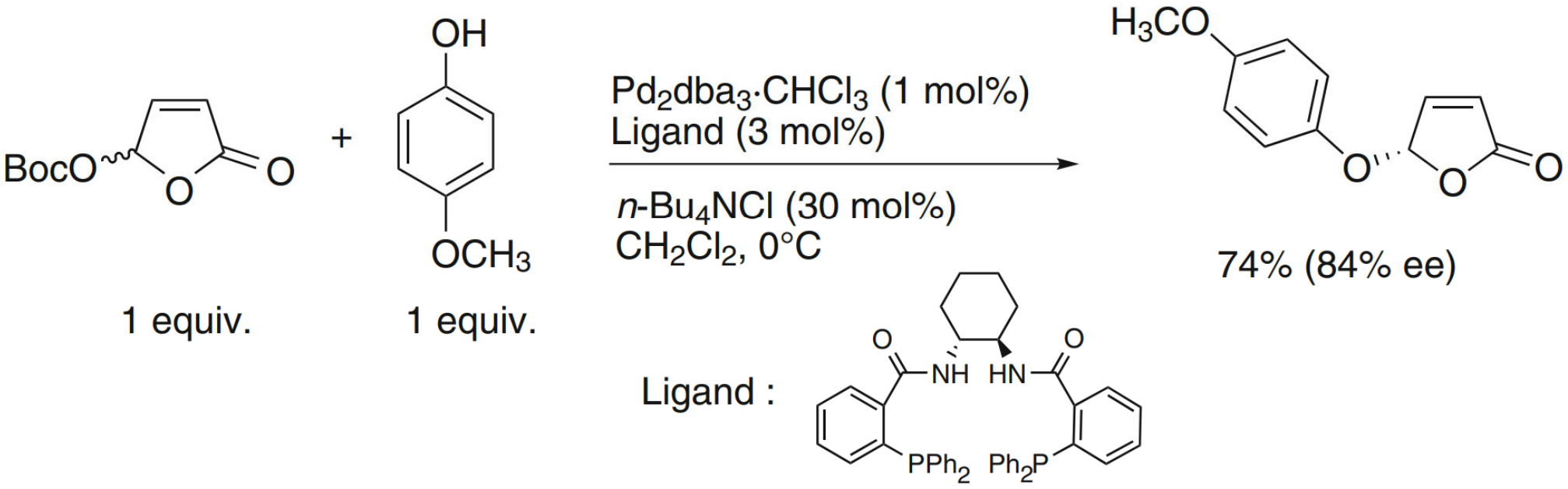
Kitagawa, O et al. *J. Org. Chem.* **2006**, *71*, 2524.

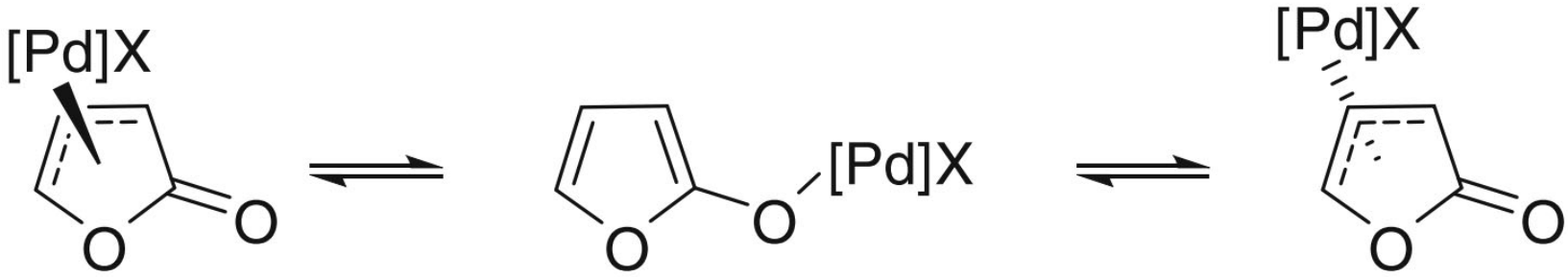
Attack Determining: SAE is Desirable



Hayashi, T et al. *Tetrahedron Lett.* **1988**, *29*, 99.

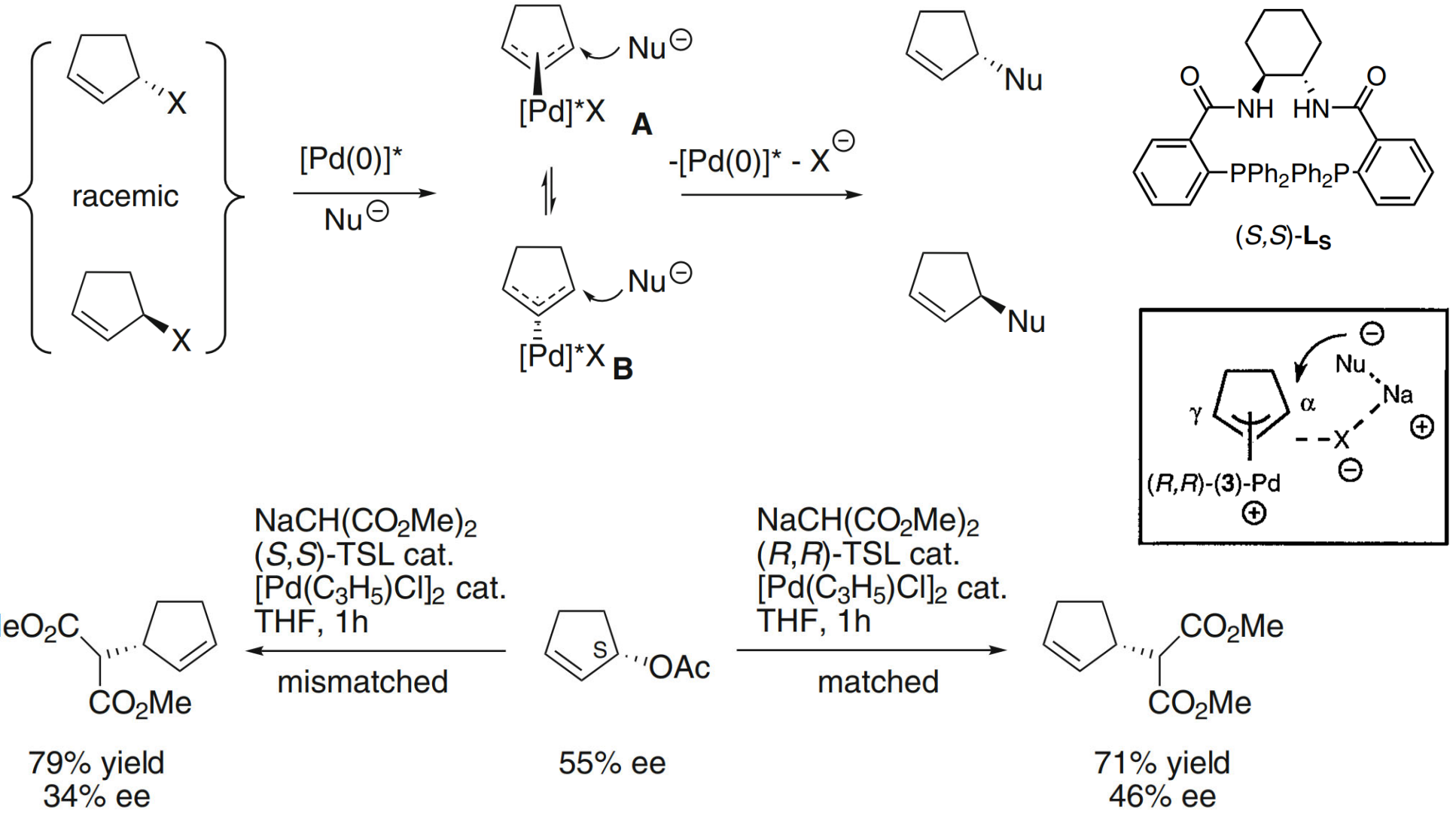
Attack Determining: AAR is Desirable





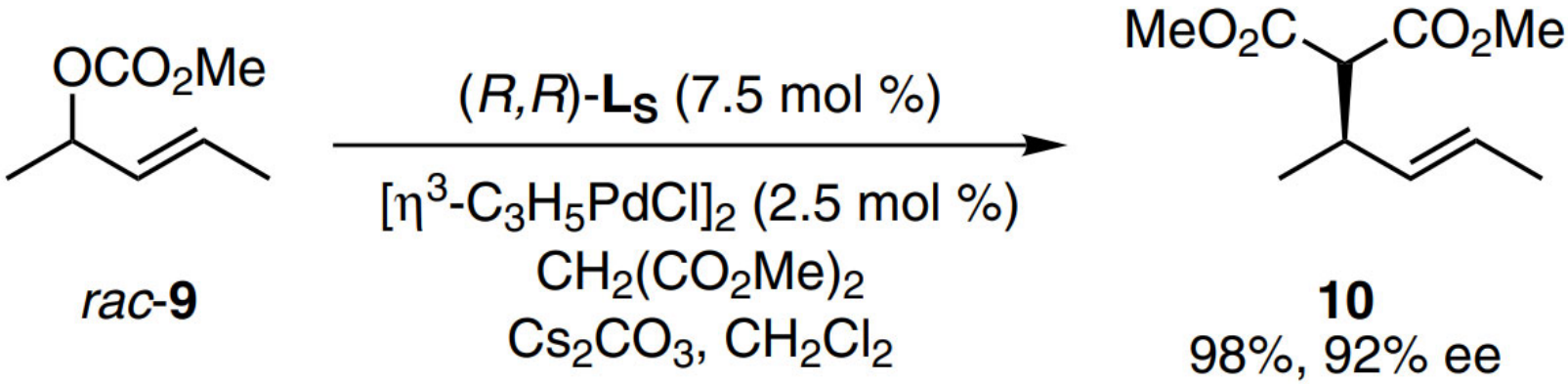
Trost, B et al. *J. Am. Chem. Soc.* **2003**, *125*, 3090.

Memory Effect: Desired or Not?



Trost, B et al. *J. Am. Chem. Soc.* **1996**, *118*, 235.

Kinetic Resolution: Block Ion Pair



rac-**9**

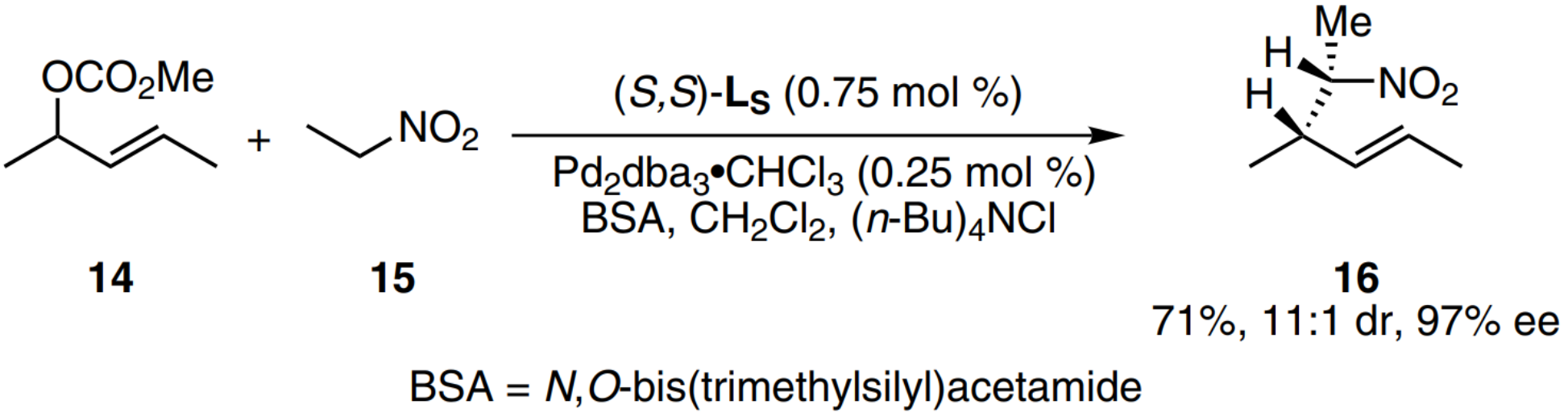
10
98%, 92% ee

entry	base	solvent	yield (%)	ee[a] (%)
1	NaH	THF	63	29
2	Cs_2CO_3	THF	62	84
3	NaH	CH_2Cl_2	86	81
4	Rb_2CO_3	CH_2Cl_2	92	91
5	Cs_2CO_3	CH_2Cl_2	98	92

[a] Determined by ^1H NMR chiral shift with $Eu(hfc)_3$ in C_6D_6.

Trost, B et al. *J. Am. Chem. Soc.* **1996**, *118*, 6520.

Kinetic Resolution: Block Ion Pair



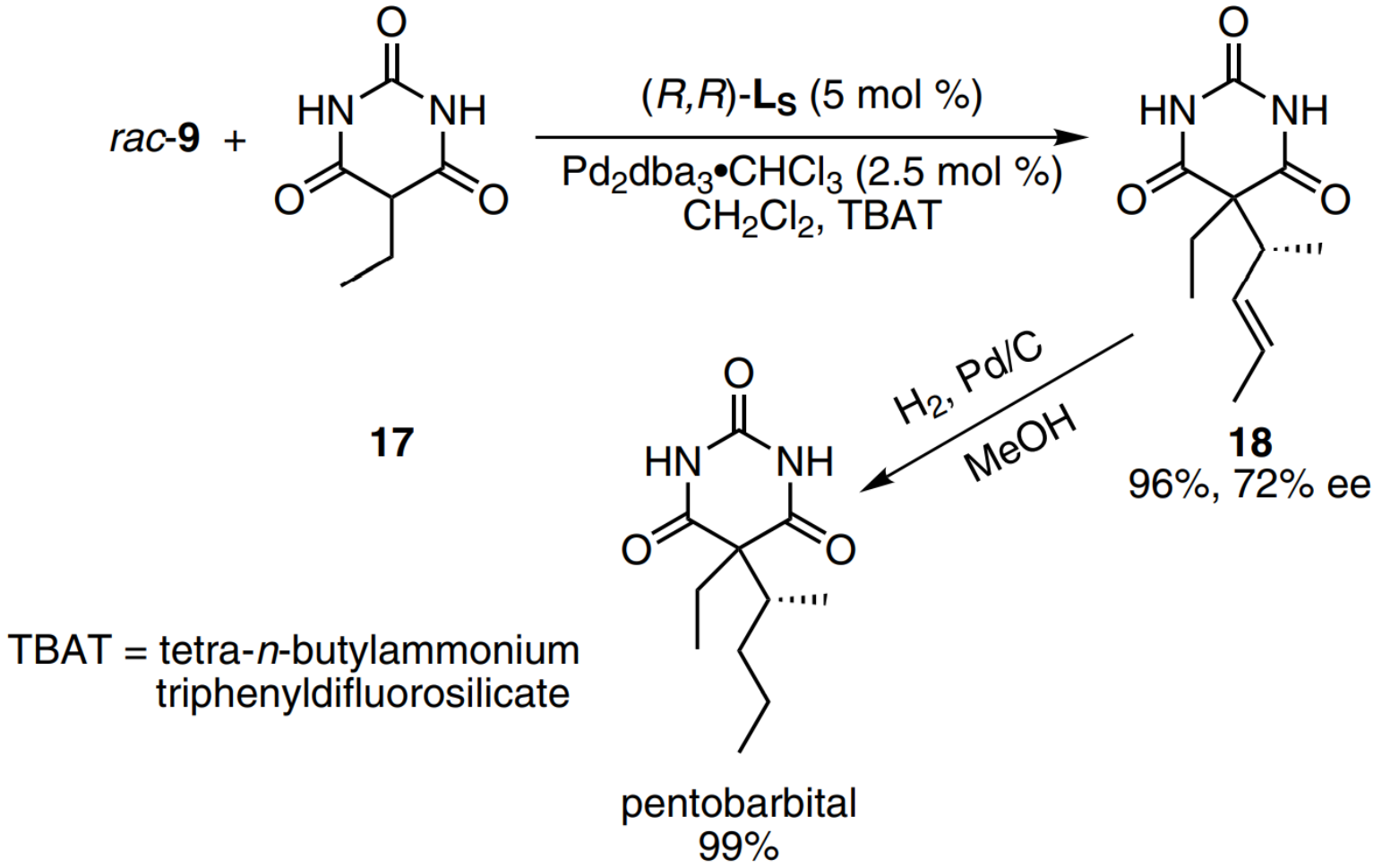
14 **15** **16**

71%, 11:1 dr, 97% ee

BSA = *N*,*O*-bis(trimethylsilyl)acetamide

Trost, B et al. *J. Org. Chem.* **2000**, *65*, 1569; Trost, B et al. *J. Am. Chem. Soc.* **2000**, *122*, 6291.

Kinetic Resolution: Block Ion Pair



Trost, B et al. *J. Org. Chem.* **2000**, *65*, 1569; Trost, B et al. *J. Am. Chem. Soc.* **2000**, *122*, 6291.

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Summary

- Mechanism: Formation, Equilibria, Trapping
- Soft reagent and Hard reagent
- SAE and AAR: relevant, depend on additives and Nu
- Selectivity controlled by asymmetric ligands, asymmetric substances
- Memory effect: sometimes we want, sometimes we don’t
- Enantioselectivity: enantiodiscriminating step, avoid tight ion pair
- **Imperfection is the foundation of development.**