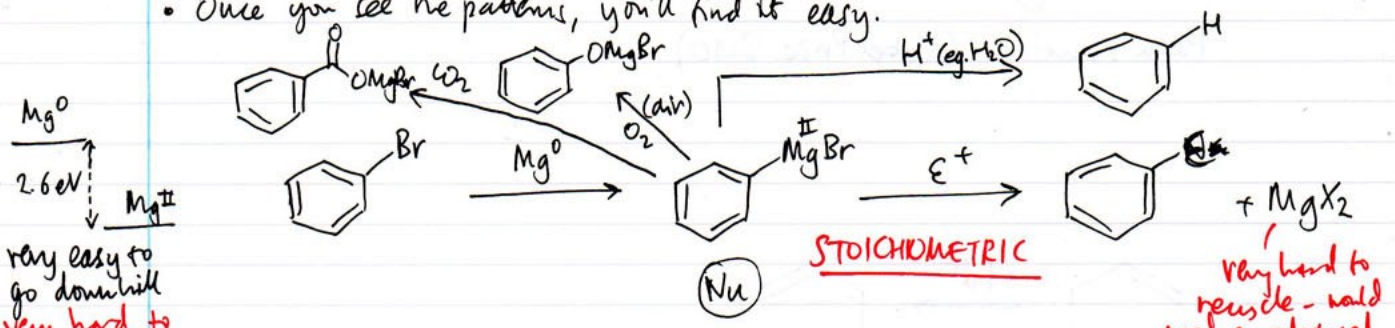
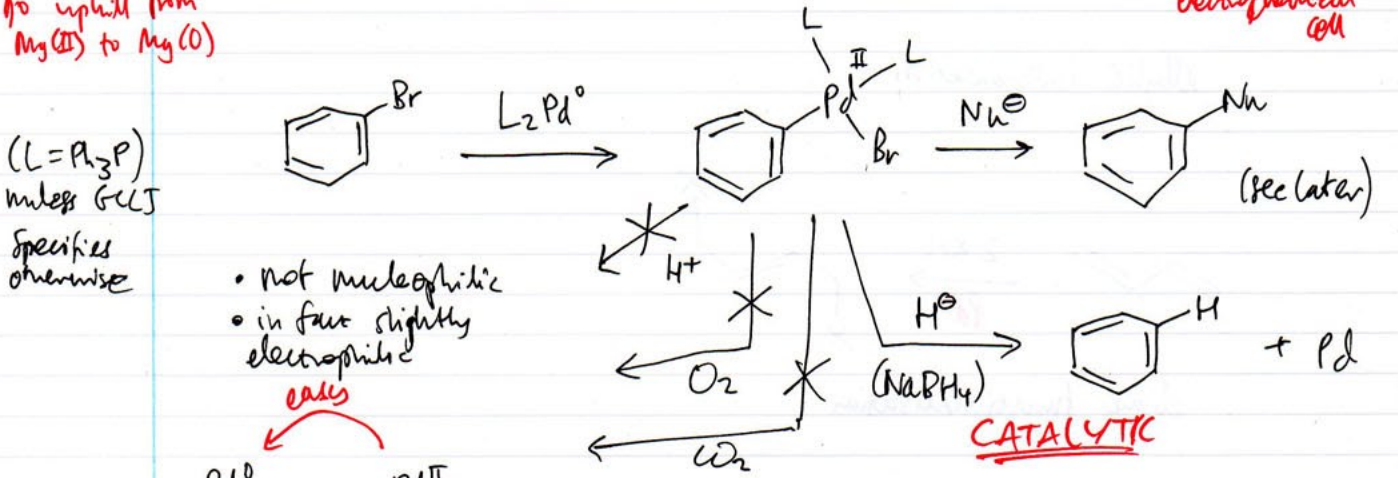
GCL-J 2: THE USE OF TRANSITION METALS IN ORGANIC SYNTHESIS

- There are a huge array of uses of TMs in organic synthesis – you'd need 100–200 lectures!
- So focus on Pd to fit 5 lectures
- Aim to have a feeling for the basic mechanisms – you'll see the patterns
- Aim to be able to say which molecules you'd need to put together to get a certain product
- Once you see the patterns, you'll find it easy.





1 mole of Mg ~ 65p – cheap as a pack of crisps

1 mole of, eg. $[PdL_4]$, – cost of a very nice car.

£16,000 – £46,000 /mol in bulk in industry, maybe £10,000 /mol. Can recruit it from Johnson Matthey, too.

X: halide or pseudohalide
M: metal

Reactions we shall look at:

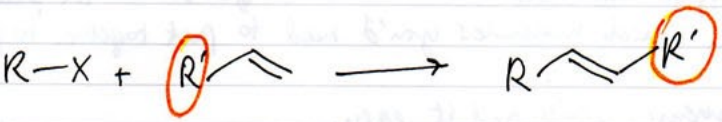
Cross-coupling rxns:

$$R\text{–}X + R'\text{–}M \xrightarrow{Pd} R\text{–}R'$$

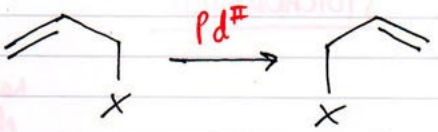
various flavours – all same mechanism
– often "named" reactions

Hartwig–Buchwald amination

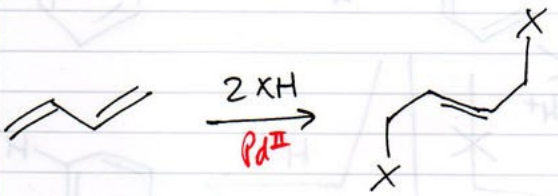
all Pd-initiated



Heck reaction (Nobel Prize 2010)

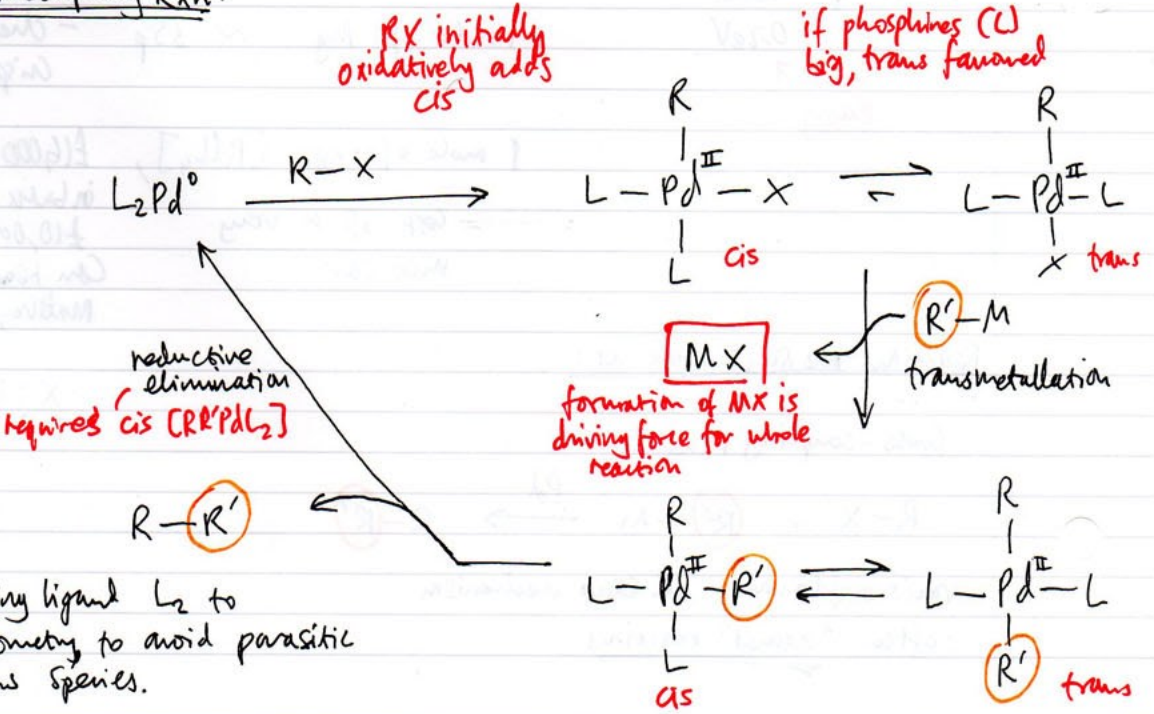


allylic isomerisation



diene functionalisation

Cross-Coupling Rxn:



use a chelating ligand L_2 to force cis geometry to avoid parasitic eqm to trans species.

One revolution through cycle = one "turnover"

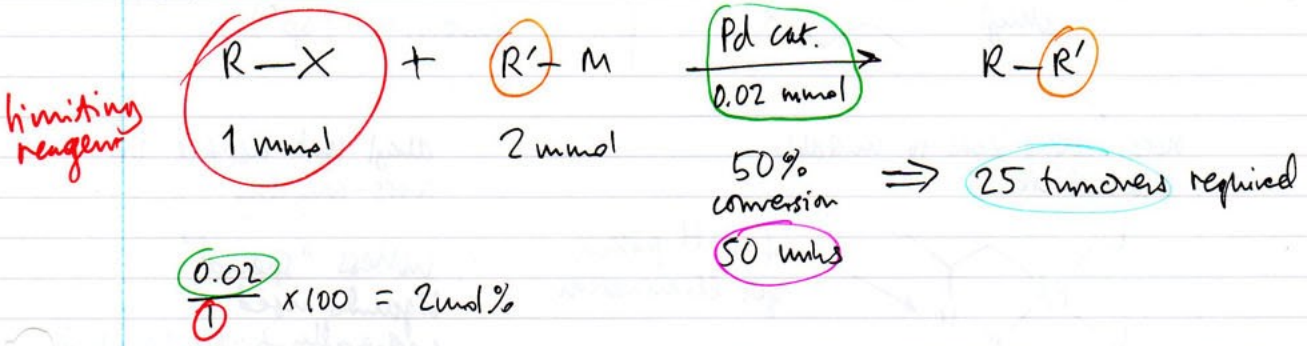
Catalyst "loading" (mol %) = $100 \times \frac{\text{moles of catalyst}}{\text{moles of substrate}}$

if one reagent is in excess, "moles of substrate" refers to the no of moles of the limiting reagent.

eg. $\frac{100 \times 0.01}{1}$ = 1 mol % therefore catalyst needs to do 100 turnovers to get 100% conversion.

2 mol % ∴ 50 turnovers to get 100% conversion

OR



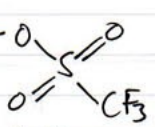
50 mins for 25 turnovers = 0.5 min^{-1}

T.O.F. turnover frequency

T.O.N. turnover number

R—X X = F × C-F is too strong a bond

Cl, Br, I — cheaper ↑ / faster ↓ — increasingly weak C—X bonds



triflate TfO

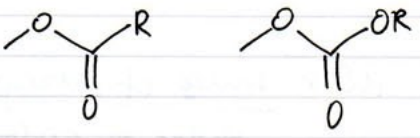
about the same reactivity as Br

R—OH $\xrightarrow[py]{Tf_2O}$ R—OTf

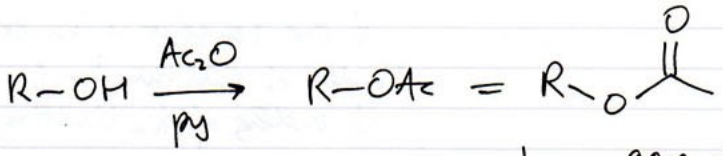
makes alcohols useful substrates for Pd-cat rxns

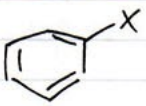
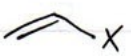
tend to choose bromide or chloride as a compromise between reactivity and cost

For allylic systems only.



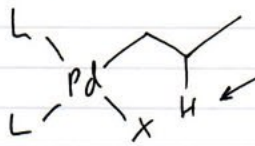
carboxylate carbonate



		Stereochemistry of oxidative addition
R = aryl		N/A
vinyl		retention (sp^2)
allyl		inversion (sp^3)
alkyl		inversion (sp^3)

- general rule
- sp^2 retention
- sp^3 inversion

note: alkyl leads to unstable intermediate

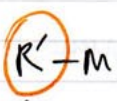


if β-H present, get elimination

alkyl not useful in cross-coupling

* see Heck (later)

unless "special" ligands used (generally trialkylphosphines)



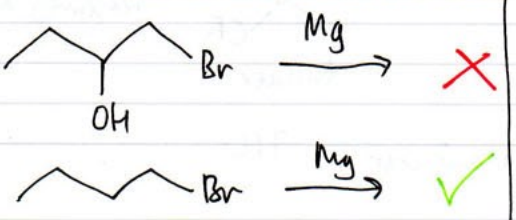
anything providing it can be made/used before decomposition

"M" =	metal	named reaction	
	MgX	Kumada	
	ZnX	Negishi	(Nobel 2010)
boronic acid	$B(OH)_2$	Suzuki	(Nobel 2010)
boronate ester	$B(OR)_2$	(or)	both need $^{\ominus}OH$ to work
	Bu_3Sn	Stille	
	Cu	Sonogashira	
		R' = alkyne	

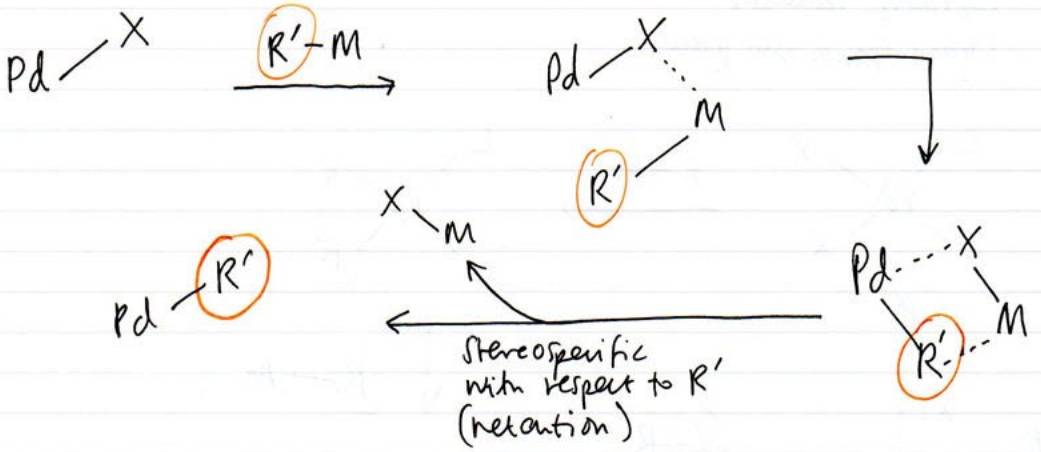
make RCu in situ - explosively unstable

need to know these five in detail

eg,



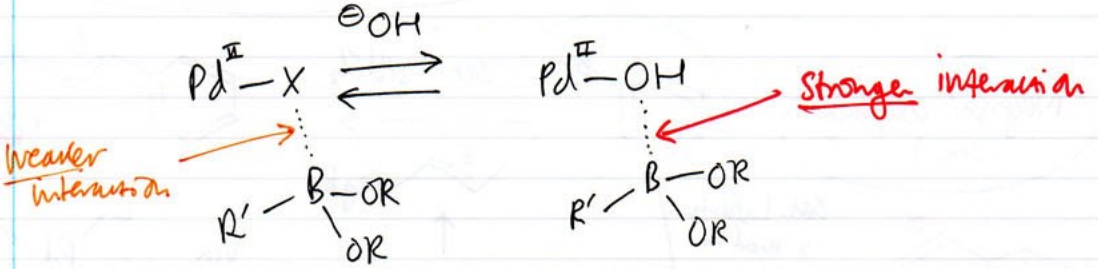
- not much known about the first step, but it is known there's pre-binding occurs.



M–X / M···X Strong interaction:

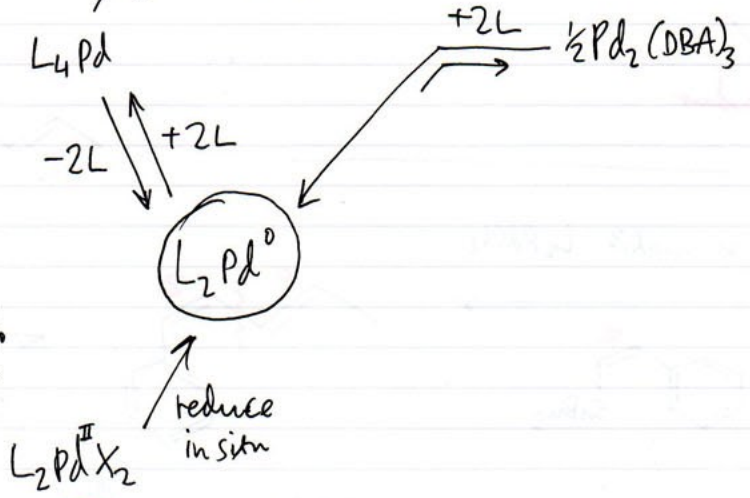
Mg, Zn, Sn, Cu

but not for B



How do we make L_2Pd^0?

L_4Pd in solid state.

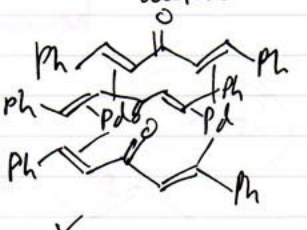


yellow solid
- moderately air sensitive

L_3Pd in solution – not active, must lose L to become active

✓ best route is this one.

DBA: dibenzylidene acetone

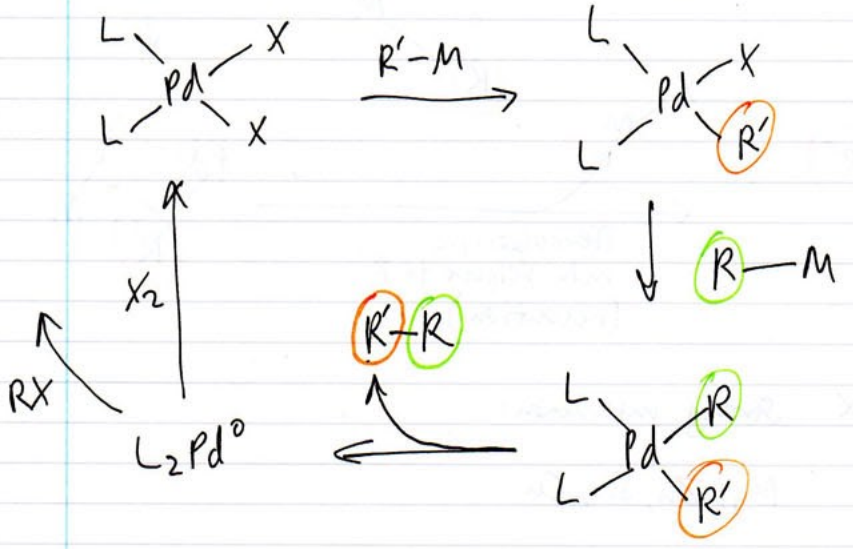


X = solvent or DBA (so a co-crystal)

dark purple with X
~~pinky~~ brown without X

DBA good ligand but not as good as PPh_3

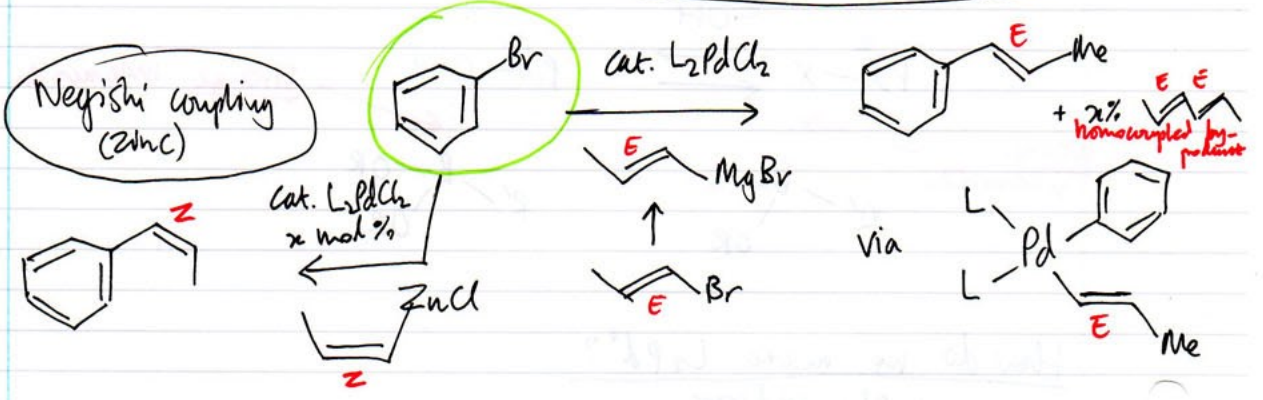
L_2PdX_2 reduction:
(trans species also present).



Some examples.

Kumada coupling (Grignard)

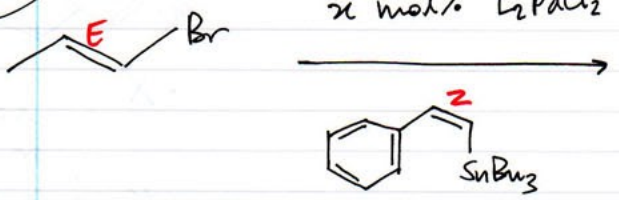
Negishi coupling (zinc)

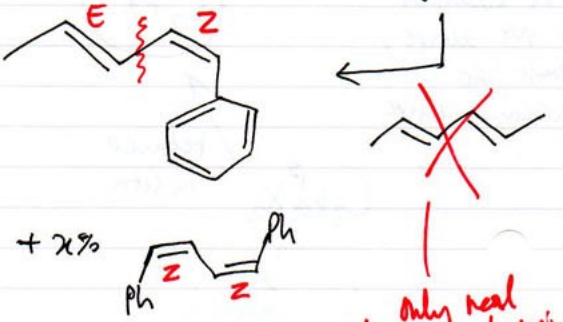


+ x%

homocoupled by-product

Stille





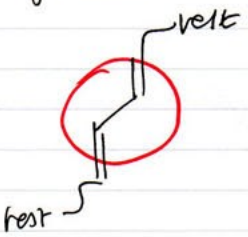
+ x%

only real advantage to using pre-reduced Pd is lack of side products

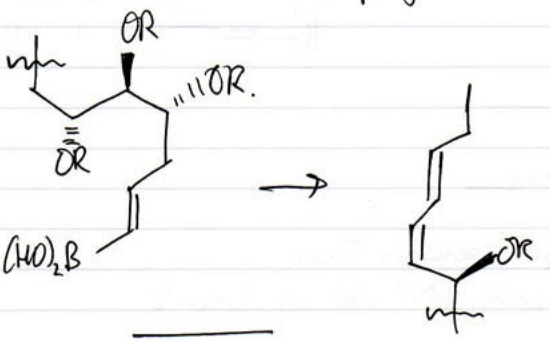
Palytoxin
- most toxic non-peptoid known?

- structure (1981)
assigned as above out of a possible ≥ 2,300,000,000,000,000,000,000,000 stereoisomers by degradation. - chopped into manageable pieces and confirmed spectroscopically.

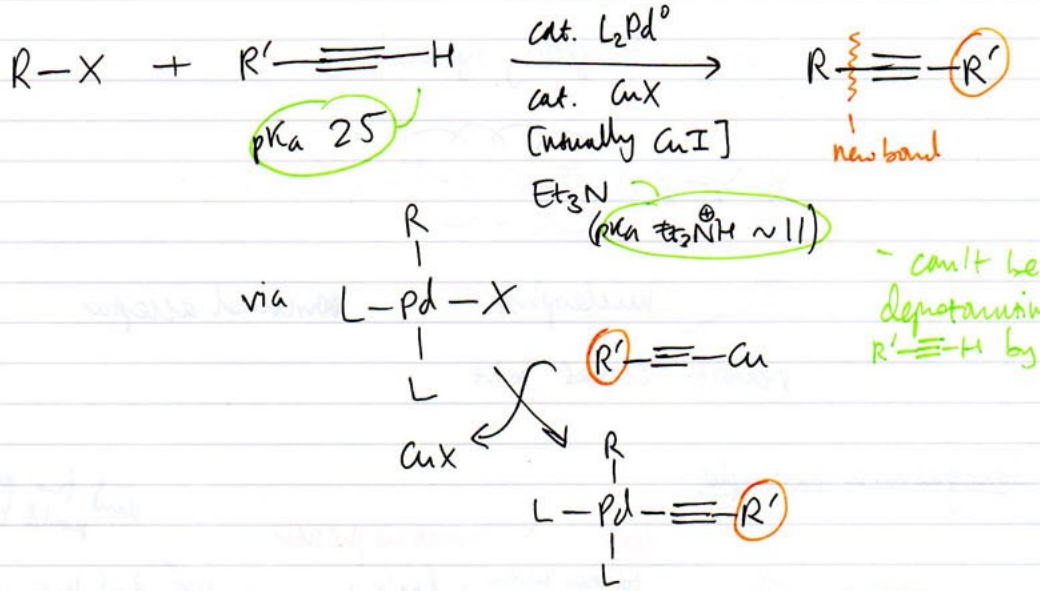
- synthesized 1994 - confirmed stereochemistry

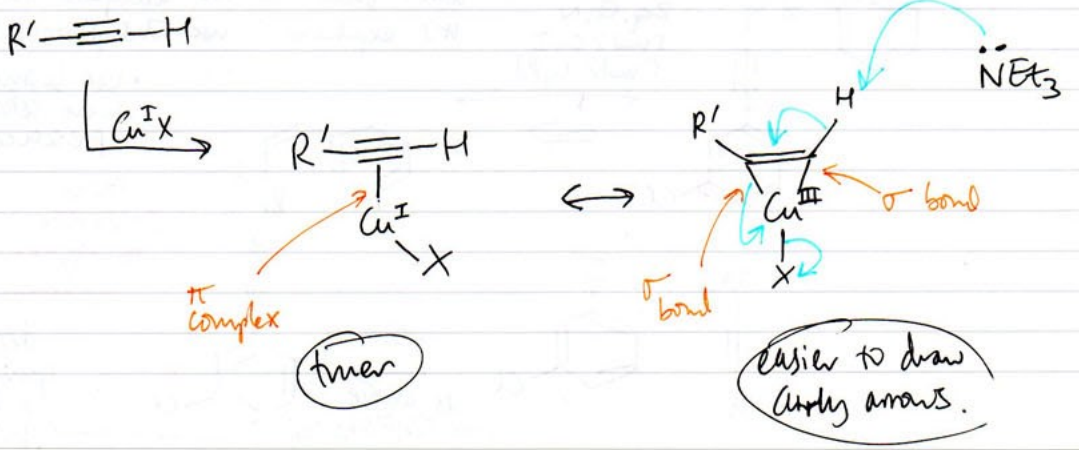


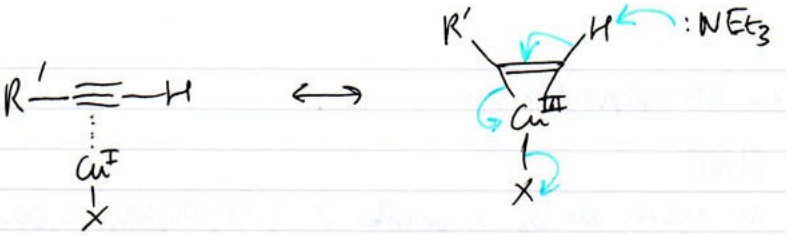
Kishi (1987) route to palytoxin.

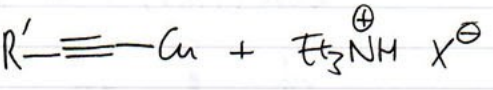


Sonogashira coupling - Pd/Cu co-catalysis









Calicheamicin

- Collected from rocks in Texas.
- Specific, active DNA cleaving molecule.

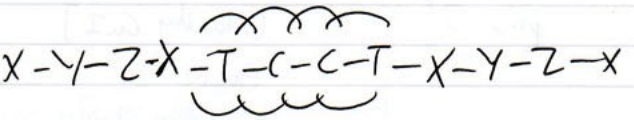
a remarkable system.

Nicolaou synthesised this with Sonogashira coupling.

Messs trigger

enediyne warhead

sugar targeting system.

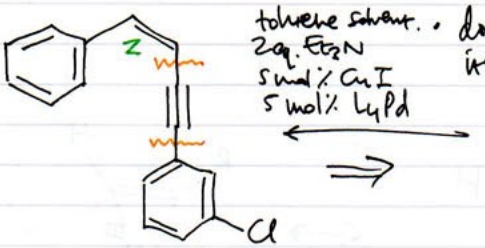


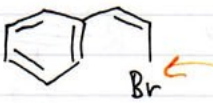
$^{\ominus}S$ nucleophile + conjugated acceptor

reaction causes twist

Sonogashira example:

Several disconnections possible

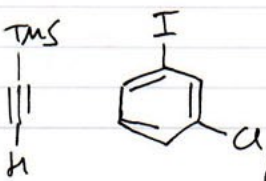




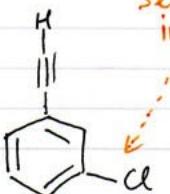
• don't want to use acetylene directly since it's explosive ∴ use TMS-protected acetylene.

• use bromo as it'll react selectively in presence of chloro.

(fairly) selective for Br in oxidative addition.



as above then TBAF/H2O/THF

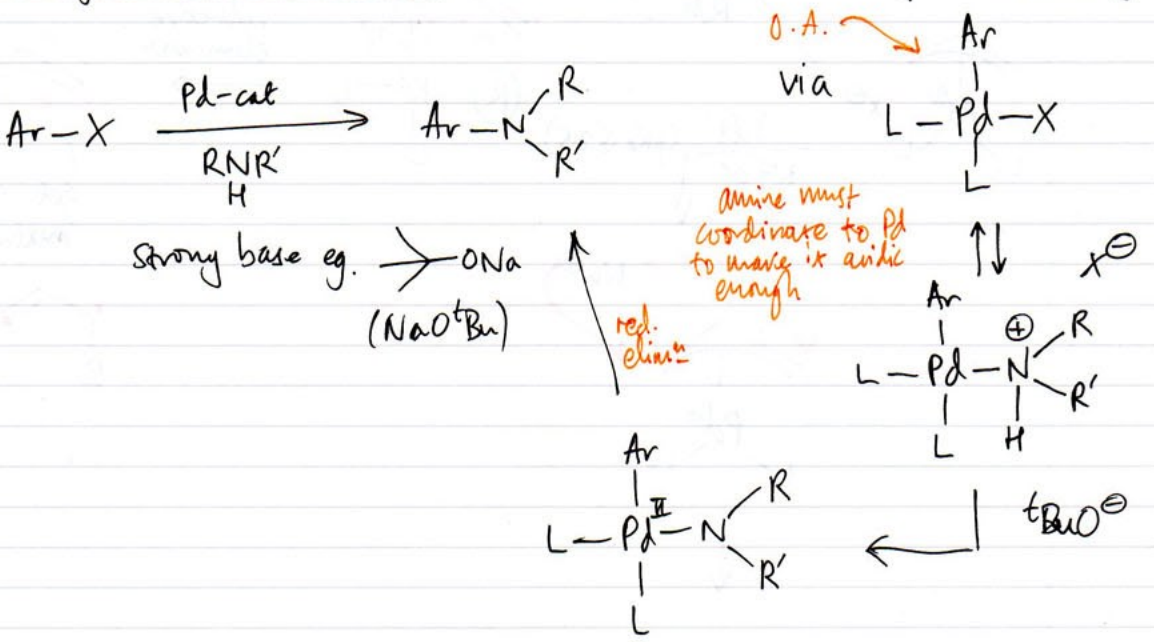


deprotects silyl group to reveal a terminal alkyne (D2O gives R≡D)

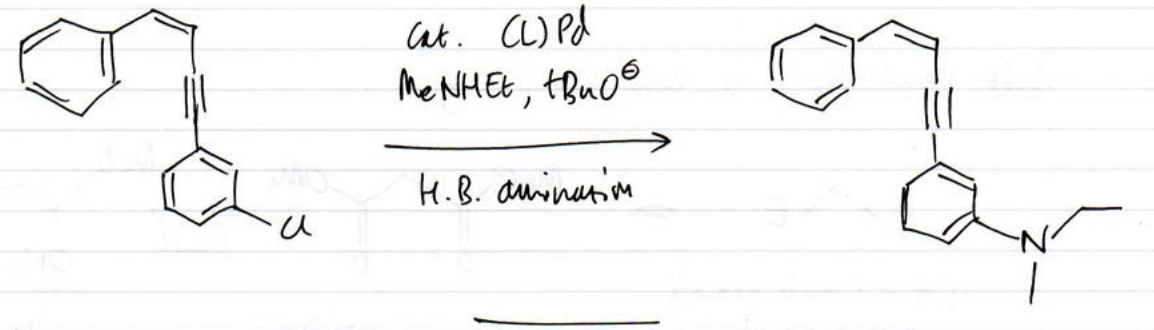
and the product would compete with C_2H_2

Hartwig-Buchwald Amination

tends to be aromatic rings with secondary amines

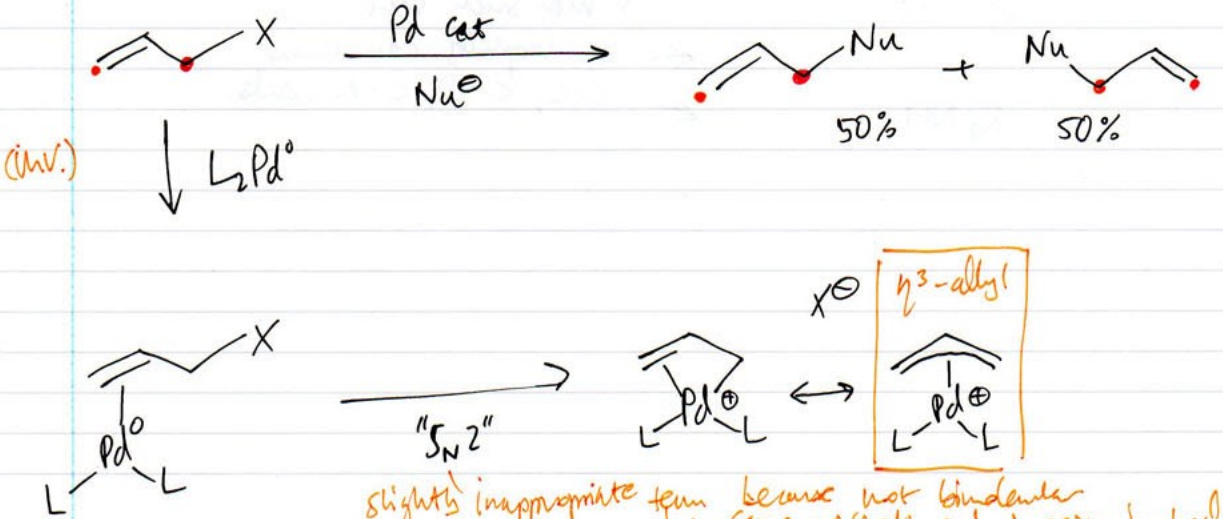


Sonogashira example again.

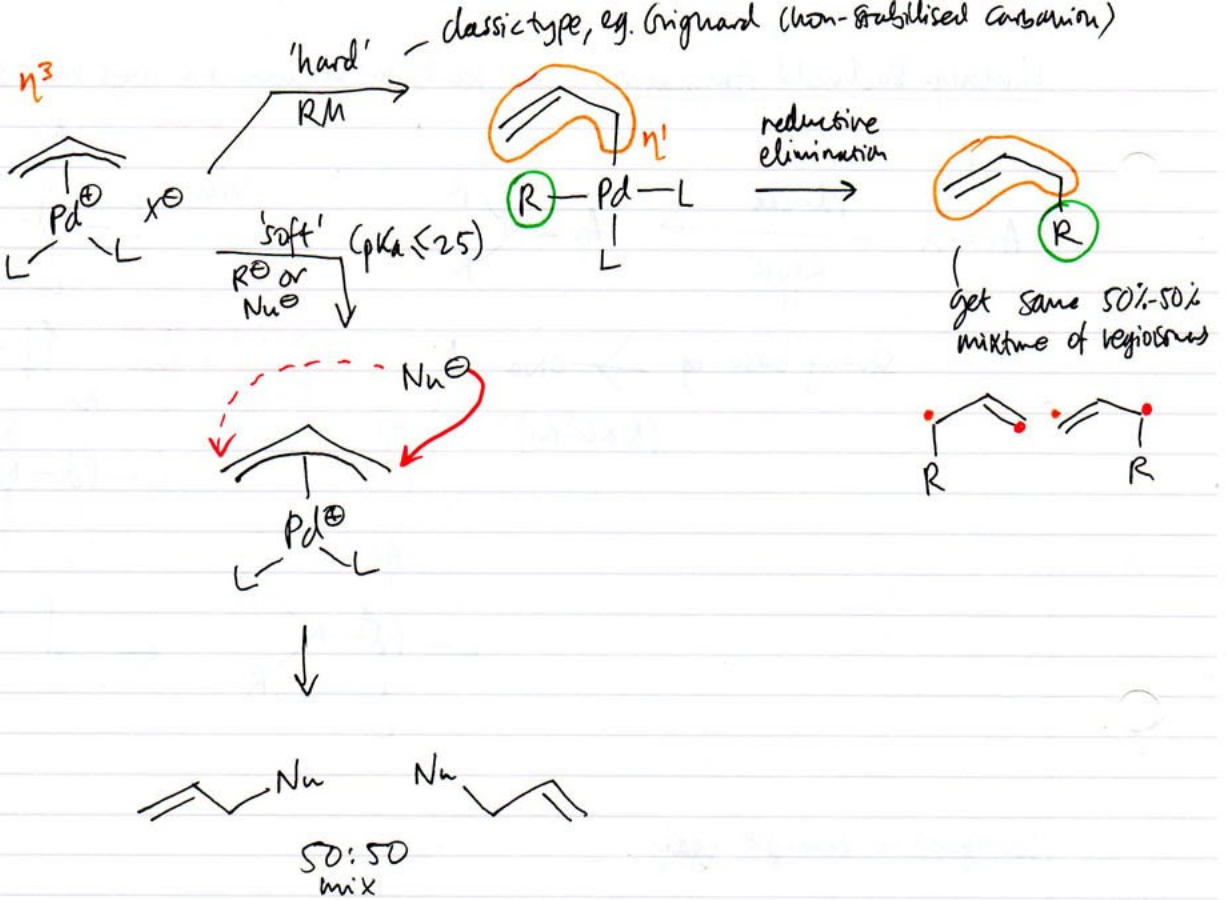


~~Allylic halide~~

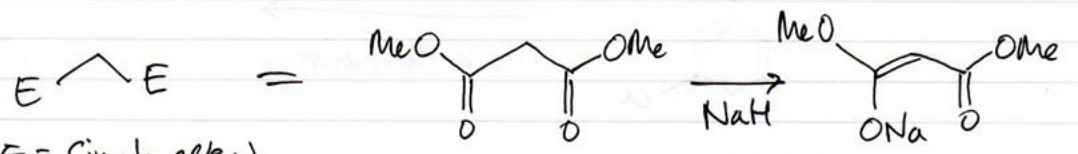
Allylic halides or allylic esters – used with 'hard' and 'soft' nucleophiles



slightly inappropriate term because not bimolecular but same orbitals and inversion involved.



Soft nucleophiles of most use; eg.

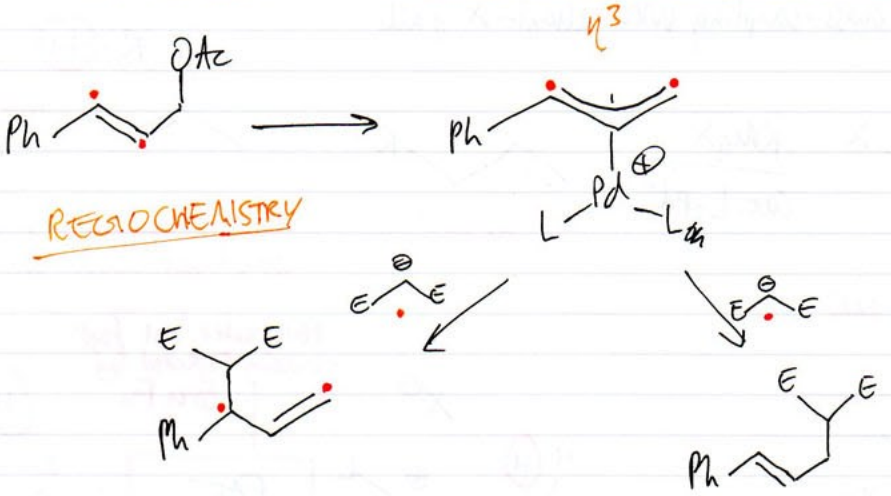


R_2NH.

↑ with such soft nucleophiles, can make C–C, C–O, C–N bonds.

GCLT2
L3/6

Adv. Organic Chem. 2 – May/June 2010 Q2.



REGIOCHEMISTRY

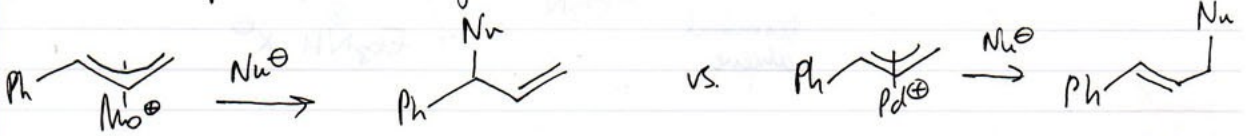
major product (≥95%) for at least two reasons

1) Nu tends to attack at least hindered position **fairly reliable rule**

2) Ph conjugated with alkene

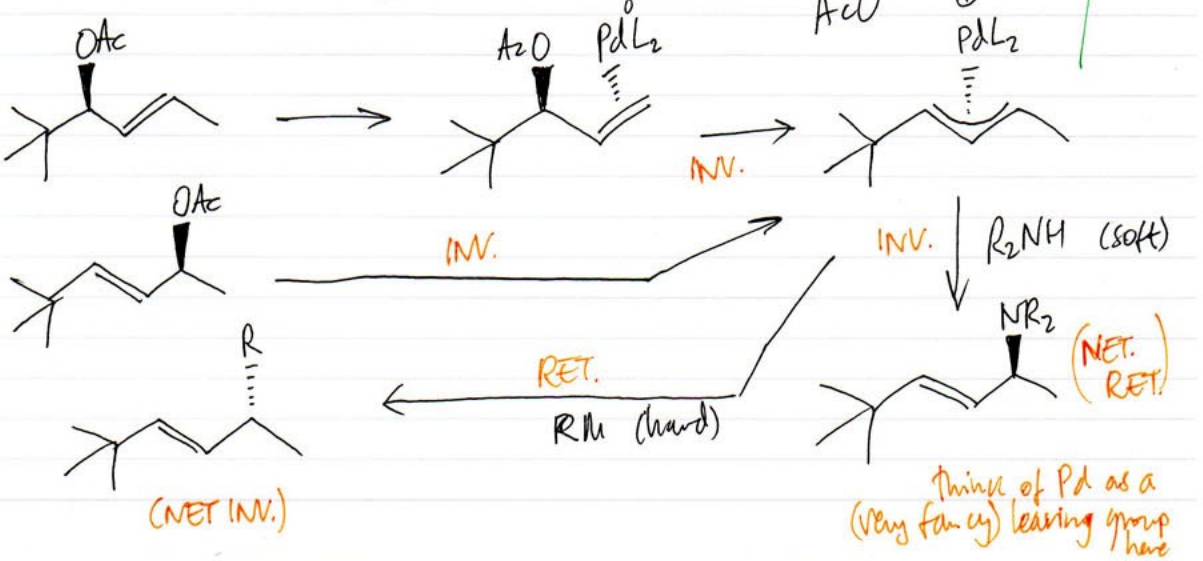
N.B. for masterclass week 23

Mo-cats give opposite regioselectivity



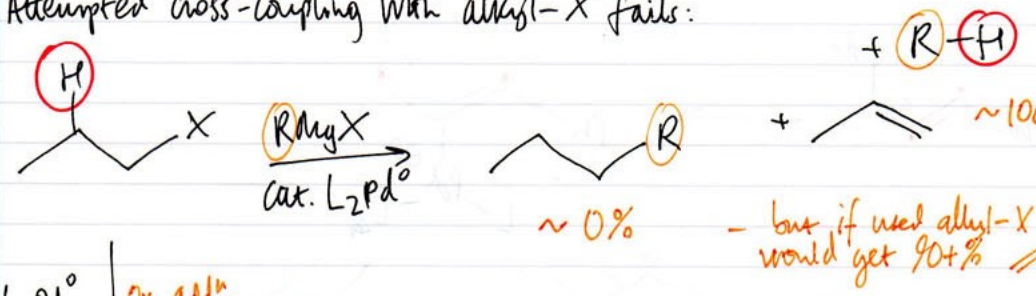
soft Nu⊖ give 2 x inv. = ret. overall

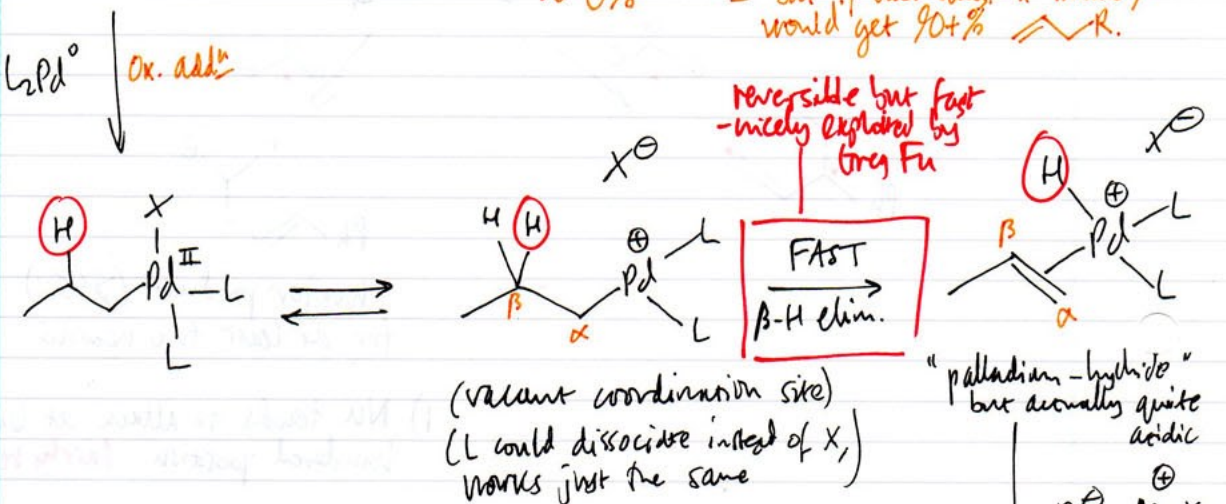
Stereochemistry



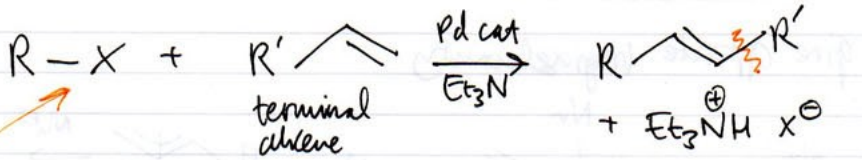
Using β-H elimination productively: the Heck reaction.

Attempted cross-coupling with alkyl–X fails:

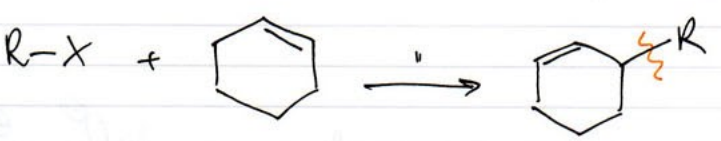




Heck Reaction.



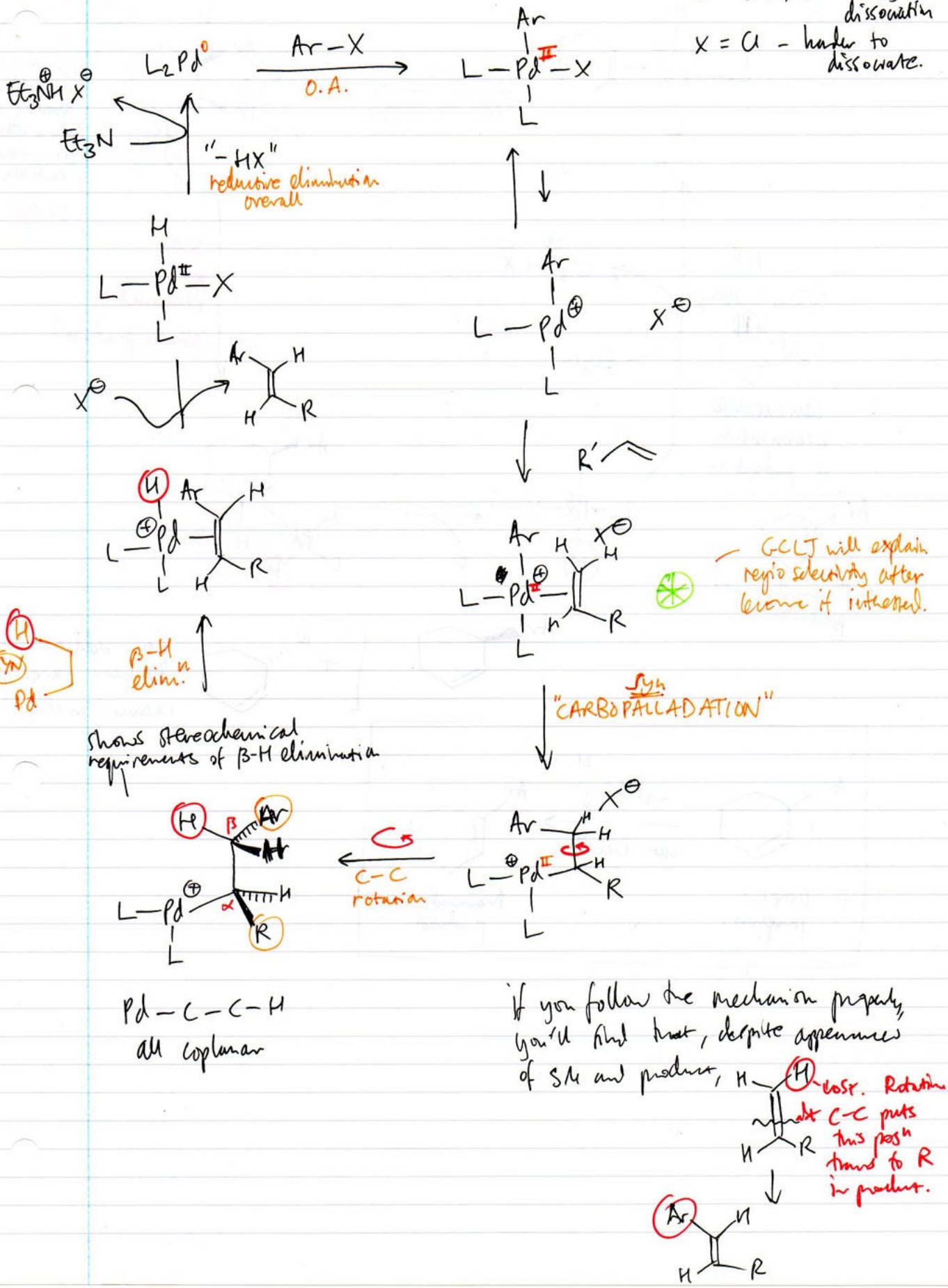
usually aryl or vinyl



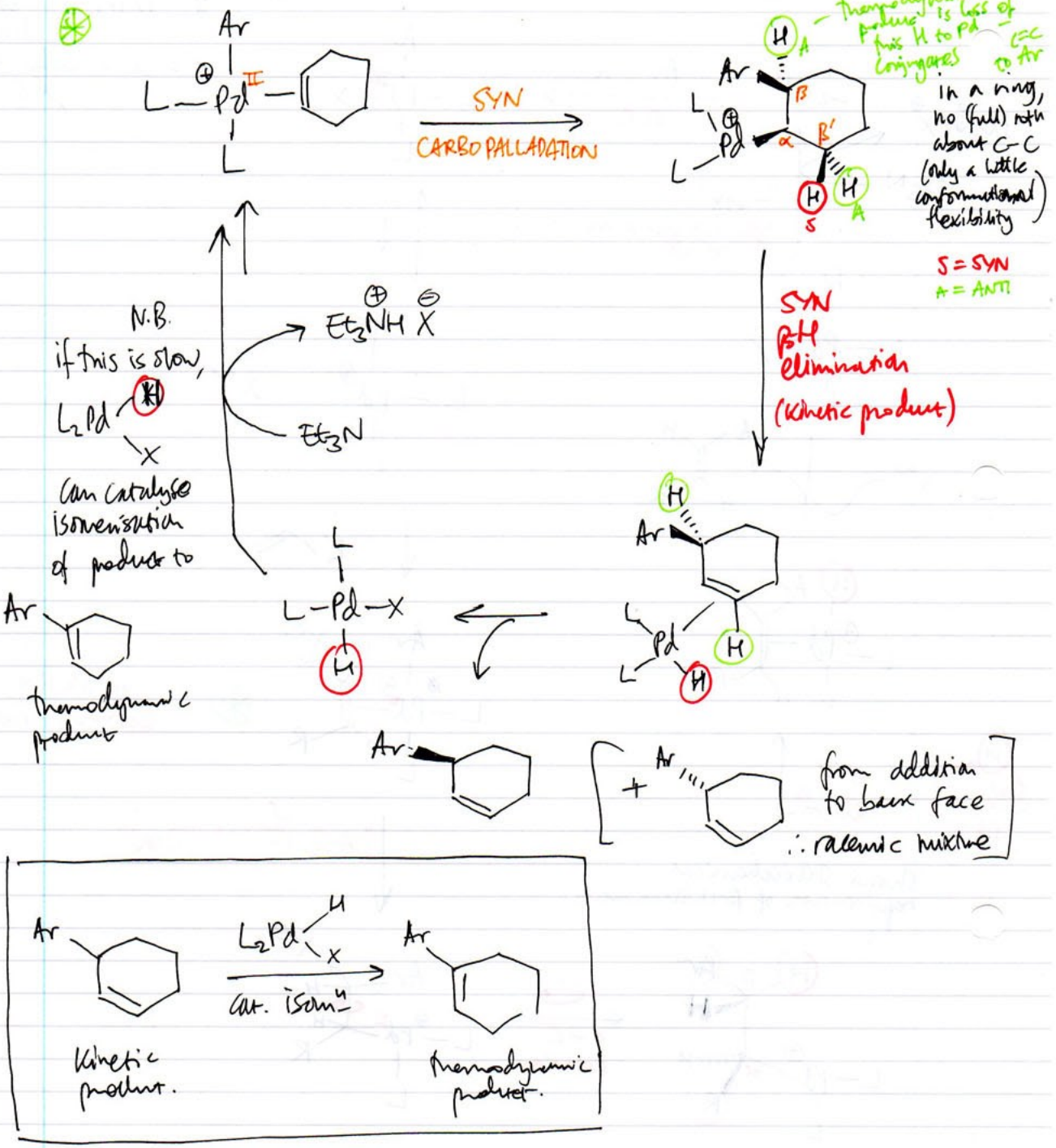
Mechanism of the Heck reaction.

X = OTf, I – easy dissociation

X = Cl – harder to dissociate.

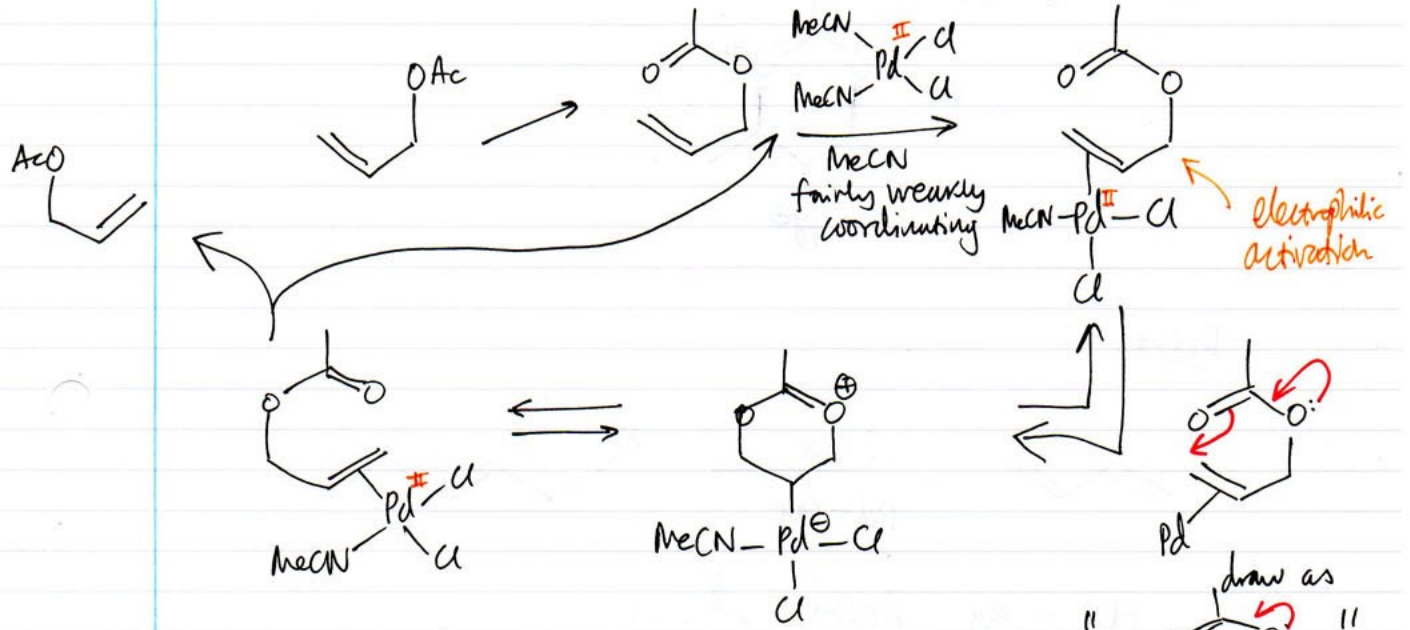


Mechanism for cyclic alkene : same as terminal : Syn, Syn.



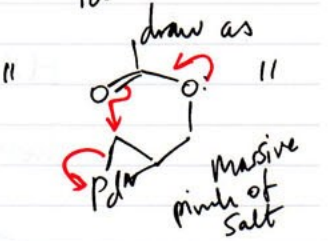
Use of Pd(II): Electrophilic activation of alkenes / dienes.

Pd(II)-catalysed allylic isomerisation
- simple but very useful in synthesis
- don't confuse this with the Pd(0) nucleophile involved in coupling of allylic species.



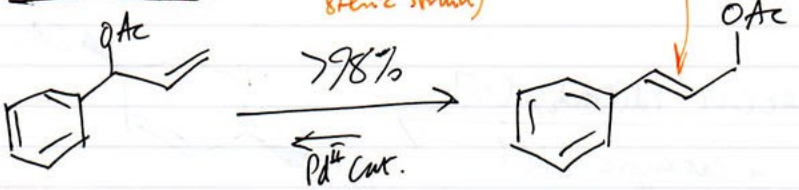
useless reaction with allyl acetate.

but with less symmetric species, is very useful.

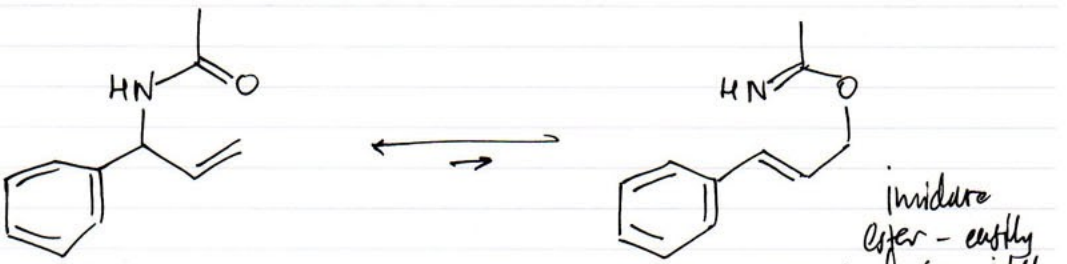


"Pd(IV)" – not at all fine!

Simple bias:

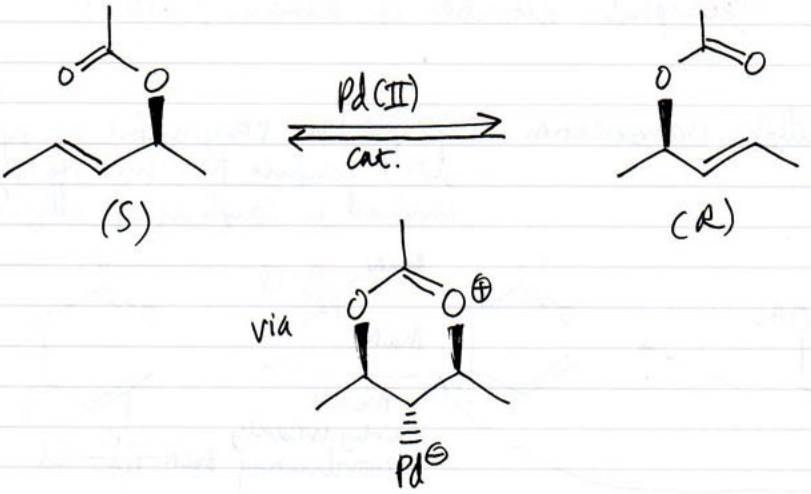


Only a weak bias – don't need much bias to push eqm to 98% RHS



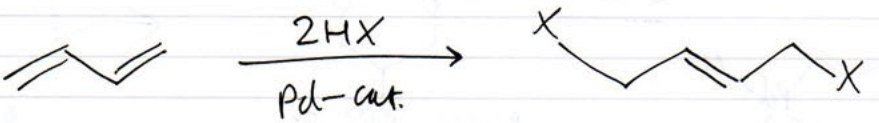
nice easy way of making amides from nitriles

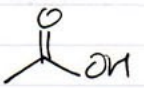
imidate ester – easily made from nitrile



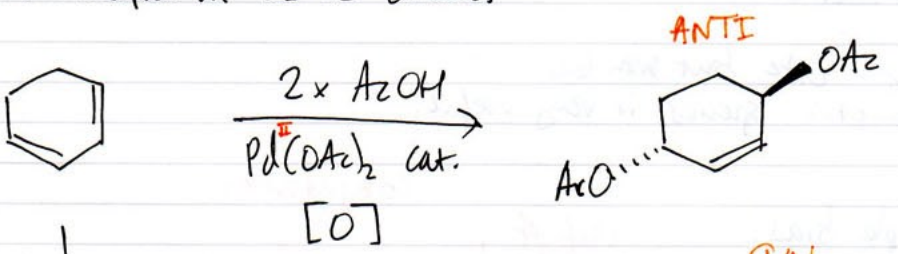
enantiomers.
- rapid racemisation.

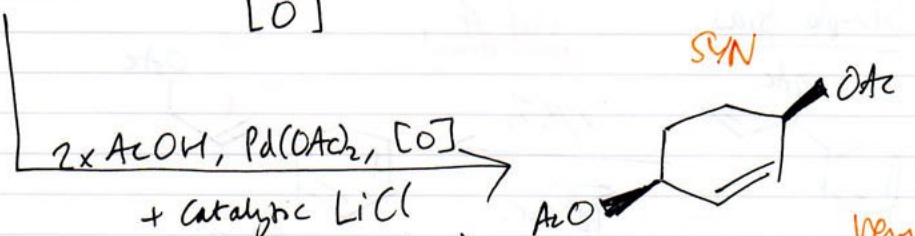
Dienes



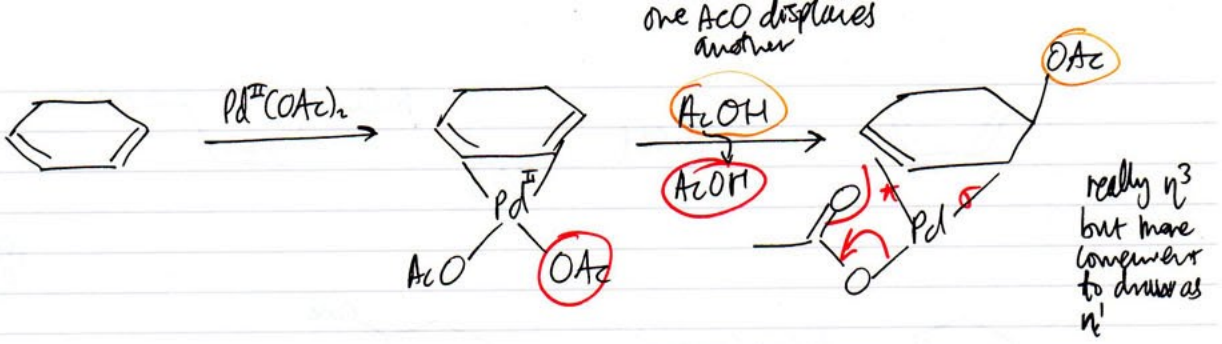
HX = e.g. AcOH 

Most useful in cyclic dienes:

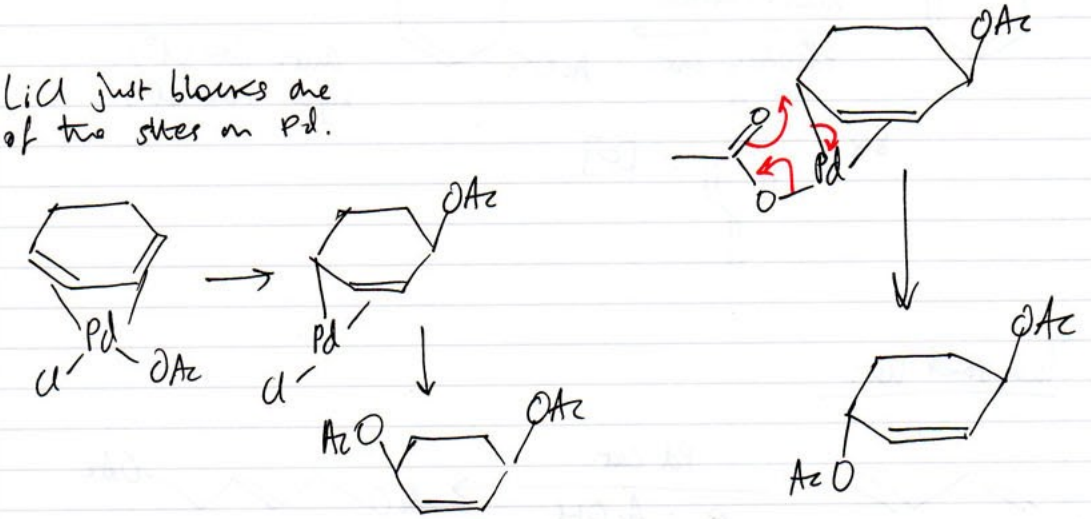




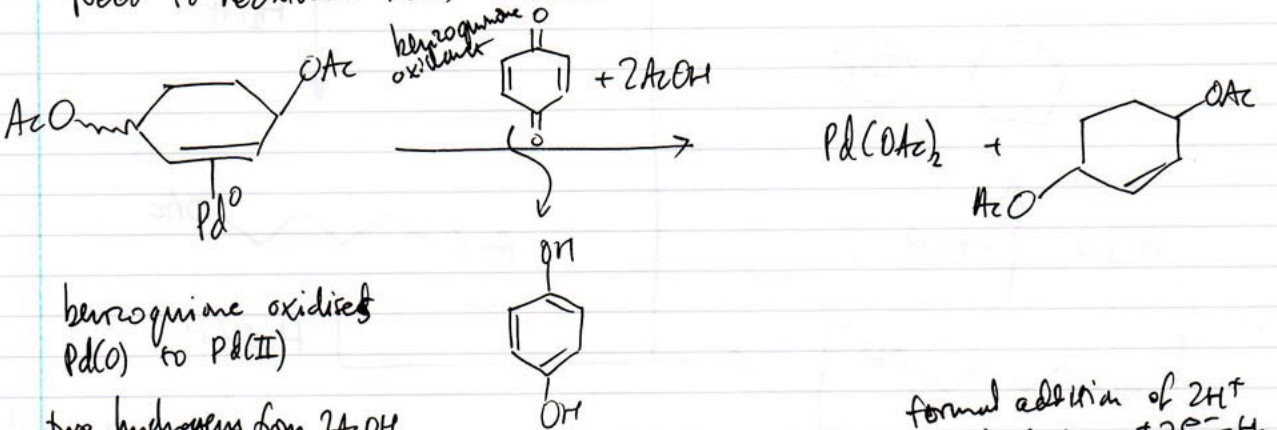
Very selective syntheses of syn and anti allylic acetates from dienes



LiCl just blocks one of two sites on Pd.



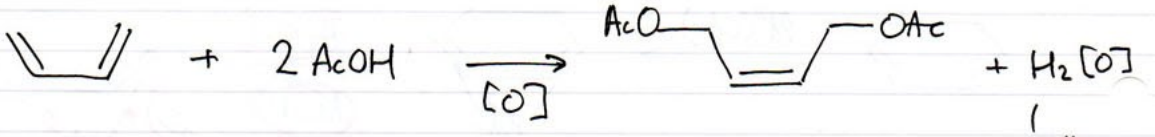
Need to reoxidise Pd(0) to Pd(II)

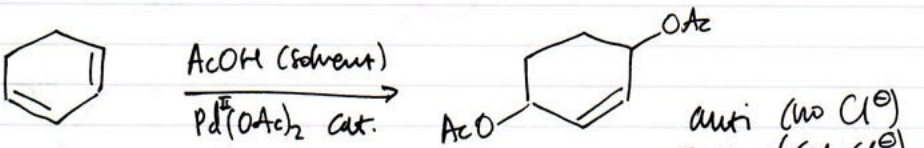


benzoquinone oxidises Pd(0) to Pd(II)

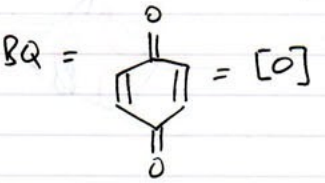
two hydrogens from 2AcOH are added to BQ, two electrons from Pd(0) also taken by BQ: ~~overall~~ formal addition of $2H^+ + 2e^- = H_2$ to BQ.

Past paper Qs: often two parts. Allylic isomerisation followed by

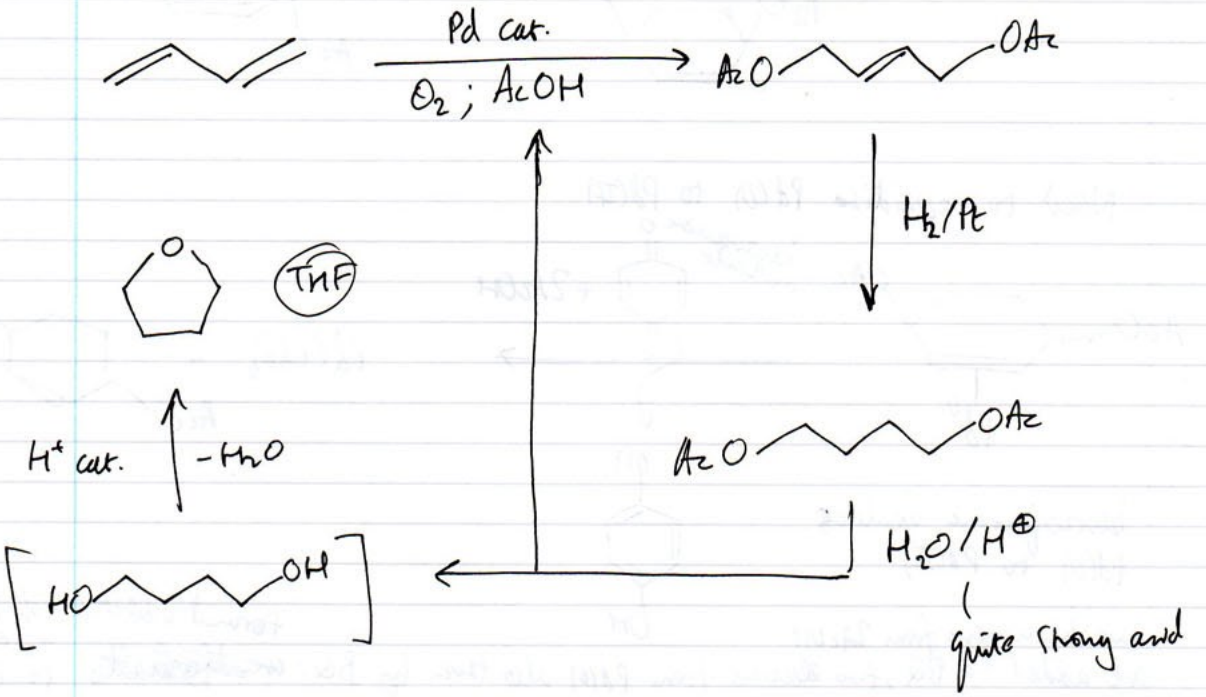




anti (no $Cl^{\ominus}$)
syn (cat. $Cl^{\ominus}$)

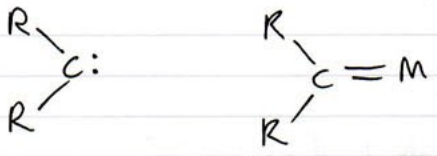


Industrial use:



was once used on a huge scale to produce THF.

Metallocarbene intermediates in catalysis

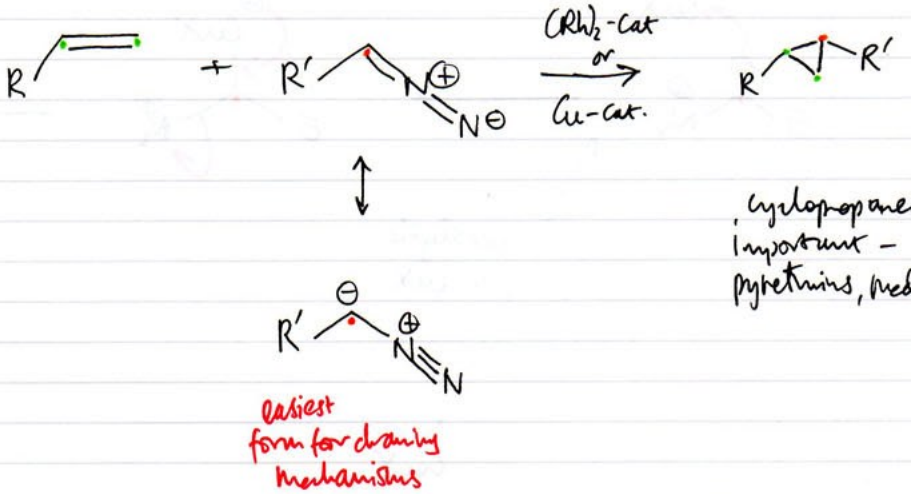


6e (carbene)

carbenoid or metallocarbene

Cyclopropanation and metathesis

Cyclopropanation of alkenes.

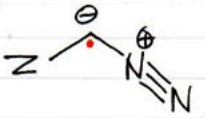


Cu catalyst

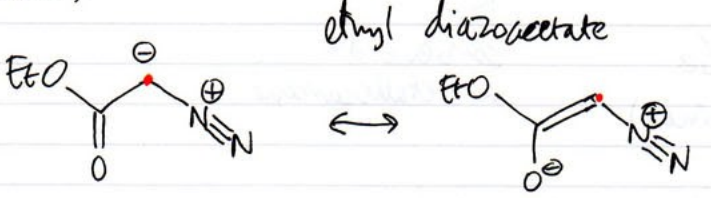
$Cu^{II}X_2$ (more easily handled) $\xrightarrow[\text{in situ}]{\text{reduced}}$ $[Cu^{I}X]$

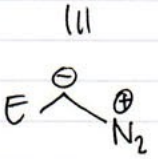
Mechanism

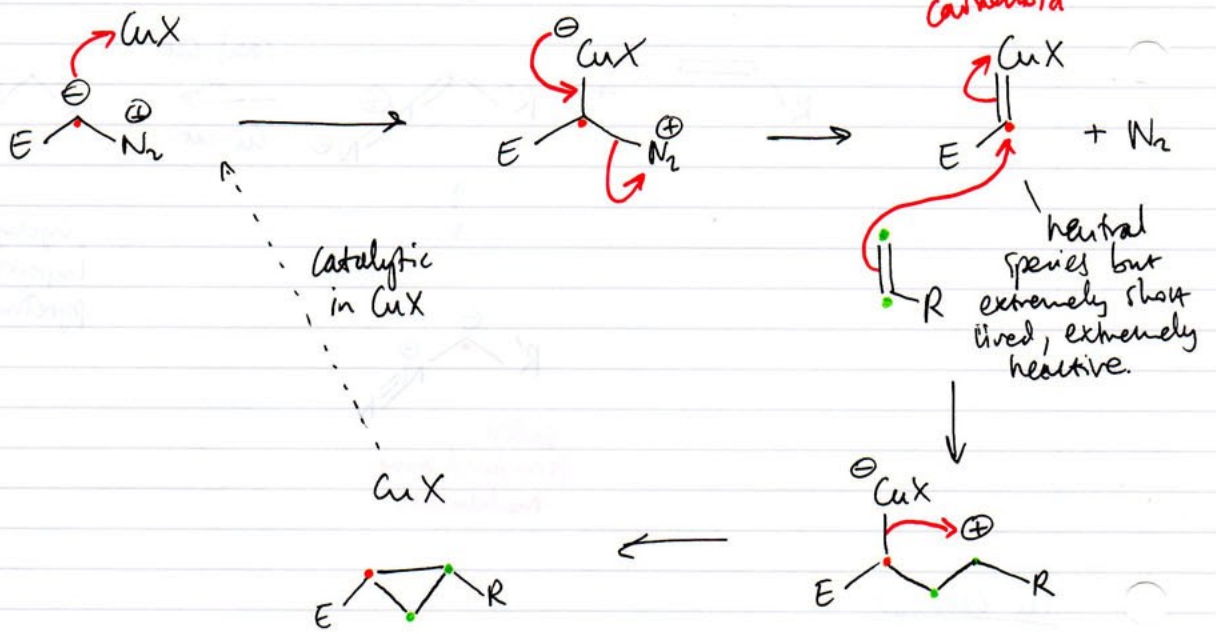
Z = Stabilising group



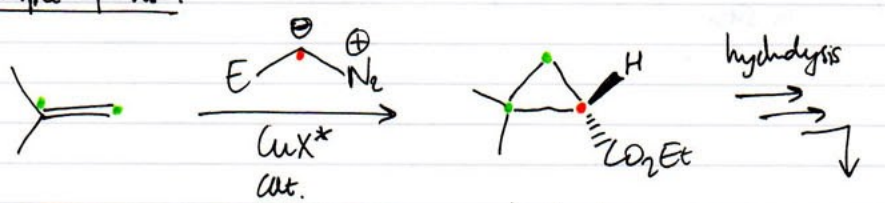
e.g. ester (enolate resonance stabilisation)





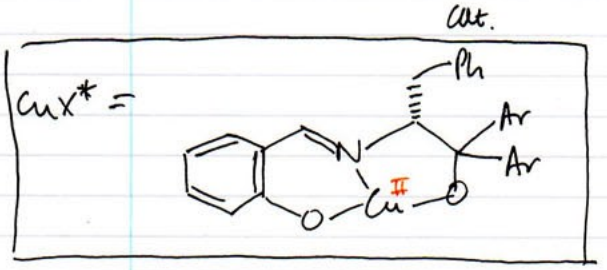


Example of use.

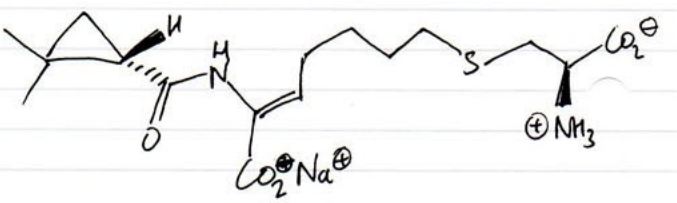


> 92% ee

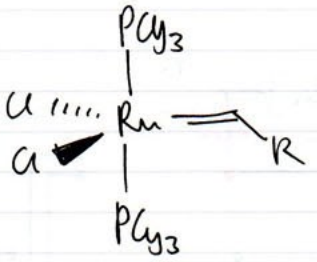
CuX* =

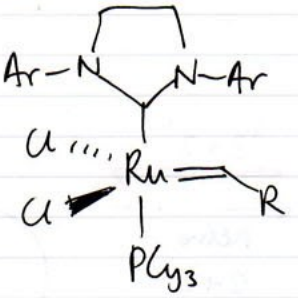


Cilastatin.



Grubbs – catalysts for metathesis:

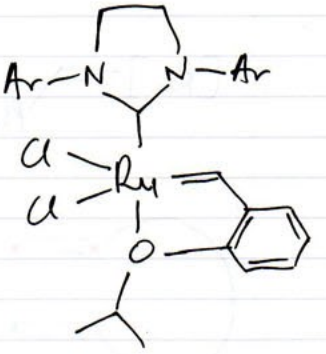




(R = Ph, i.e. benzylidene-[Ru])

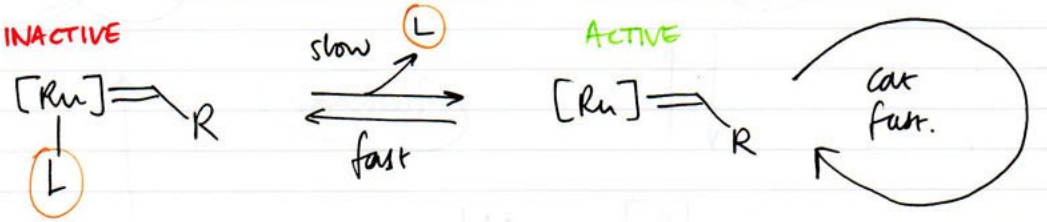
"Grubbs I" (first-generation)

"Grubbs II" (second-generation).



"Grubbs-Hoveyda II"

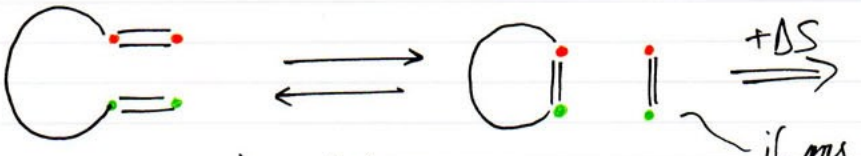
(Grubbs-Hoveyda I nowhere near as effective)



took a long time to understand why certain sets of ligands more readily dissociated to the active form

Metathesis

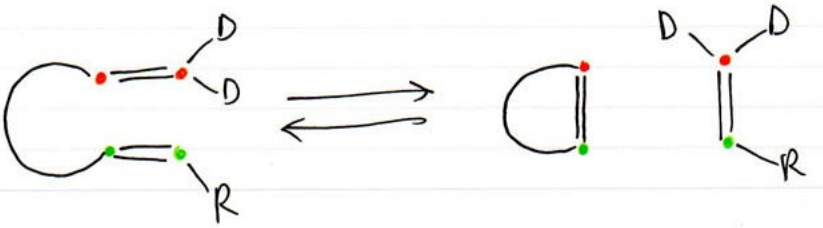
no driving force to push rxn to right hand side.



ring-closing metathesis (RCM)

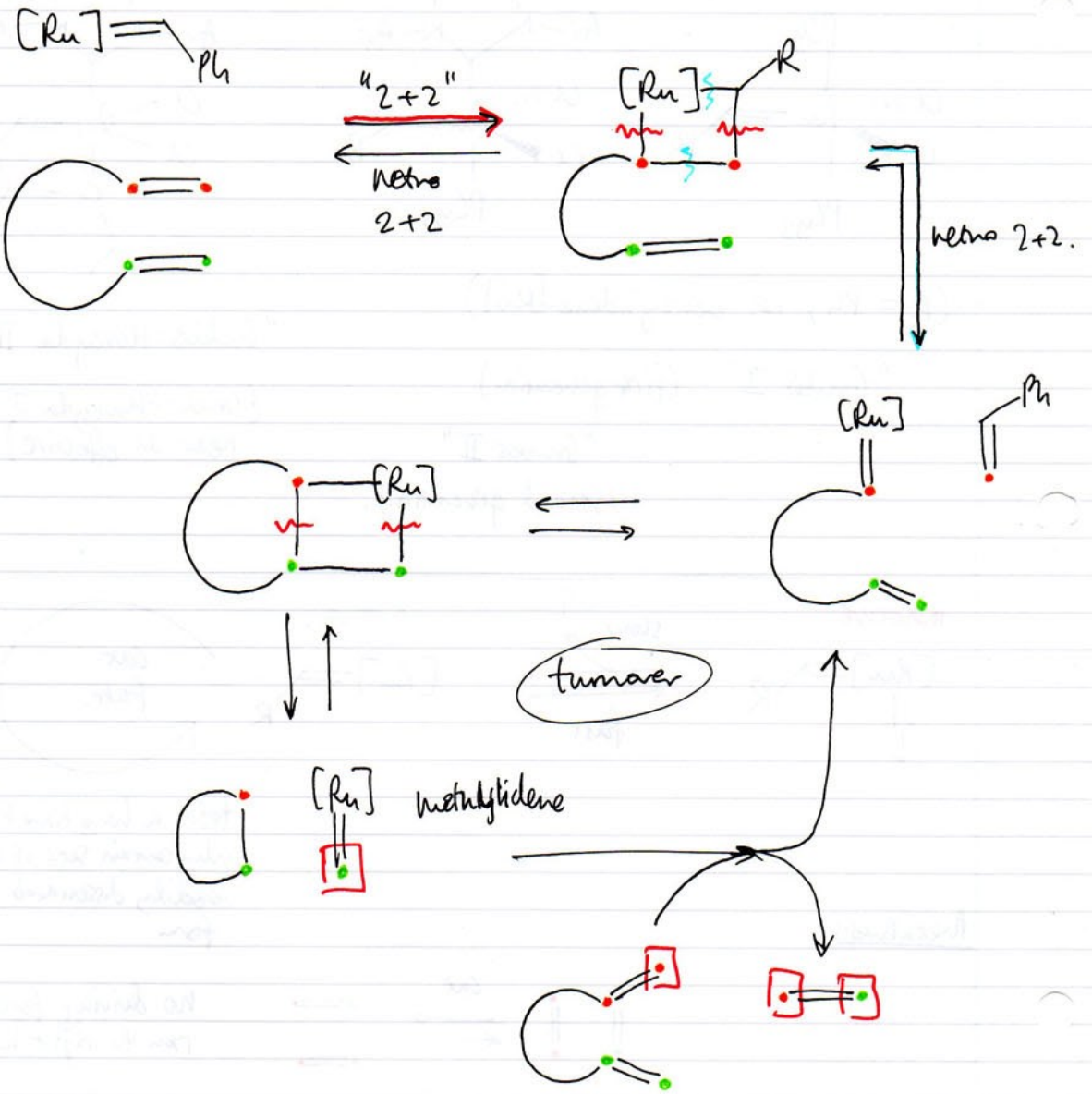
if gas can vent from rxn, get highly +ve ΔS

reminds me of Sop's ^{18}O-allyl alcohol paper.



✱ remember this for revision – be aware you can use RCM to make a non-ring (ring is just by-product!)

Initiation.


[Ru]
Ph
"2+2"
retro 2+2
[Ru]
R
retro 2+2.
[Ru]
[Ru]
Ph
turnover
[Ru]
methylidene