What Reactions will Innovate Target-Oriented Syntheses ?

Lit. Seminar D3 part / 2007.10.13
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0. Let´s summarize and systematize fundamentals for discussions.

0-1. What does *´efficiency´* mean on (multistep) target-oriented syntheses ?

Microscopic viewpoint

(developers of reaction, reagent & catalysis)

- **# high reactivity, high yield**
- **# high chemoselectivity**
- **# high substrate generality**
- (# operational easiness)
- (# environmental friendness)
- (# usability of commercial resource)
- **# high atom economy**

Macroscopic viewpoint

(total synthetic chemists)

 # Baran's 8 rules (*Nature* **2007**, *446*, 404.)

1) less redox reaction	5) cascade reaction
2) more C-C formation	6) no protective groups
3) maximize convergency	7) new methodology
4) linear escalation of [O]	8) biomimetic pathways

 # designed reactivity & selectivity

 # high step economy

High correlations with use of "common FGs"

I think this is the most important factor both on efficiency and diversity.

Not mentioned unequivocally. Is there any guides ?

0-2. What is the Synthetic Target (Organic Molecules) ?

Organic Molecules (= synthetic target)

often involved in final target

Functional Groups (FGs)

additional elements require preparation steps and generate wastes.

C, H, N, O

- ***"common FG"***: (alkane), alkene, ether, alcohol, ketone, ester, amide, carboxylic acid, (hetero)arenes, amine; nitrile, epoxide, alkyne, aldehyde
- ***"uncommon FG"***: aziridine, imine, azide, nitro, cyclopropane, cyclobutane, allene, acetal

later subjection to FG-interconversion is postulated (***ghost FG***)

other elements

- ***"stable elements"***: P, S, B, Si, Cl, Br, I, etc.
- ***"toxic elements"***: Se, Sn, Hg etc.
- ***"unstable elements"***: Li, Mg, Zn, Al etc.

generated in situ.

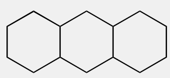
stable, storable / less reactive / various prep. method ⟷ *unstable, instorable / more reactive / limited prep. method*

Carbon Skeleton

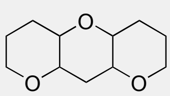
The worth of bond-formation is C-H < C-O < C-N < C-C

(poly)cyclic structure

carbocylcles

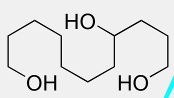


heterocycles

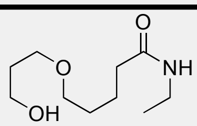


acyclic structure

carbon chain



heteroatom-contained

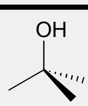


low accessibility ⟷ *high accessibility*

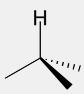
Stereocenters

quarternary

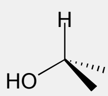
tetrasubstituted



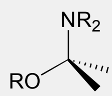
tertiary



trisubstituted



> 2 heteroatoms

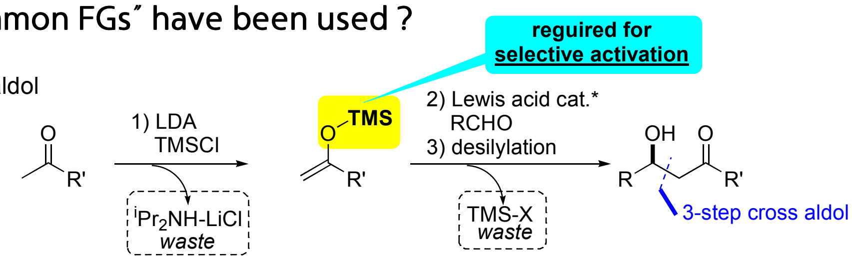


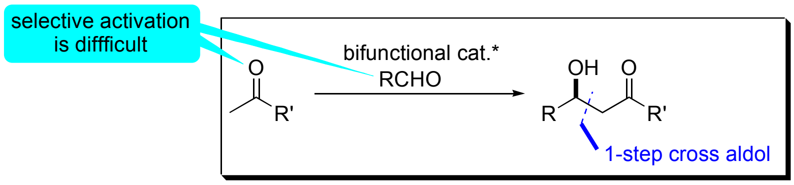
stereo-robust / low accessibility ⟷ *stereo-llabile / high accessibility*

very labile

0-3. Why "uncommon FGs" have been used ?

ex. Cross aldol



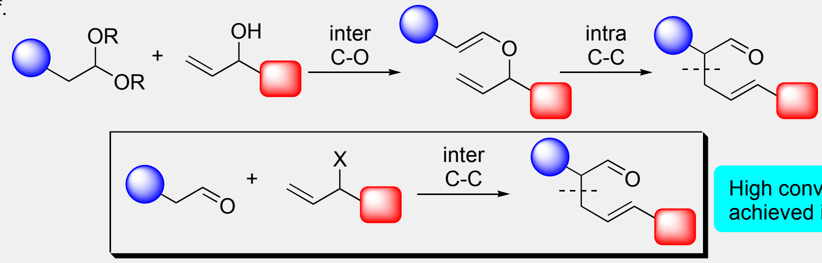


uncommon FG reguires longer steps for attachment / removal (less step economy)
and causes more generation of wastes (less atom economy)

0-4. PROPOSAL: "Six Criteria" to design synthetically useful reactions

I) Develop *Intermolecular* C-C bond-forming reactions.

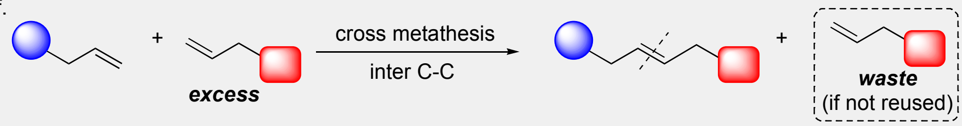
cf.



High convergency can be achieved in less steps !!

II) Develop cross reactions.

cf.



It is much better that equimolar amount of donar & acceptor is principly enough.

III) Use minimal co-redox agent as far as you can.

minimal co-redox reagent = O_2/H_2O_2 or H_2

Stoichiometric co-oxidant/reductant directly become *wastes*.

IV) Activator should be catalytic amount.

to achieve less waste, easy-workup, cheaper reaction

V) Use *common FG.*

C-C forming-reaction between two common FGs always afford common FG !!

PROBLEM: difficult to achieve presice chemoselectivity

VI) Create new stereogenic centers.

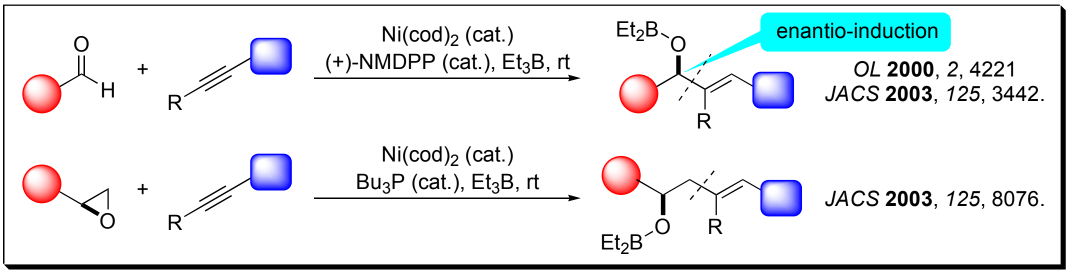
ex.) present fragment-coupling rections

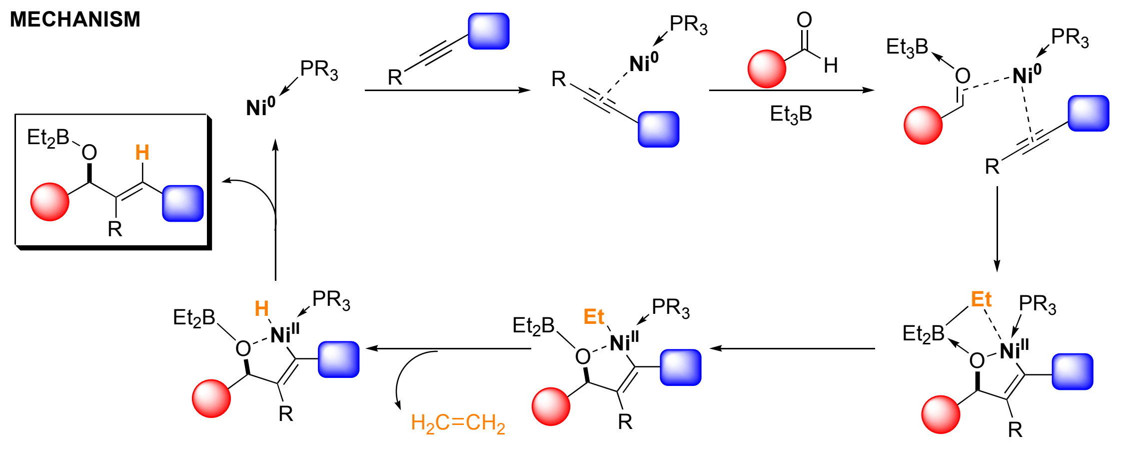
Carbonyl olefination (Horner-Emmons / Julia etc.)	→ I, II, (III)	requires strong (highly basic) conditions
Carbonyl addition to organometallics (lithium enolate etc.)	→ I, II, (VI)	
Nozaki-Hiyama-Kishi reaction	→ I, II, IV, (VI)	sometimes requires toxic reagents, uncommon FGs
Cross coupling (Suzuki, Stille, Negishi etc)	→ I, II, III, IV	
Olefin cross metathesis	→ I, III, IV, V	→ requires excess partners
Jamison's (Ni) system	→ **I, II, IV, V, VI**	
Trost's (Ru, Pd) system	→ **I, II, III, IV, V**	
Direct cross aldol, Baylis-Hillman etc.	→ I, II, III, IV, V, VI	- - → high potential, but little applied yet to large molecules

1. The power of fragment coupling with use of common FGs

1-1. Jamison's Ni system and applications

Review: *Chem Commun.* **2007**, Advance articles.

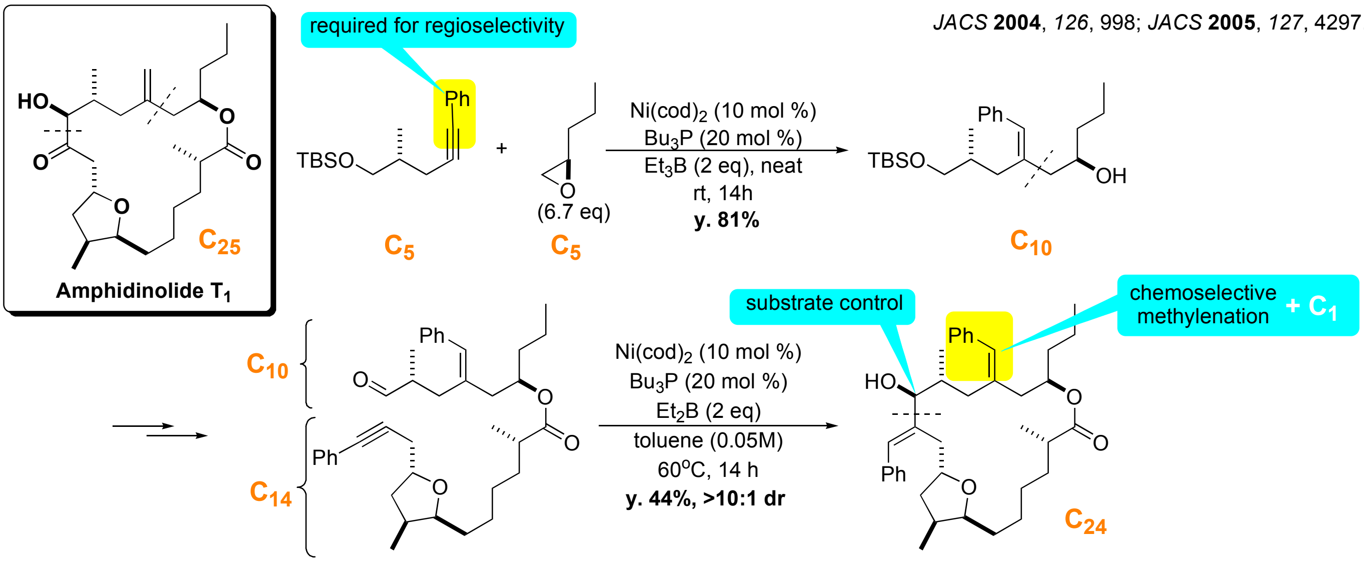




* Krische improved similar reactions with use of Rh cat. and H_2 gas as co-reductant. *Acc. Chem. Res.* **2007**, ASAP.

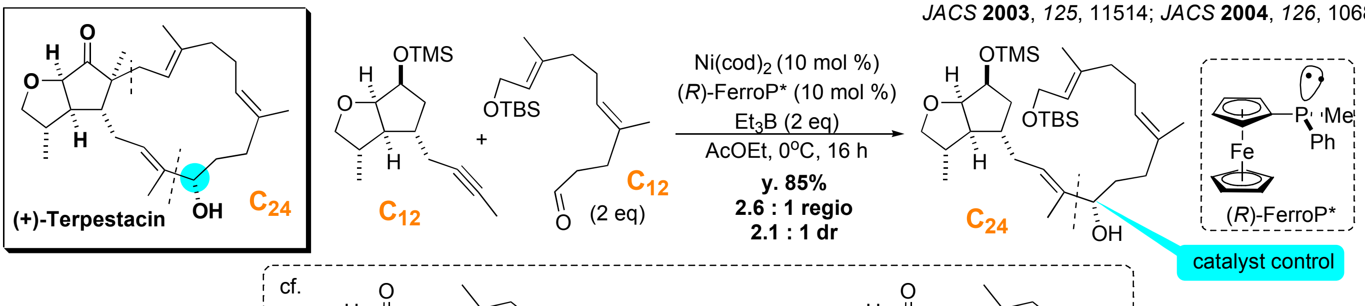
SYNTHETIC APPLICATIONS

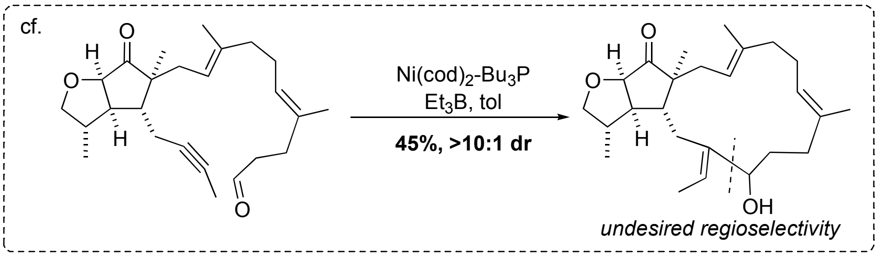
JACS **2004**, *126*, 998; *JACS* **2005**, *127*, 4297.



Olefin, ester, ether is tolerant.

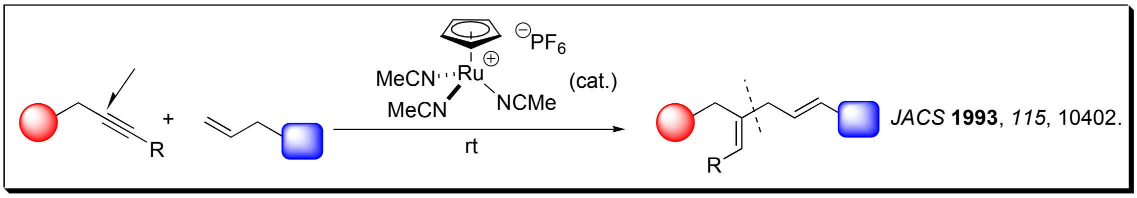
JACS **2003**, *125*, 11514; *JACS* **2004**, *126*, 10682.

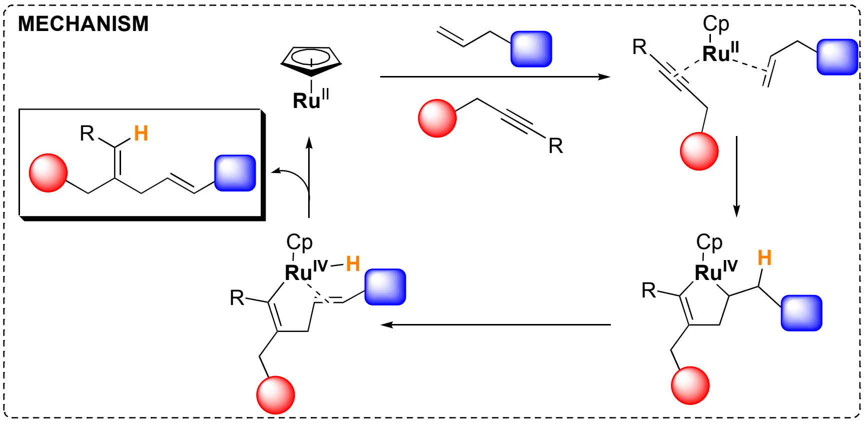


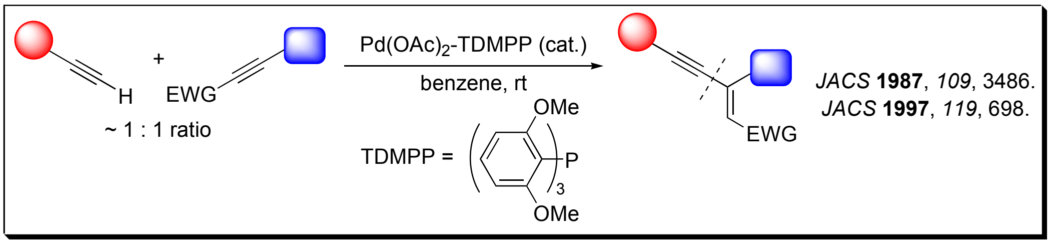


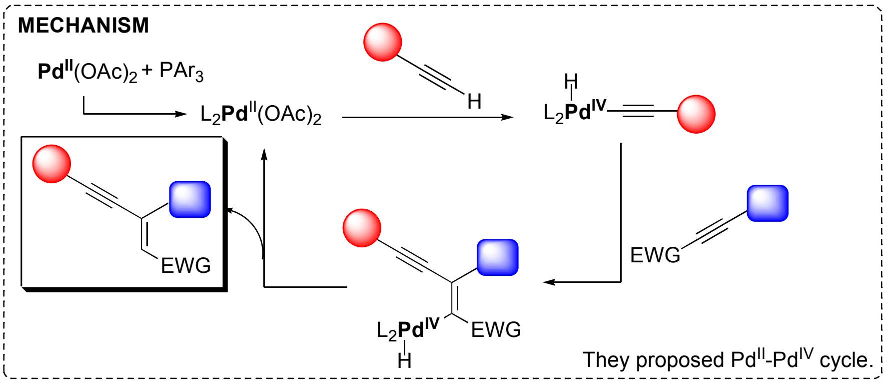
1-2. Trost's Ru/Pd system and applications

Review of Ru: *ACIE* **2005**, *44*, 6630; *Chem. Rev.* **2001**, *101*, 2067.

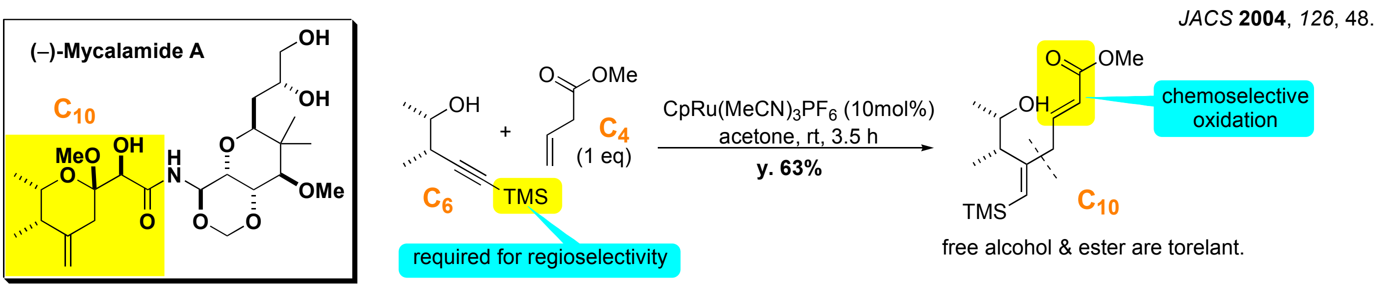


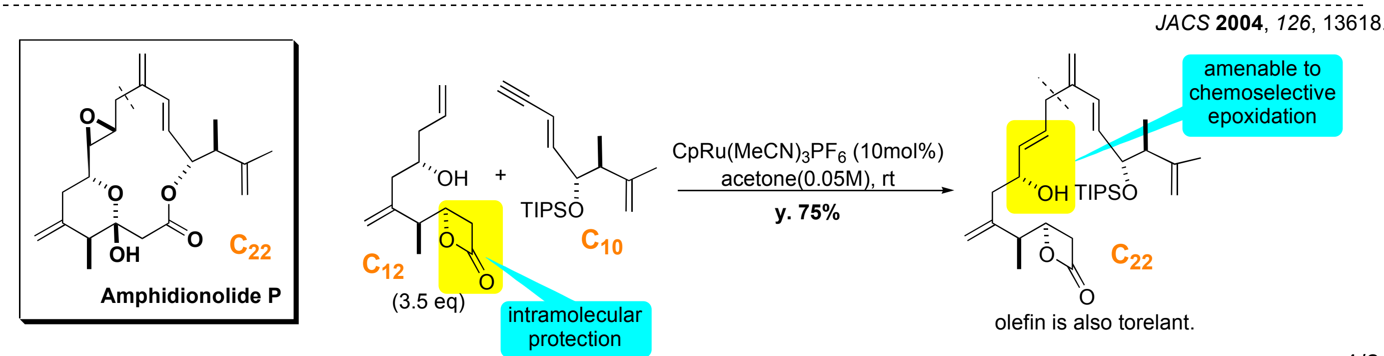


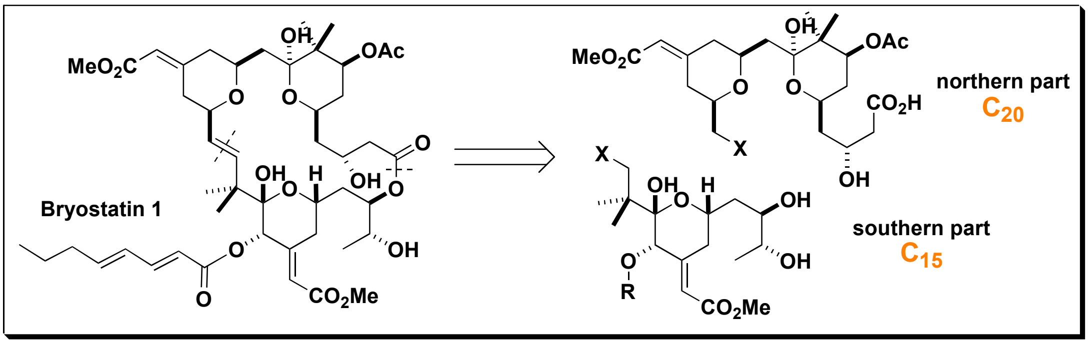




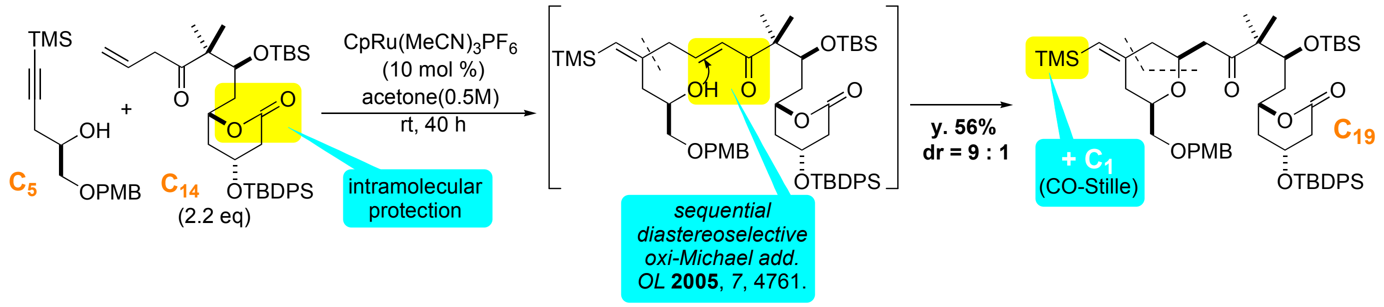
SYNTHETIC APPLICATIONS



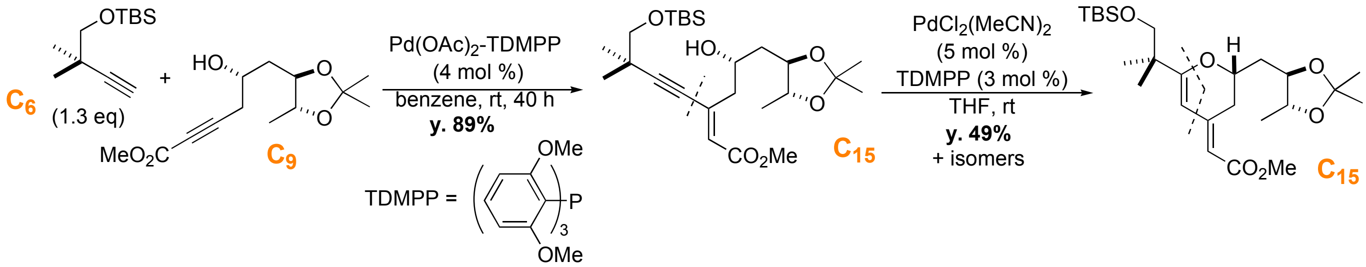




Synth. of northern part *JACS* **2007**, *129*, 2206.

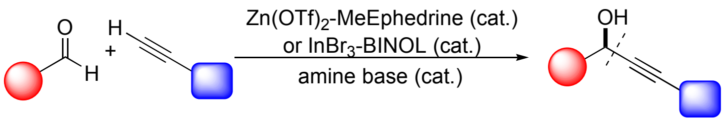


Synth. of southern part

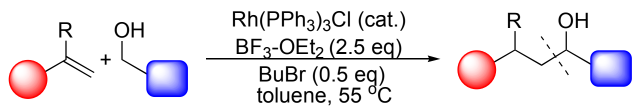


1-3. Recent Important Findings about Catalytic C-C Formations with Common FGs

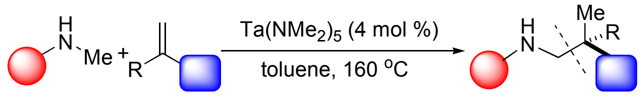
Direct Alkynylation
Carreira, E. M. et al. *JACS* **2001**, *123*, 9687.
Takita, Shibasaki *JACS* **2005**, *127*, 13760.



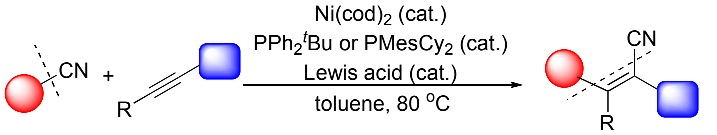
C-H activation forming sp^3-sp^3 bond
Tu, Y.-Q. et al *JACS* **2005**, *127*, 10836.



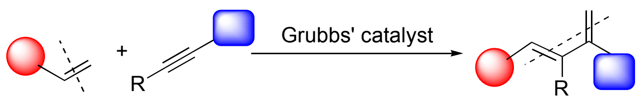
Hartwig, J. F. et al. *JACS* **2007**, *129*, 6691.



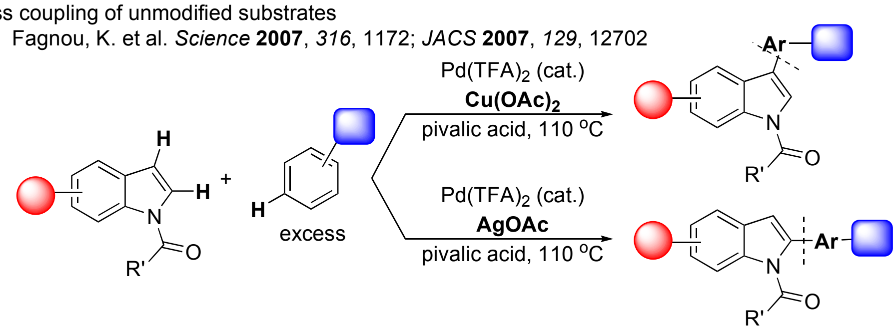
Intermolecular C-C bond reorganization
Nakao, Y.; Hiyama, T. et al. *JACS* **2004**, *126*, 13904; *JACS* **2006**, *128*, 7420
JACS **2006**, *128*, 7116; *JACS* **2007**, *129*, 2428.



Enyne metathesis (C=C bond reorganization)
Review: *Chem. Rev.* **2004**, *104*, 1317.



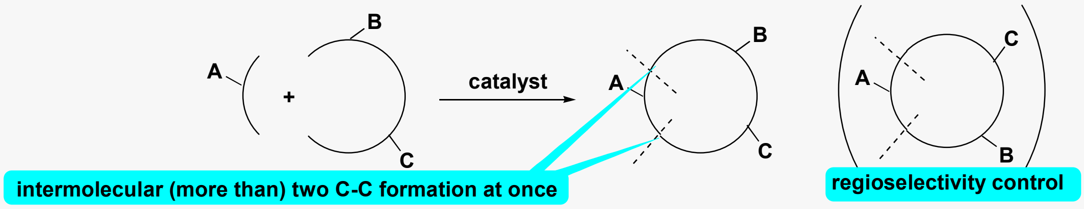
Cross coupling of unmodified substrates
Fagnou, K. et al. *Science* **2007**, *316*, 1172; *JACS* **2007**, *129*, 12702



2. Unsolved Problem: Convergent Catalytic Synthesis of Carbocycles

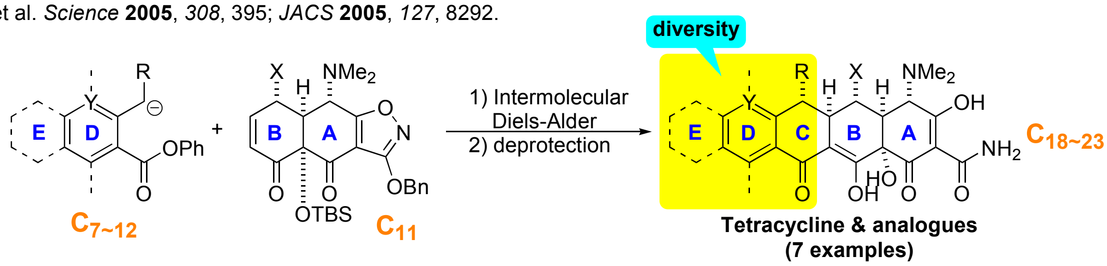
Present synthetic strategies for polycyclic structures are *substrate-dependent* and *require linear route*.

Intermolecular **synthetic methodologies of 5-/6- membered rings are highly demanded.**

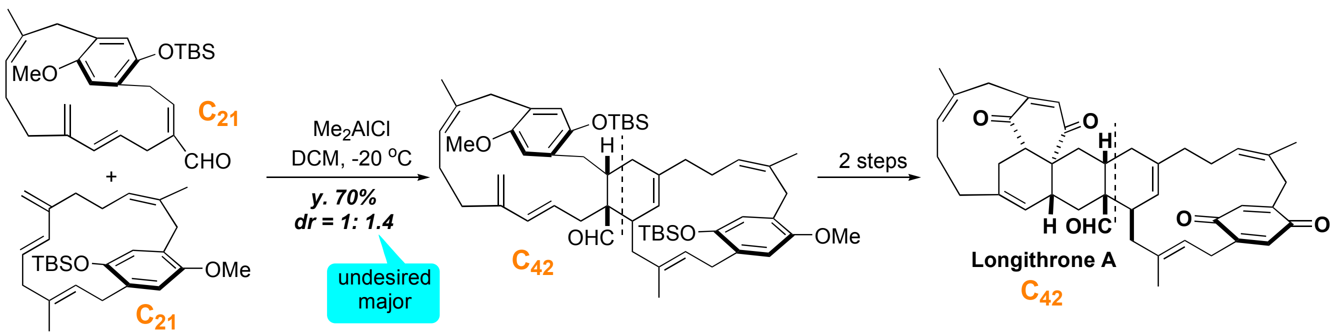


2-1. Masterpieces of Convergent Route toward Polycyclic Structures using Common FGs

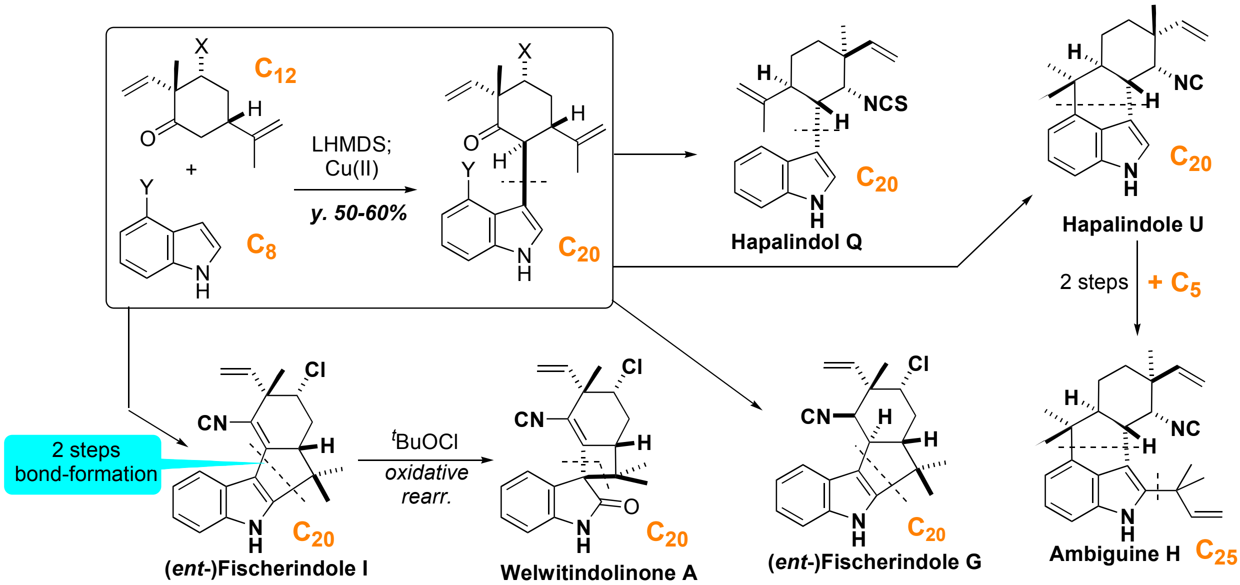
Myers, A. G. et al. *Science* **2005**, *308*, 395; *JACS* **2005**, *127*, 8292.



Shair, M. D. et al. *JACS* **2002**, *124*, 773.

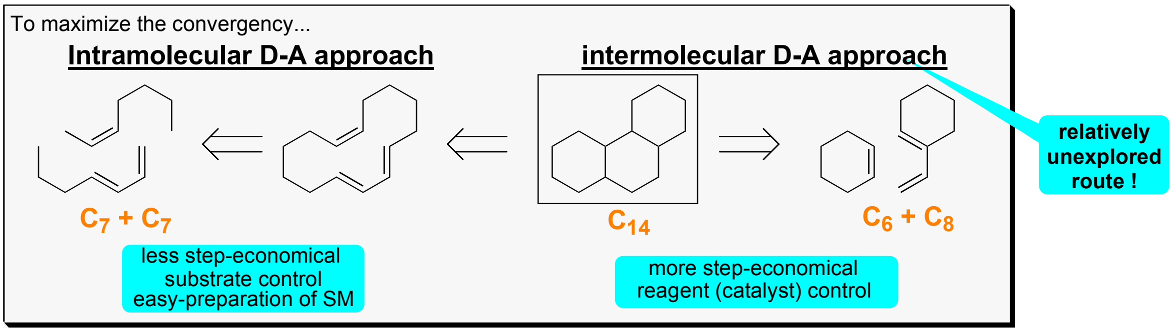


Baran, P. S. et al. *JACS* **2004**, *126*, 7450; *JACS* **2005**, *127*, 15394; *Nature* **2007**, *446*, 404.

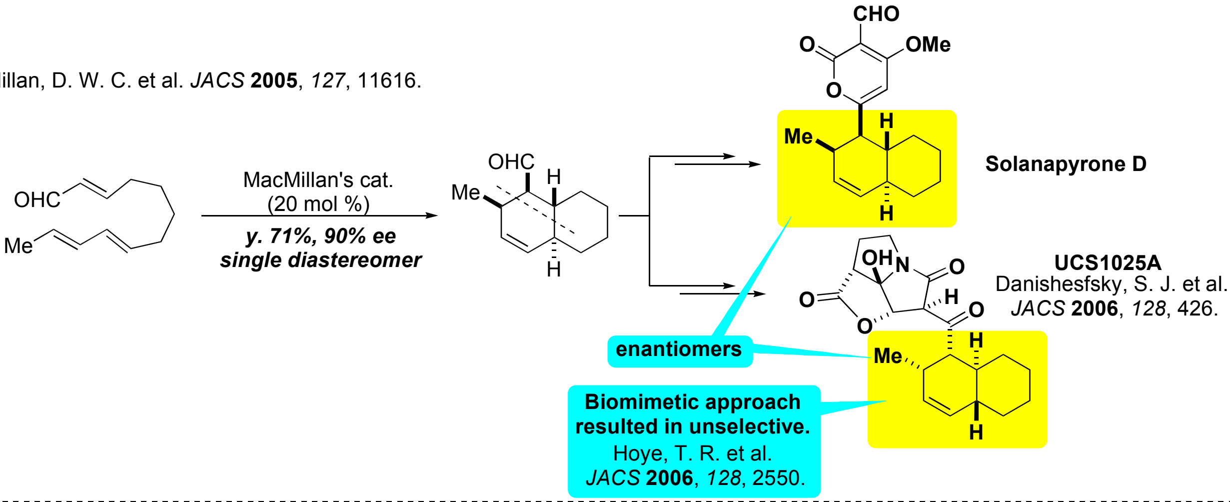


masterpieces of non-D-A convergent approaches toward polycylclic skeletons with common FGs

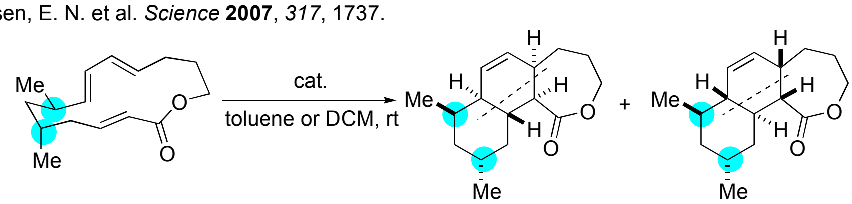
2-2. State-of-the-Art: Catalytic (Convergent) Synthesis of 6-membered Carbocycles

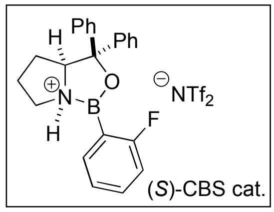


MacMillan, D. W. C. et al. *JACS* **2005**, *127*, 11616.



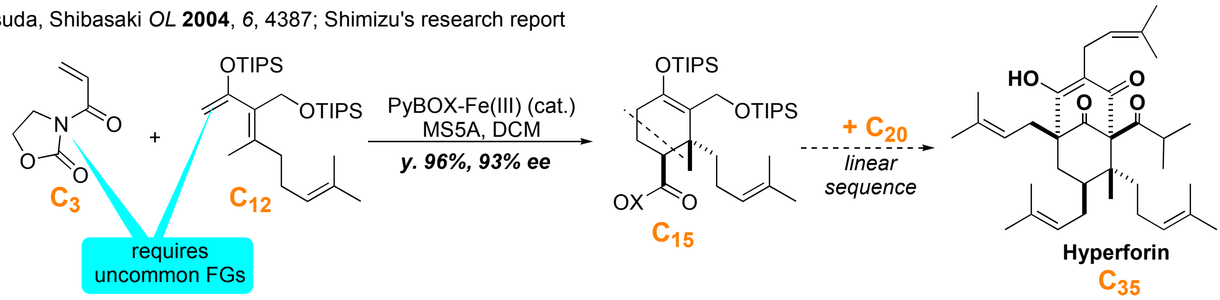
Jacobsen, E. N. et al. *Science* **2007**, *317*, 1737.





cat.	*endo* yield	*exo* yield
$MeAlCl_2$ (80 mol %)	50	50
none, 120 °C (thermal)	45	**55**
(*S*)-CBS (20 mol %)	3	**97**
(*R*)-CBS (20 mol %)	**78**	22

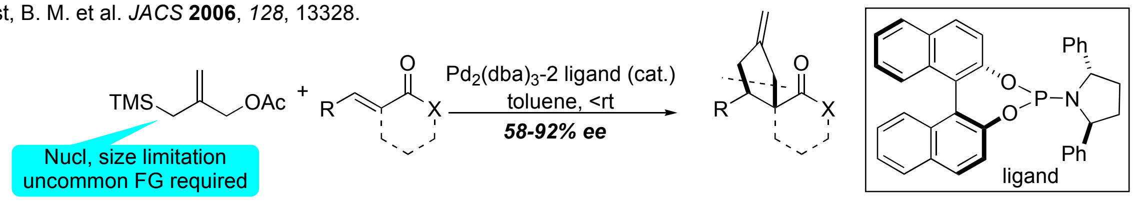
Usuda, Shibasaki *OL* **2004**, *6*, 4387; Shimizu's research report



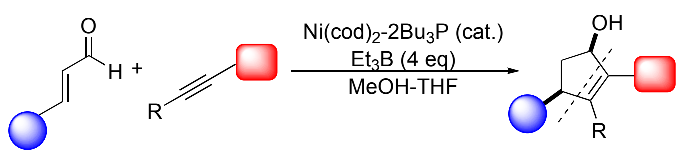
2-3. Catalytic Convergent Synthesis of 5-membered Carbocycles

Few methodologies are present.

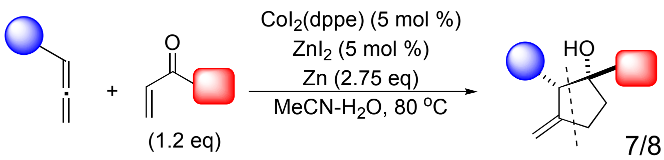
Trost, B. M. et al. *JACS* **2006**, *128*, 13328.



Montogomery, J. et al. *JACS* **2006**, *128*, 14030.



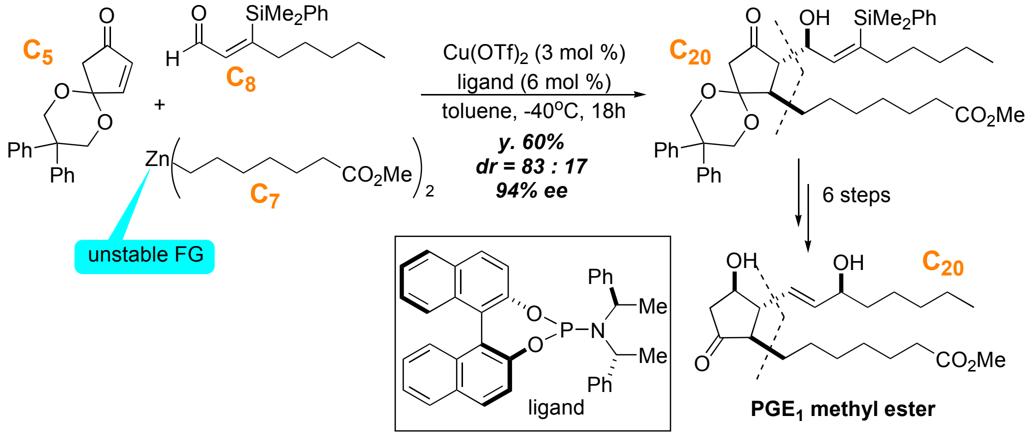
Cheng, C.-H. et al. *JACS* **2007**, *129*, 4166.



3. Future Prospect: What reactions should be developed ?

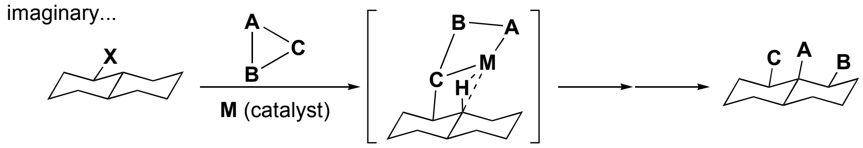
A) Multicomponent C-C bond-formation (with common FGs)

cf. Feringa, B. L. et al. *JACS* **2001**, *123*, 5841.



cf. domino rxn = intramolecular multiple bond-formation (substrate control) = specific

B) Multiple (more than triple) FG-interconversion & introduction at once



multi-activespecies catalyst → for multiple bond-formations

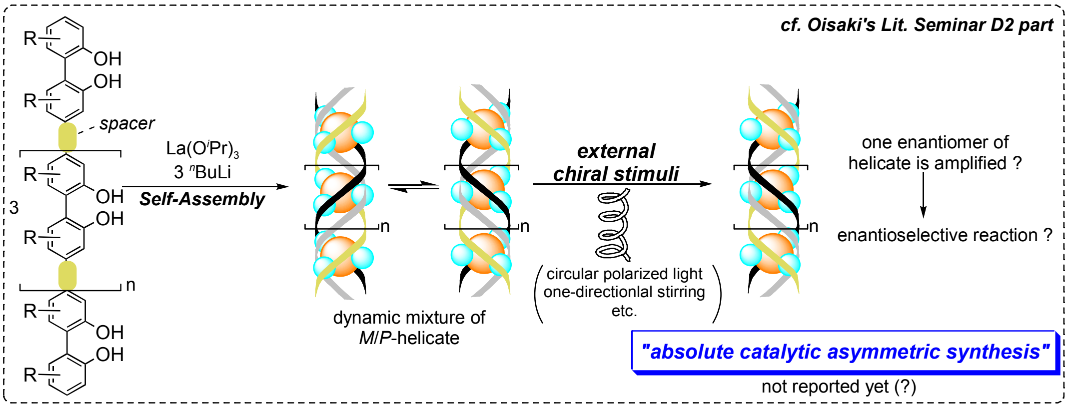
high-resolution catalyst → for precise chemoselectivity on common FGs

C) Pursuit for far efficient "Absolute Synthesis"

no practical concepts are present. see Vijay's lit. seminar (2003)

Control of Chemoselectivities

substrate control	auxilirary control	reagent control	catalyst control	absolute control
sure specific (strong bond dependent)				less sure general (weak bond dependent)



> *"What I cannot create, I do not understand."*
>
> ———— *Richard P. Feynman*