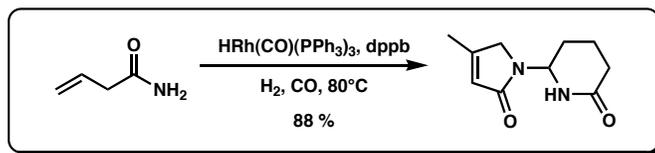
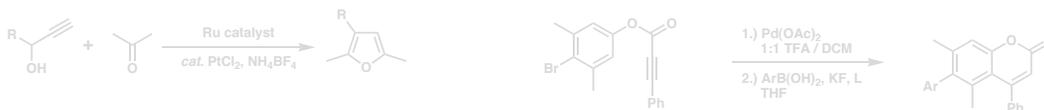
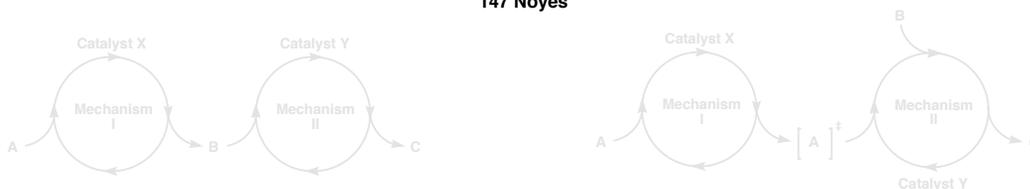


Tandem Catalysis

A Highly Efficient and Rapid Approach to Synthetic Elaboration



Stoltz Group Literature Meeting
John Enquist
Monday, October 3rd, 2005
8 pm
147 Noyes



Tandem Catalysis - Outline

1.) Introduction

- A.) Definitions and classifications: What is tandem catalysis?
- B.) Costs and benefits: Why use tandem catalysis?

2.) Assisted tandem catalysis

- A.) Zinc mediated tandem catalysis
- B.) Titanium catalyzed allylation - epoxidation
- C.) Cross coupling and tandem annulation
- D.) Metathesis and assisted tandem catalysis
- E.) Palladium in tandem catalysis

3.) Auto-tandem catalysis

- A.) Increasing efficiency in palladium catalyzed reactions
- B.) Samarium diiodide catalyzed Mukaiyama Michael-aldol reactions
- C.) Zirconium catalyzed synthesis of β -cyanohydrins
- D.) Tandem hydrocarbonylation - cross coupling

4.) Orthogonal Catalysis

- A.) Palladium catalyzed alkylation and rhodium catalyzed annulation.
- B.) Cobalt catalyzed annulation and cycloaddition
- C.) Rapid synthesis of pyrroles and furans
- D.) Organocatalytic / Lewis acid tandem catalysis

5.) Conclusions

Tandem catalysis reviews:

- Fogg, D.; Santos, E. *Coord. Chem. Rev.*, **2004**, *248*, 2365
- Gleason, J.; Ajamain, A. *Angew. Chem. Int. Ed.*, **2004**, *43*, 3754
- Baker, R.; Bazan, G. *Chem. Rev.*, **2005**, *105*, 1001
- Chang, S. *Chem. Soc. Rev.*, **2004**, *33*, 302

Definitions and Classifications

What is tandem catalysis?

Tandem catalysis: One-pot procedures involving multiple catalytic transformations.

• However, several other terms throughout the literature are used interchangeably with this definition, including:

- **Domino catalysis**
- **Cascade catalysis**
- **Multifunctional catalysis**
- **Multicomponent catalysis**
- **"One-Pot" reactions**

• Often these terms are also used to describe reactions wherein a single catalytic process is followed by a stoichiometric reaction.

1.) Fogg, D.; Santos, E. *Coord. Chem. Rev.*, **2004**, *248*, 2365

Definitions and Classifications

What is tandem catalysis?

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• Often these terms are also used to describe reactions wherein a single catalytic process is followed by a stoichiometric reaction.

"We reserve the term **Tandem catalysis** to describe coupled catalyses in which sequential transformation of the substrate occurs via two (or more) mechanistically distinct processes", with "all catalytic species - whether masked or apparent - present from the outset."¹

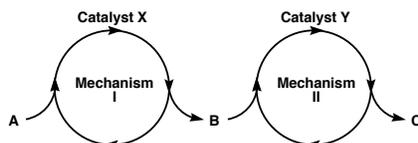
- Multiple catalytic transformations which directly involve the substrate
- Different mechanisms for each catalytic cycle
- All catalysts or precatalysts present from the beginning of the reaction

1.) Fogg, D.; Santos, E. *Coord. Chem. Rev.*, **2004**, *248*, 2365

Definitions and Classifications

Classes of Tandem Catalysis

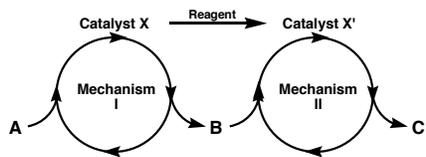
Orthogonal tandem catalysis: A subclass of tandem catalysis which involves two or more functionally distinct and (in principle) non-interfering catalysts or precatalysts. Often these catalytic mechanisms operate concurrently, though the substrate is transformed *sequentially*.



Auto-tandem catalysis: A subclass of tandem catalysis in which two or more mechanistically distinct reactions are promoted by a *single* catalyst. Both catalytic cycles occur spontaneously by cooperative interaction of species present from the outset of reaction, and no change in conditions is required to trigger the change in catalytic mechanism.



Assisted tandem catalysis: A subclass of tandem catalysis in which a change in reaction conditions (with the exclusion of catalyst addition) causes a shift from one catalytic mechanism toward a different mechanism. These transformations are not concurrent.



Fogg, D.; Santos, E. *Coord. Chem. Rev.*, **2004**, *248*, 2365

Why Use Tandem Catalysis?

Costs and Benefits

Advantages to using tandem catalysis:

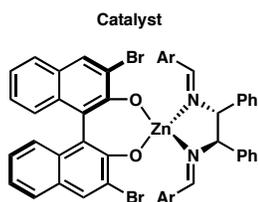
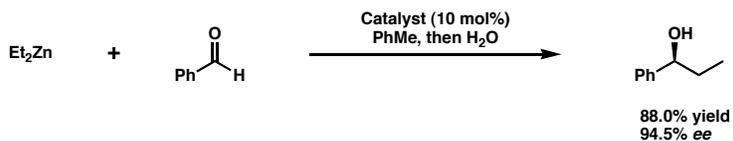
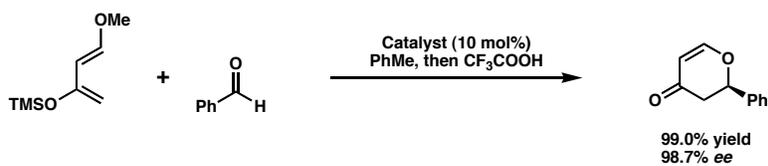
- Elimination of intermediate workup and isolation steps simplifies synthesis by saving both time and energy. Additionally, increased yields may result if intermediates are hard to isolate or purify.
- Catalyst efficiency is increased for cases of auto-tandem or assisted tandem catalysis.
- Process efficiency is increased for cases of auto-tandem or orthogonal catalysis.
- For orthogonal tandem and auto-tandem catalysis, high-energy intermediates from one catalytic cycle can be introduced into the next catalytic cycle before decomposition or transformation. This (potentially) allows for synthetic elaboration of normally unstable structures.

Disadvantages to using tandem catalysis:

- Orthogonal tandem catalysis often suffers from detrimental catalyst-catalyst interactions. Poisoning by another catalyst, or an undesired reactive intermediate, is very possible.
- Optimizing conditions for two simultaneous and distinct catalytic processes can be extremely difficult (with the exception of auto tandem catalysis).
- Assisted tandem catalysis suffers from low process efficiency.
- Catalyst recovery can be problematic.

Fogg, D.; Santos, E. *Coord. Chem. Rev.*, **2004**, *248*, 2365

Assisted Tandem Catalysis
Hetero Diels-Alder and Diethylzinc Addition

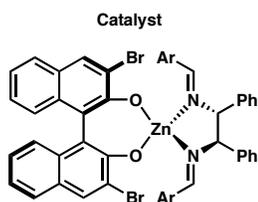
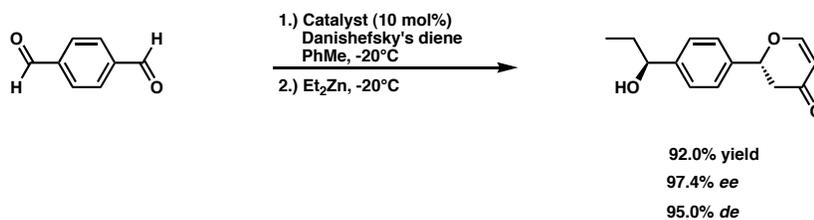


Ar = 2,4,6-Trimethylphenyl

- One catalyst was found to independently promote two different asymmetric reactions, starting from the same substrate.
- Added reagents alter the mechanism of catalytic action.
- Could this single catalyst be used to perform a desymmetrizing tandem catalytic reaction?

Ding, K. *Org. Lett.*, **2003**, *5*, 1091
Ding, K. *Org. Lett.*, **2002**, *4*, 4349

Assisted Tandem Catalysis
Hetero Diels-Alder and Diethylzinc Addition

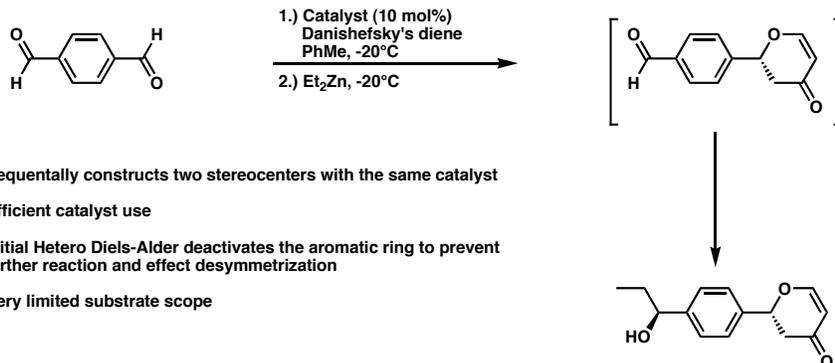


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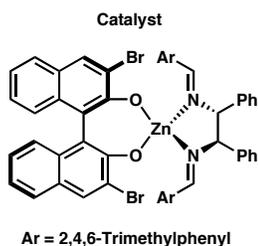
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Assisted Tandem Catalysis

Hetero Diels-Alder and Diethylzinc Addition



- Sequentially constructs two stereocenters with the same catalyst
- Efficient catalyst use
- Initial Hetero Diels-Alder deactivates the aromatic ring to prevent further reaction and effect desymmetrization
- Very limited substrate scope



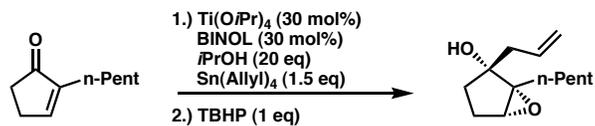
92.0% yield
 97.4% ee
 95.0% de

Ding, K. *Org. Lett.*, **2003**, *5*, 1091
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Assisted Tandem Catalysis

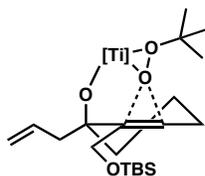
Titanium Catalyzed Tandem Reaction

- More elegant examples of tandem catalysis exploit the nature of the intermediate structure as well as the catalytic species.
- Simple addition of TBHP to an asymmetric titanium catalyzed allylation provides diastereoselective epoxidation of enones:



- The chiral alcohol generated in the first catalytic step directs epoxidation by the still-active titanium catalyst upon TBHP addition. Only one diastereomer is observed.

- After allylation, guided epoxidation occurs through the expected transition state.

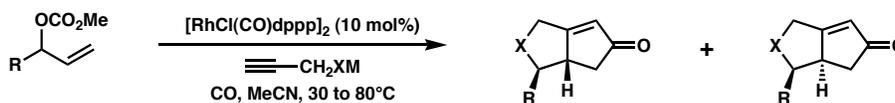


| Substrate | Product | Yield (%) | ee (%) |
|-----------|---------|-----------|--------|
| | | 72 | 94 |
| | | 84 | 96 |
| | | 89 | 95 |
| | | 88 | 88 |

- Walsh, P. *J. Am. Chem. Soc.*, **2004**, *126*, 12580

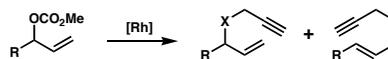
Assisted Tandem Catalysis Rhodium Catalyzed Cross-Coupling and Tandem Annulation

- Rhodium catalysts can be used for the coupling of allyl carbonates with electron deficient alkynes. Under an atmosphere of carbon monoxide, elevated temperatures initiate subsequent Pauson-Khand annulation.



| X | M | R | Yield | dr (<i>cis:trans</i>) |
|-------------------------------------|----|----|-------|-------------------------|
| (CO ₂ Me) ₂ C | Na | H | 82 | 5:1 |
| (CO ₂ Me) ₂ C | Na | Me | 80 | 6:1 |
| (CO ₂ Me) ₂ C | Na | Ph | 78 | 9:1 |
| TsN | Li | H | 79 | 3:1 |
| TsN | Li | Me | 84 | 6:1 |
| TsN | Li | Ph | 81 | 7:1 |

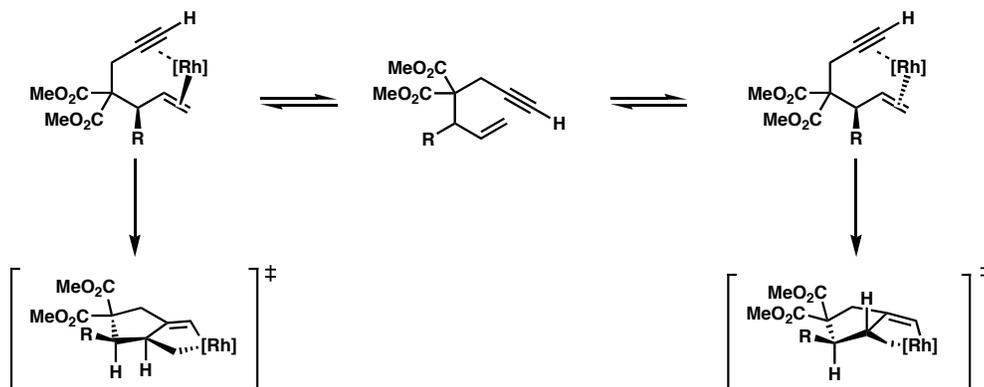
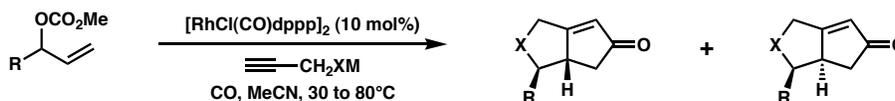
Note: Initial allylic alkylation results in two isomeric products, in a ratio greater than 12:1 favoring the terminal olefin.



Evans, P. A. *J. Am. Chem. Soc.*, **2001**, 123, 4609

Assisted Tandem Catalysis Rhodium Catalyzed Cross-Coupling and Tandem Annulation

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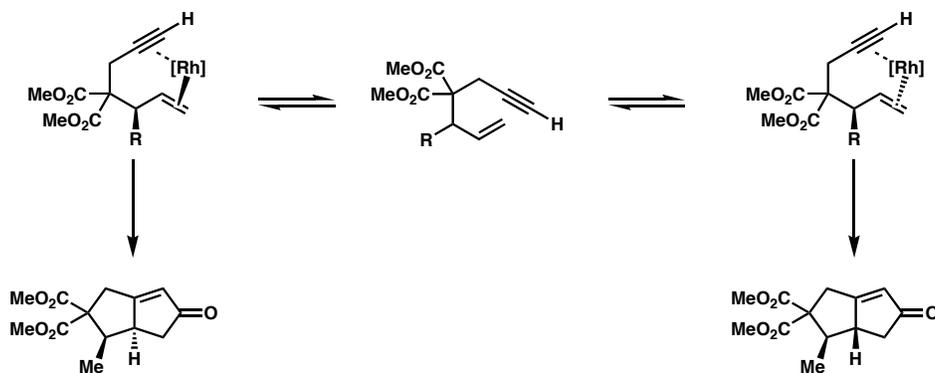
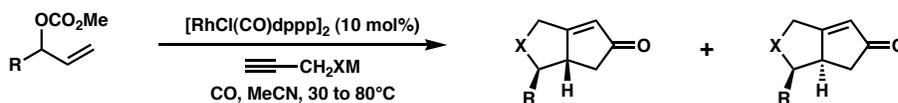


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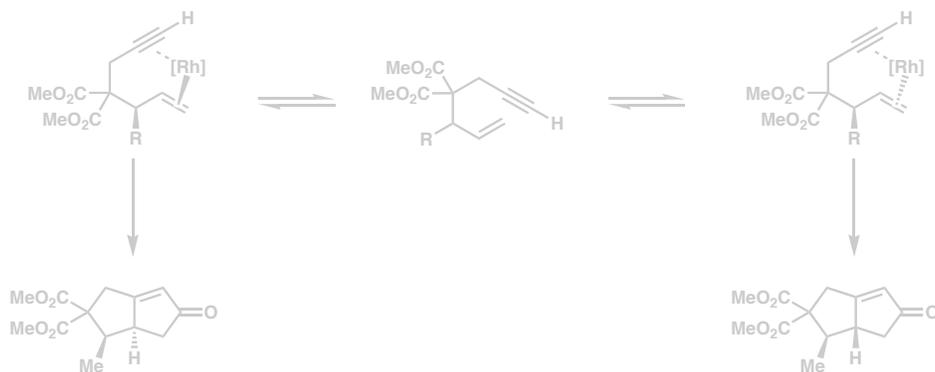
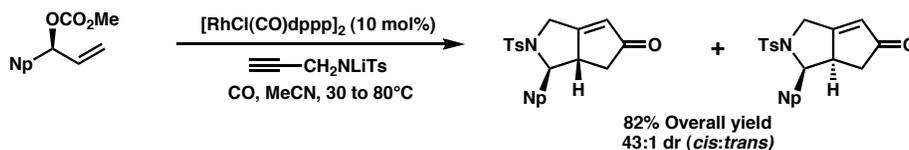


Evans, P. A. *J. Am. Chem. Soc.*, **2001**, 123, 4609

Assisted Tandem Catalysis

Rhodium Catalyzed Cross-Coupling and Tandem Annulation

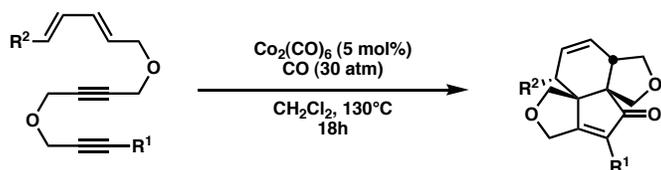
- Increasing the steric bulk at the C2 position favors formation of the *cis* isomer over the *trans* due to interaction with coordinating rhodium during the annulation step.



Evans, P. A. *J. Am. Chem. Soc.*, **2001**, 123, 4609

Auto Tandem Catalysis Cobalt Annulation and the Diels-Alder in Tandem

- Cobalt catalyzed Pauson-Khand reactions can be followed by cyclizations which are presumably promoted by the same metal:

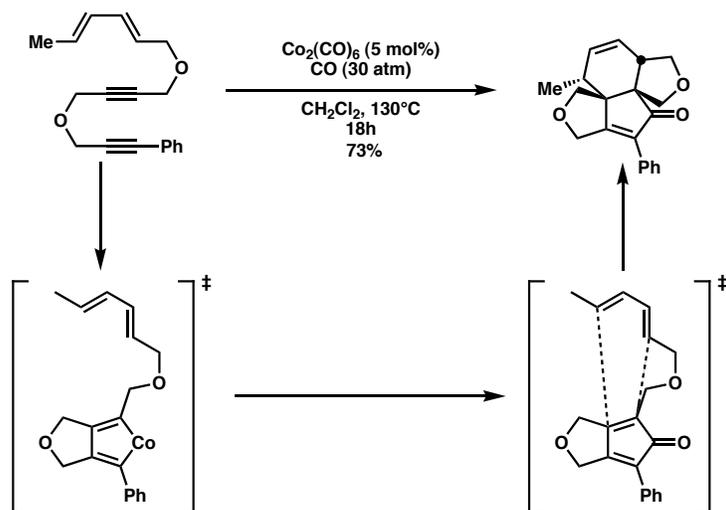


| R ¹ | R ² | Yield (%) |
|----------------|-----------------|-----------|
| Me | Me | 64 |
| Me | ⁿ Bu | 57 |
| Me | Ph | 73 |
| Ph | Ph | 52 |

Chung, Y. *Synlett*, 2005, 1889

Auto Tandem Catalysis Cobalt Annulation and the Diels-Alder in Tandem

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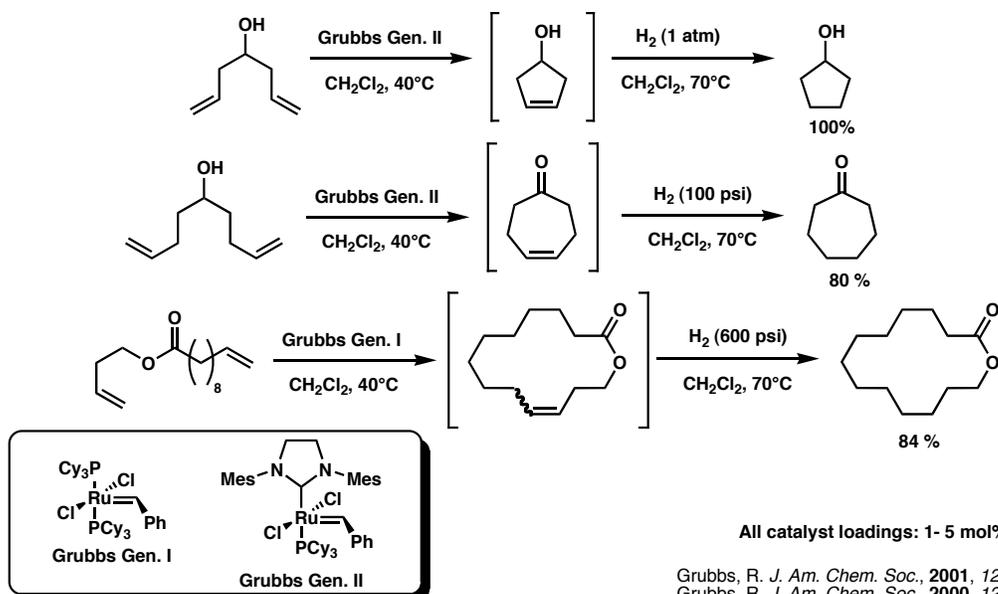


- Initial annulation provides an anti-aromatic intermediate after demetalation, which is subsequently cyclized.
- Auto-tandem (and orthogonal) processes can access thermodynamically unstable intermediates!

Chung, Y. *Synlett*, 2005, 1889

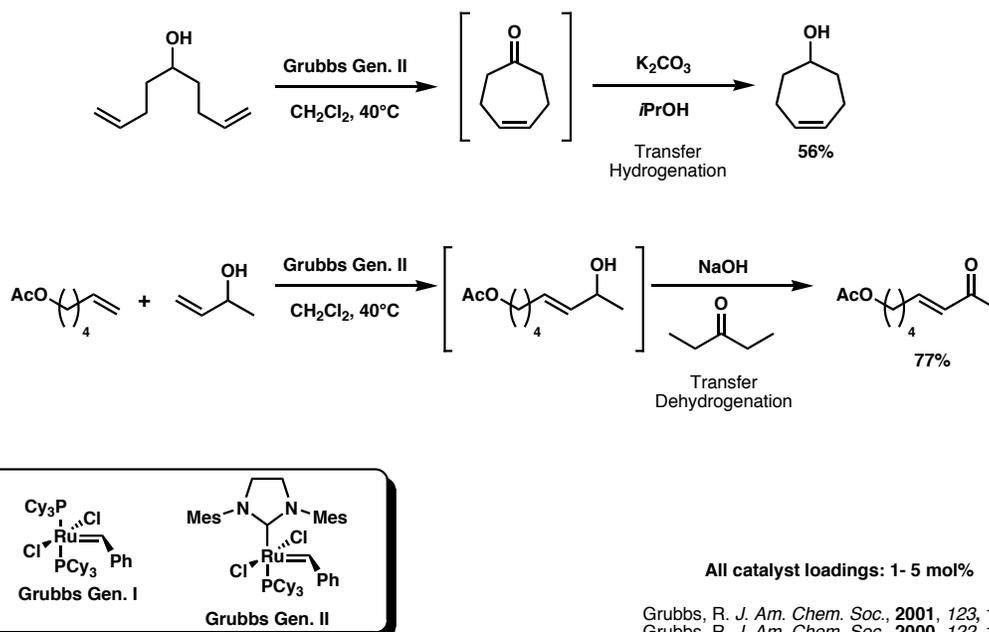
Assisted Tandem Catalysis Metathesis and Tandem Catalysis

- Metathesis reactions performed with either generation Grubbs catalyst can be followed by subsequent hydrogenation.
- By placing an RCM reaction under an atmosphere of hydrogen, the function of the Grubbs catalysts can be altered.



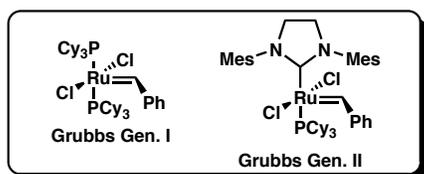
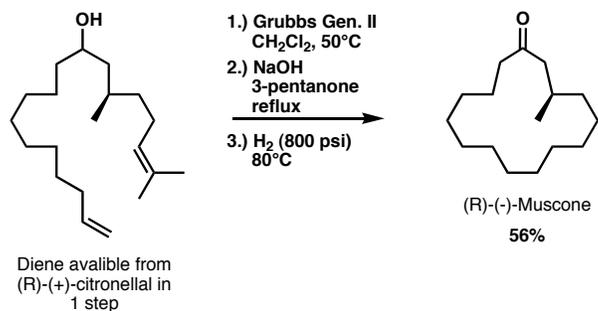
Assisted Tandem Catalysis Metathesis and Tandem Catalysis

- Transfer hydrogenation and transfer dehydrogenation are also possible, provided that suitable hydrogen donors or acceptors are added to the reaction after metathesis is complete.



Assisted Tandem Catalysis Metathesis and Tandem Catalysis

- Grubbs ruthenium catalysts can be sequentially "tuned" and change reactivity based on the order of added reagents.
- Total synthesis of (R)-(-)-Muscone:

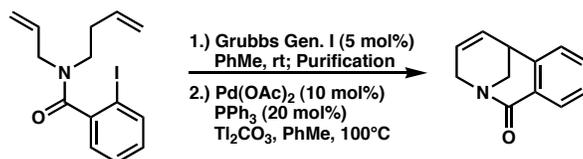


All catalyst loadings: 1- 5 mol%

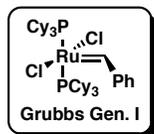
Grubbs, R. *J. Am. Chem. Soc.*, **2001**, *123*, 11312
Grubbs, R. *J. Am. Chem. Soc.*, **2000**, *122*, 12872

Assisted Tandem Catalysis Metathesis Plus Palladium Catalysis

- Tandem metathesis-Heck reaction illustrates the difficulties of orthogonal catalysis...



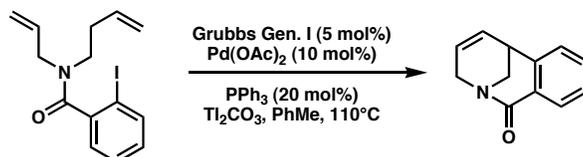
| Technique | Yield (%) |
|-------------------------------------|-----------|
| Sequential (Intermediate isolation) | 48 |



Grigg, R. *Tet. Lett.*, **2000**, *41*, 7255
Grigg, R. *Tet. Lett.*, **1998**, *39*, 4139

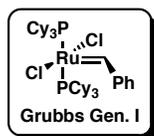
Assisted Tandem Catalysis Metathesis Plus Palladium Catalysis

- Tandem metathesis-Heck reaction illustrates the difficulties of orthogonal catalysis...



- Addition of both catalysts and all reagents simultaneously gave much lower yields than observed for sequential reactions.
- Further study indicated that both the palladium species and phosphine ligands used in the Heck reaction poison the ruthenium catalyst and halt metathesis.

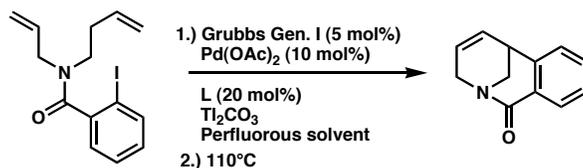
| Technique | Yield (%) |
|-------------------------------------|-----------|
| Sequential (Intermediate isolation) | 48 |
| Simultaneous (Orthogonal) | 22 |



Grigg, R. *Tet. Lett.*, **2000**, 41, 7255
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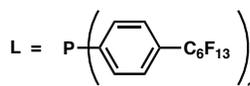
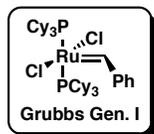
Assisted Tandem Catalysis Metathesis Plus Palladium Catalysis

- Tandem metathesis-Heck reaction illustrates the difficulties of orthogonal catalysis... and a solution in assisted catalysis.



- Ruthenium poisoning was circumvented by sequestering palladium in a perfluorous solvent phase.
- Heating to the temperature required for Heck reaction caused the reaction to turn monophasic. Reaction did not occur at the interphase boundary.

| Technique | Yield (%) |
|-------------------------------------|-----------|
| Sequential (Intermediate isolation) | 48 |
| Simultaneous (Orthogonal) | 22 |
| Perfluorous Biphasic (Assisted) | 67 |

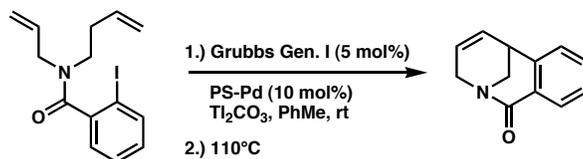


Perfluorous solvent = PhMe : Hex : C₆F₁₁(CF₃) (2:2:3)

Grigg, R. *Tet. Lett.*, **2000**, 41, 7255
 Grigg, R. *Tet. Lett.*, **1998**, 39, 4139

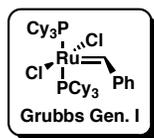
Assisted Tandem Catalysis Metathesis Plus Palladium Catalysis

- Tandem metathesis-Heck reaction illustrates the difficulties of orthogonal catalysis... and a solution in assisted catalysis.



- Polymer swelling at room temperature is insufficient to allow exposure of bound palladium. Upon heating to 110°C, swelling increases, and Heck reaction can proceed.
- This procedure provides benefits over the sequential approach, but is it truly tandem catalysis...?

| Technique | Yield (%) |
|-------------------------------------|-----------|
| Sequential (Intermediate isolation) | 48 |
| Simultaneous (Orthogonal) | 22 |
| Perfluorous Biphasic (Assisted) | 67 |
| Polystyrene bound Pd (Assisted) | 73 |

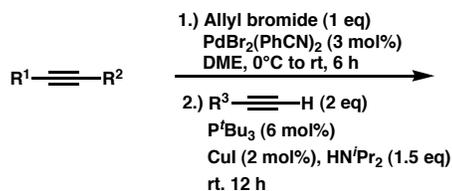


PS-Pd: Polystyrene bound palladium catalyst

Grigg, R. *Tet. Lett.*, **2000**, *41*, 7255
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Assisted Tandem Catalysis Palladium: Versatile Assisted Catalysis

- Palladium's ability to catalyze reactions as both Pd(II) and Pd(0) make it an excellent candidate for assisted catalysis.
- *In situ* reduction of Pd(II) by introduction of appropriate ligands can effectively initiate a new, separate reaction.

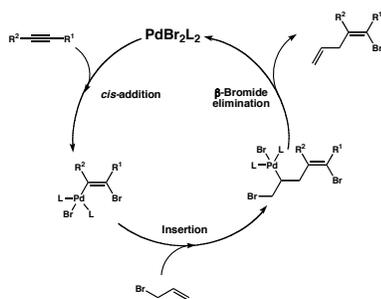
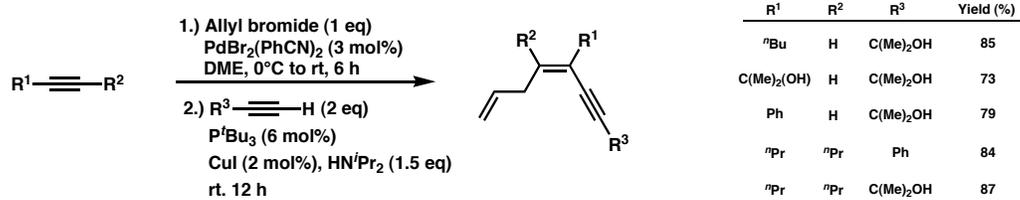


| R ¹ | R ² | R ³ | Yield (%) |
|-----------------------|-----------------|-----------------------|-----------|
| ⁿ Bu | H | C(Me) ₂ OH | 85 |
| C(Me) ₂ OH | H | C(Me) ₂ OH | 73 |
| Ph | H | C(Me) ₂ OH | 79 |
| ⁿ Pr | ⁿ Pr | Ph | 84 |
| ⁿ Pr | ⁿ Pr | C(Me) ₂ OH | 87 |

Rawal, V. *Org. Lett.*, **2002**, *4*, 4321
Rawal, V. *Org. Lett.*, **2002**, *4*, 4317

Assisted Tandem Catalysis Palladium: Versatile Assisted Catalysis

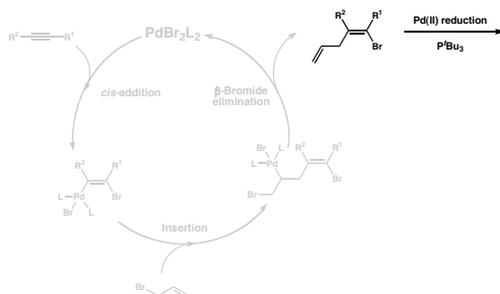
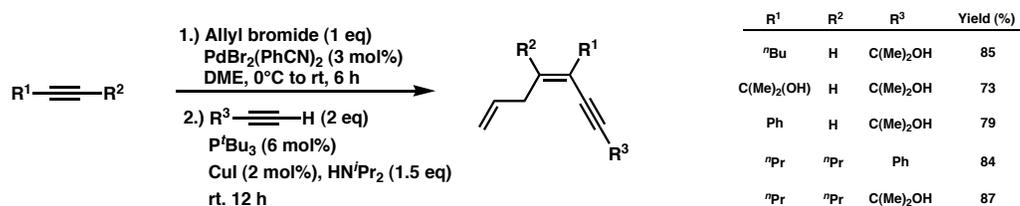
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Assisted Tandem Catalysis Palladium: Versatile Assisted Catalysis

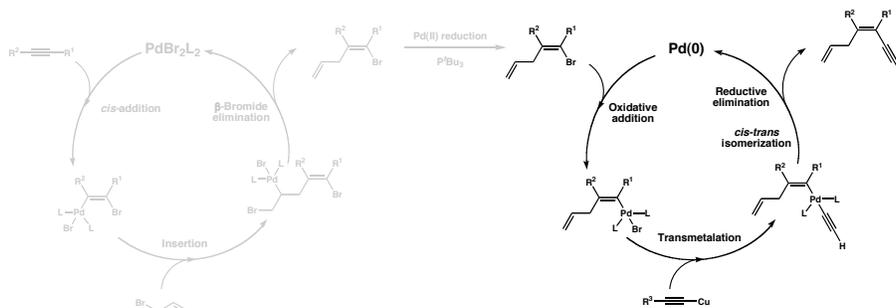
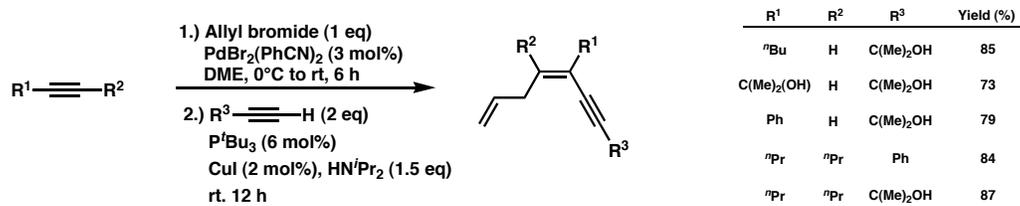
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Assisted Tandem Catalysis Palladium: Versatile Assisted Catalysis

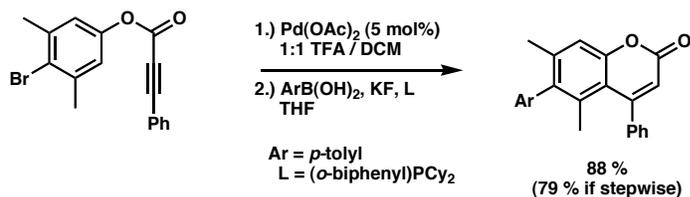
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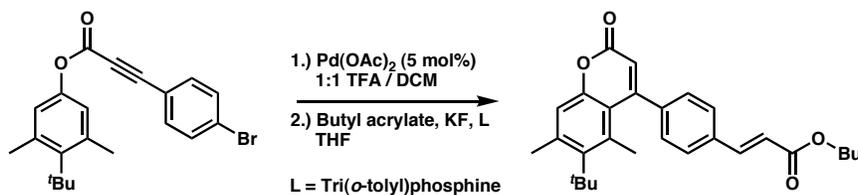
Rawal, V. *Org. Lett.*, 2002, 4, 4321
 Rawal, V. *Org. Lett.*, 2002, 4, 4317

Assisted Tandem Catalysis Palladium: Versatile Assisted Catalysis

- Because Pd(II) does not readily undergo oxidative addition, its chemistry can be exploited in the presence of vinyl or aryl halides. Subsequent reduction by addition of appropriate ligands can then initiate cross coupling reactions.



- Catalysts don't always 'die' after completion of a reaction! This kind of palladium reduction allows access to other Pd(0) based transformations, including the Heck reaction.

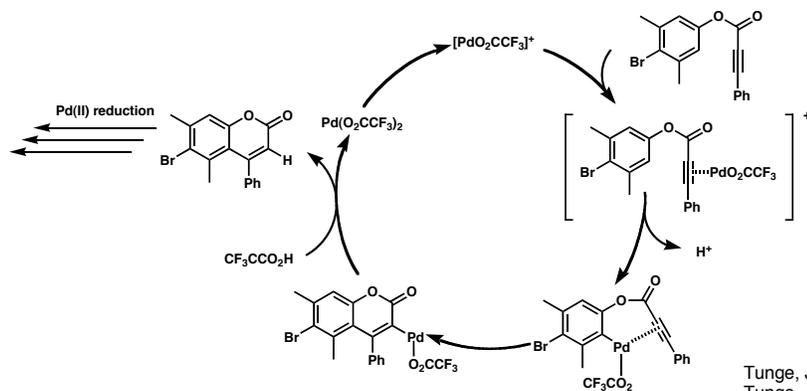
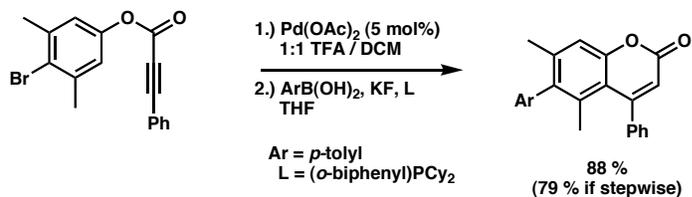


Tunge, J. *JOC*, 2005, 70, 6515
 Tunge, J. *JOC*, 2000, 65, 7519

Assisted Tandem Catalysis

Palladium: Versatile Assisted Catalysis

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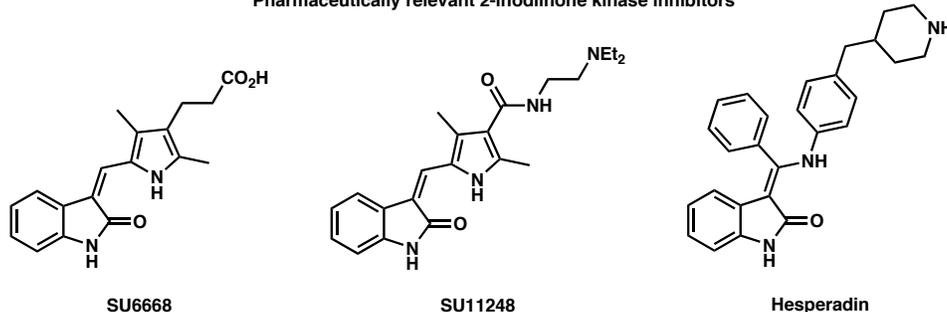


Auto Tandem Catalysis

Palladium: Versatile Tandem Catalysis

- 2-Indolinone systems bearing an exocyclic methylene at the 3 position have become desirable targets in the pharmaceutical industry. Very few display differentially disubstituted exocyclic methylenes.

Pharmaceutically relevant 2-indolinone kinase inhibitors

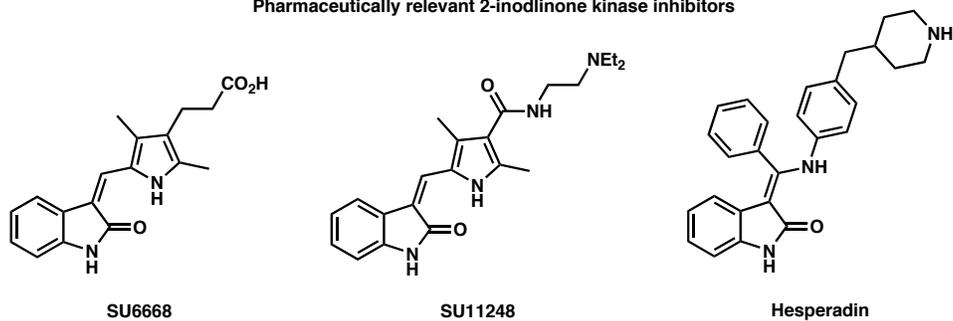


Auto Tandem Catalysis
Palladium: Versatile Tandem Catalysis



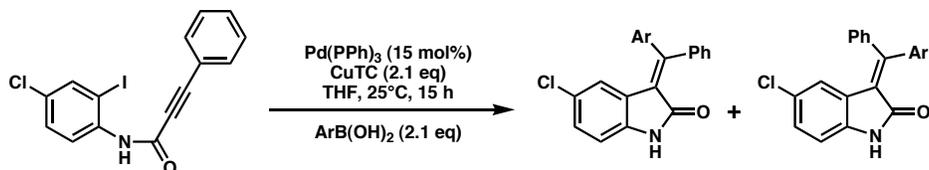
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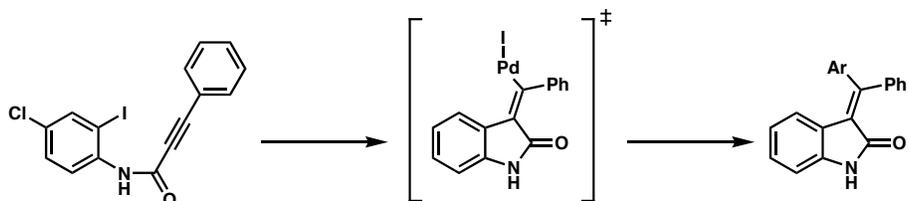


Player, M. *J. Org. Chem.* 2005, 3741

Auto Tandem Catalysis
Palladium: Versatile Tandem Catalysis

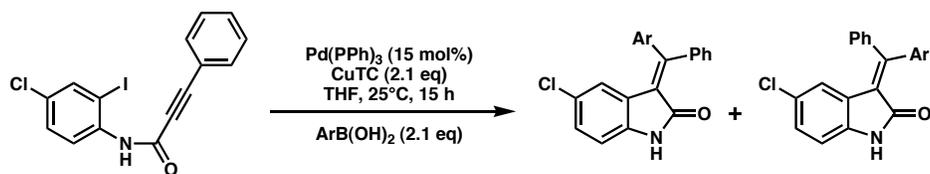


- 2-Indolinone systems bearing an exocyclic methylene at the 3 position have become desirable targets in the pharmaceutical industry. Very few display differentially disubstituted exocyclic methylenes.
- Use of a tandem Heck-Suzuki reaction provides for high levels of (*E*) selectivity, via transmetalation of the palladium alkyne insertion intermediate.



Player, M. *J. Org. Chem.* 2005, 3741

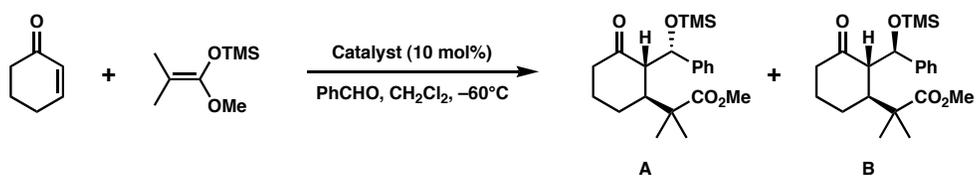
Auto Tandem Catalysis
Palladium: Versatile Tandem Catalysis



| ArB(OH) ₂ | Yield (%) | Isomeric ratio (E:Z) | ArB(OH) ₂ | Yield (%) | Isomeric ratio (E:Z) |
|----------------------|-----------|----------------------|----------------------|-----------|----------------------|
| | 96 | (E)-isomer | | 80 | (E)-isomer |
| | 91 | (E)-isomer | | 85 | 15:1 |
| | 93 | (E)-isomer | | 83 | 13:1 |
| | 82 | (E)-isomer | | 87 | 25:1 |

Player, M. *J. Org. Chem.* **2005**, 3741

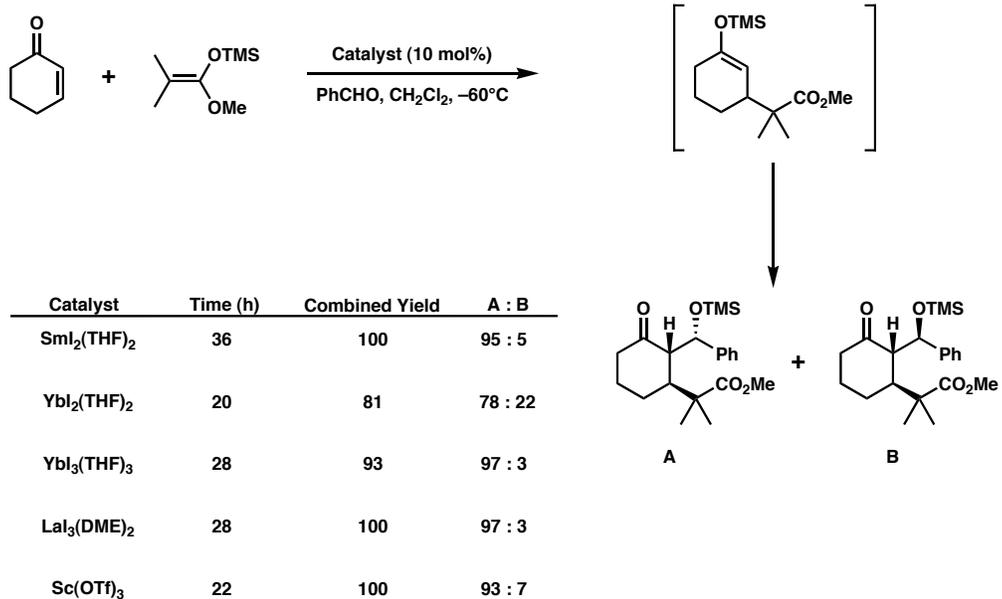
Auto-Tandem Catalysis
Tandem Mukaiyama Micheal - Aldol Reactions



| Catalyst | Time (h) | Combined Yield | A : B |
|-------------------------------------|----------|----------------|---------|
| SmI ₂ (THF) ₂ | 36 | 100 | 95 : 5 |
| YbI ₂ (THF) ₂ | 20 | 81 | 78 : 22 |
| YbI ₃ (THF) ₃ | 28 | 93 | 97 : 3 |
| LaI ₃ (DME) ₂ | 28 | 100 | 97 : 3 |
| Sc(OTf) ₃ | 22 | 100 | 93 : 7 |

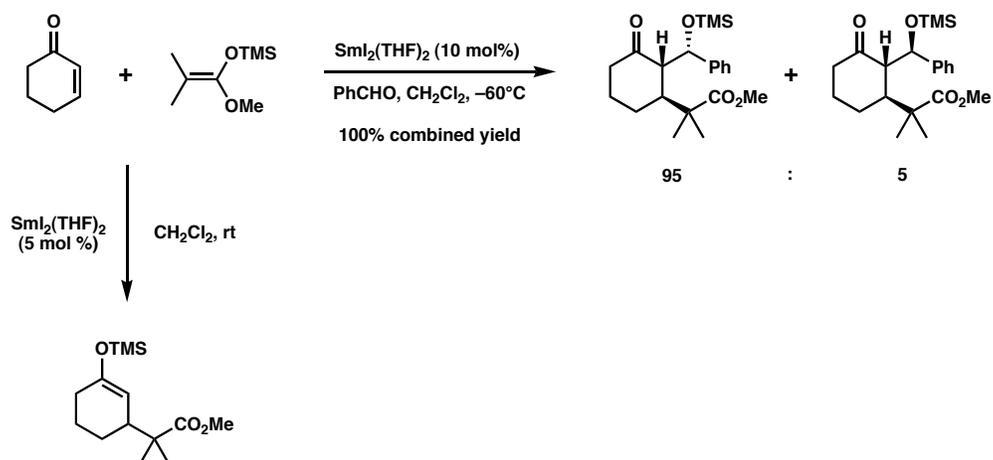
Collin, J. *Tetrahedron* **2001**, 57, 8989
Collin, J. *Tet. Lett.* **1993**, 34, 3881

Auto-Tandem Catalysis
Tandem Mukaiyama Micheal - Aldol Reactions



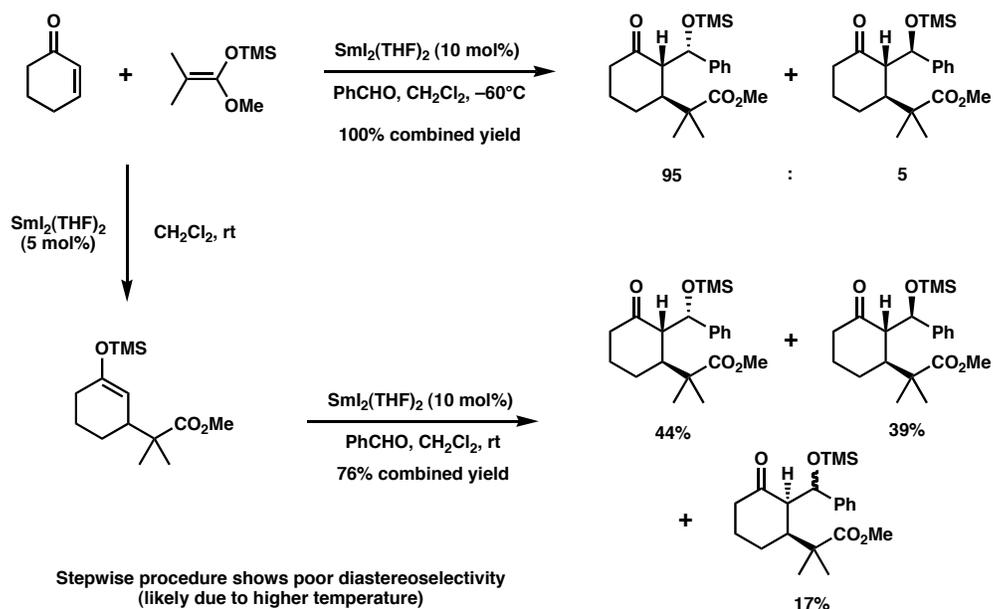
Collin, J. *Tetrahedron* **2001**, *57*, 8989
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Auto-Tandem Catalysis
Tandem Mukaiyama Micheal - Aldol Reactions



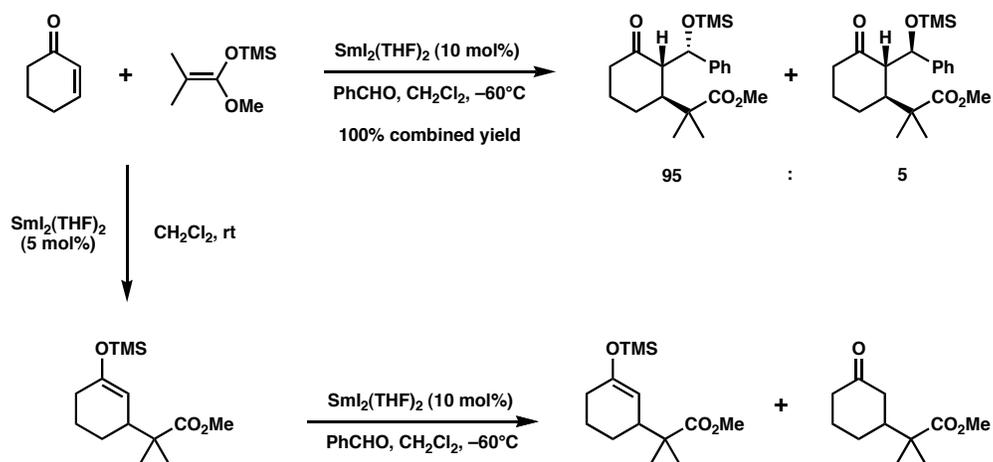
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Auto-Tandem Catalysis
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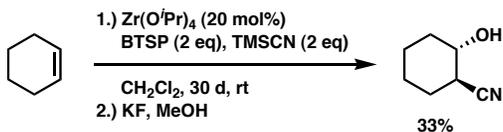


Collin, J. *Tetrahedron* **2001**, *57*, 8989
Collin, J. *Tet. Lett.* **1993**, *34*, 3881

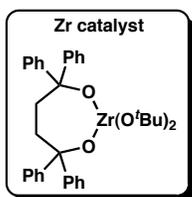
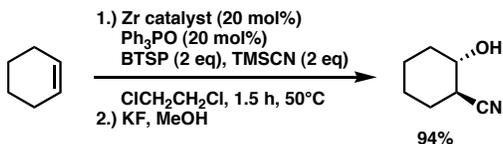
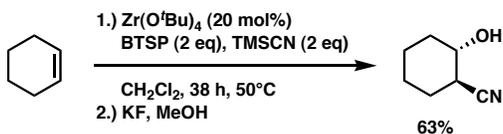
Auto Tandem Catalysis

An Illustration of Auto Tandem Benefits

- Zirconium catalyzed cyanohydrin formation was initially found to be sluggish and ineffective:



- Tuning the catalytic conditions allowed for increased yields and reduced reaction times:



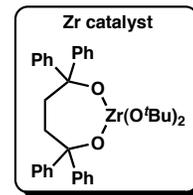
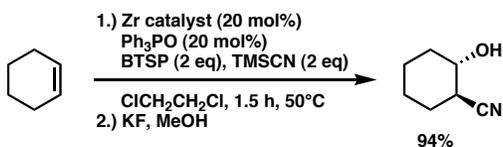
- Auto tandem catalysis conditions can be rationally optimized to accommodate both reaction mechanisms.

Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 1256

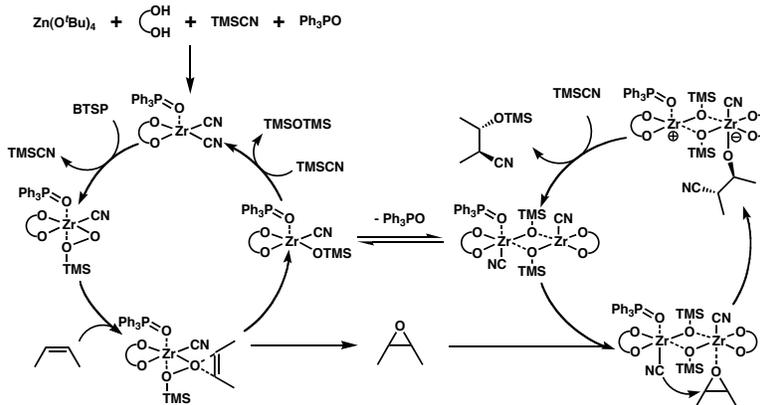
Auto Tandem Catalysis

An Illustration of Auto Tandem Benefits

- Optimized conditions allow both catalytic mechanisms to function together:



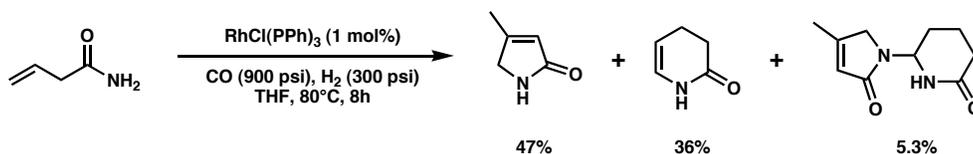
- Rate studies revealed a first-order dependency upon the catalyst concentration for epoxide formation, and a second order dependency for epoxide opening.



Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 1256

Auto Tandem Catalysis Hydrocarbonylation and Cross Coupling by Rhodium

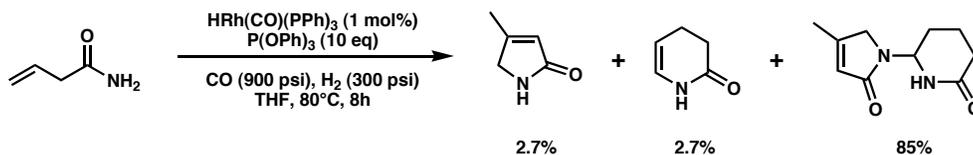
- Attempts to investigate amide directed hydrocarbonylation of olefins gave an unexpected heterodimer.
- Neither homodimer was observed, nor the isomeric heterodimer.



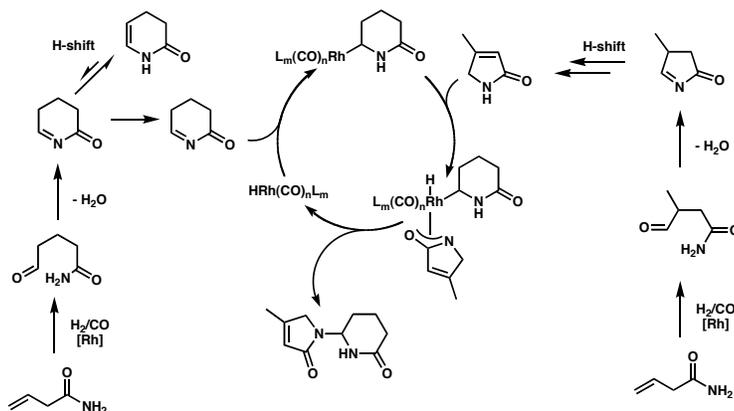
Ojima, I. *J. Org. Chem.*, **1991**, 56, 2024

Auto Tandem Catalysis Hydrocarbonylation and Cross Coupling by Rhodium

- Attempts to investigate amide directed hydrocarbonylation of olefins gave an unexpected heterodimer.
- Neither homodimer was observed, nor the isomeric heterodimer.



- Attempts to thermally couple the dihydropyridinone and the pyrrolone failed.
- Coupling also failed in the absence of either H₂ or CO.
- Rhodium catalyzes both hydrocarbonylation events, as well as the coupling reaction.

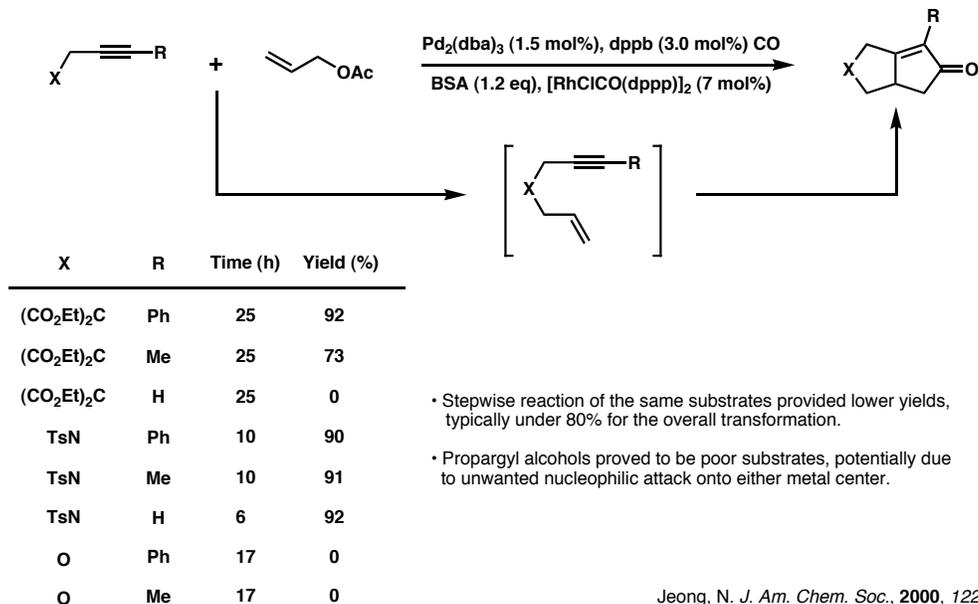


Ojima, I. *J. Org. Chem.*, **1991**, 56, 2024

Orthogonal Tandem Catalysis

Palladium Catalyzed Alkylation and Rhodium Catalyzed Annulation

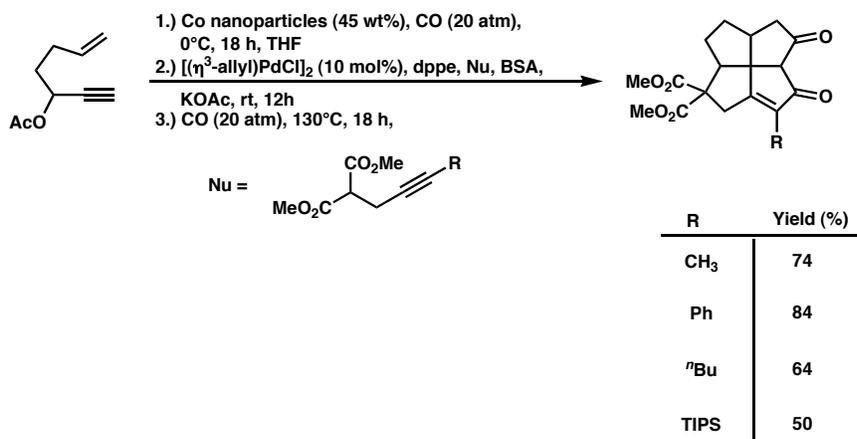
- In addition to the assisted and auto-tandem catalytic methods for alkylation / annulation couples, orthogonal methods also exist.
- Initial palladium cross-coupling provides suitable ene-yne substrates for Pauson-Khand annulation.
- Both palladium and rhodium catalysts coexist under the same reaction conditions throughout the entire process.



Assisted Tandem Catalysis

Cobalt Annulation and Palladium Alkylation in Tandem

- Cobalt catalyzed Pauson-Khand annulation of ene-yne can produce substrates suitable for Pd(II) catalyzed allylic alkylation. Alkylation products can then undergo an additional Pauson-Khand in the presence of carbon monoxide.
- Rapid construction of tetracyclic fenestranes from acyclic starting materials:

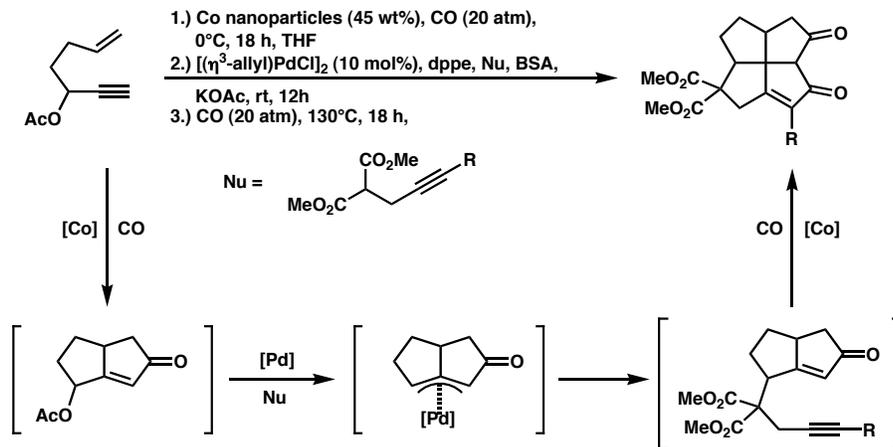


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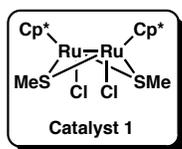
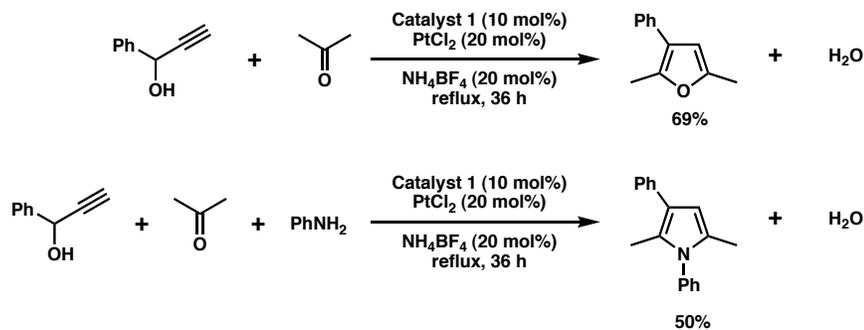


• Though this is a three-step "one-pot" process, only the final two steps are tandem catalytic.

Chung, Y. *J. Am. Chem. Soc.*, **2002**, *124*, 6838

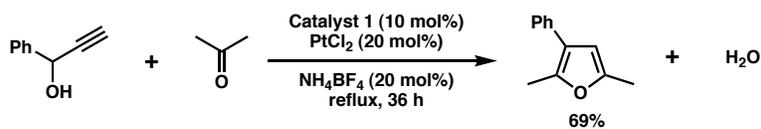
Orthogonal Tandem Catalysis

Ruthenium and Platinum Catalyzed Heterocycle Formation

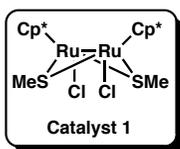
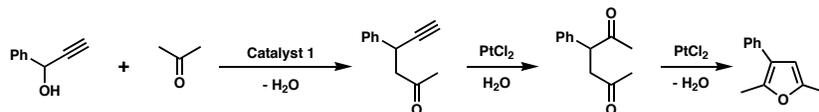


Hidai, M.; Uemura, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 2681
Nishibayashi, Y.; Uemura, S. *Chem. Commun.* **2004**, 2712

Orthogonal Tandem Catalysis
Ruthenium and Platinum Catalyzed Heterocycle Formation

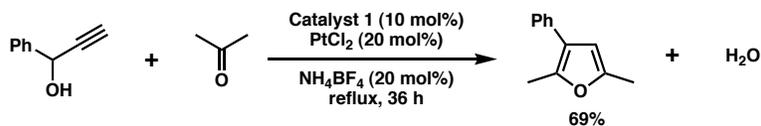


• Propargylic substitution catalyzed by a thiolate bridged diruthenium complex is followed by platinum catalyzed hydration and intramolecular cyclization.

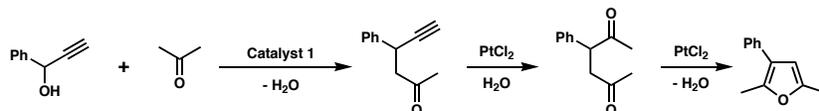


Hidai, M.; Uemura, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 2681
Nishibayashi, Y.; Uemura, S. *Chem. Commun.* **2004**, 2712

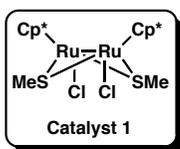
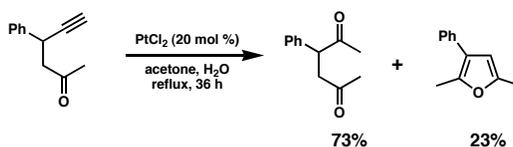
Orthogonal Tandem Catalysis
Ruthenium and Platinum Catalyzed Heterocycle Formation



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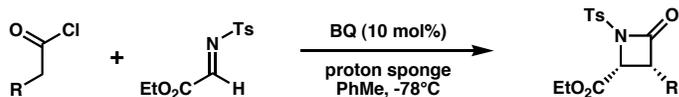
• Isolation of the intermediate alkyne followed by exposure to PtCl₂ to effect stepwise transformation showed lower yields. This implies that the coexistence of Catalyst 1 and PtCl₂ is actually *beneficial* to the reaction.



Hidai, M.; Uemura, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 2681
Nishibayashi, Y.; Uemura, S. *Chem. Commun.* **2004**, 2712

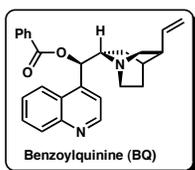
Orthogonal Tandem Catalysis Concurrent Construction of β -Lactams

- Benzylquinine catalyzes the addition of ketenes into appropriate imines, but yields are typically low.



- Under conditions of nucleophilic catalysis, the ketene undergoes dimerization, thus preventing β -lactam formation.

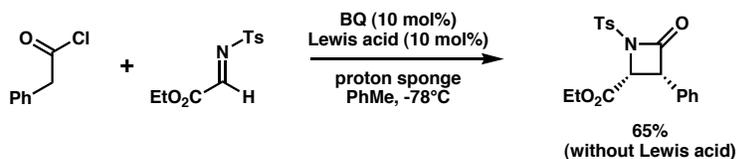
| R | Yield (%) | ee (%) | dr (<i>cis:trans</i>) |
|-----|-----------|--------|-------------------------|
| Ph | 65 | 96 | 99:1 |
| OPh | 45 | 99 | 99:1 |
| OAc | 56 | 98 | 99:1 |
| OBn | 56 | 95 | 99:1 |



Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206
 Lectka, T. *Org. Lett.* **2002**, *4*, 1603
 Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831

Orthogonal Tandem Catalysis Concurrent Construction of β -Lactams

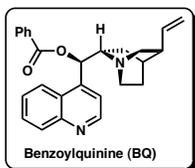
- Addition of an appropriate Lewis acid catalyst was expected to activate the imine:



- Most Lewis acids added actually decreased the observed yield.
- Lewis acids interaction with benzylquinine impedes catalysis by either.



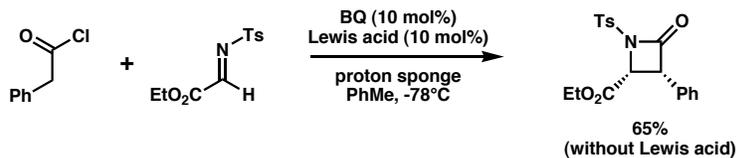
| Lewis acid | Yield (%) |
|----------------------|-----------|
| Cu(OTf) ₂ | 35 |
| Mg(OTf) ₂ | 36 |
| Sn(OTf) ₂ | 44 |
| Sm(OTf) ₃ | 45 |
| Yb(OTf) ₃ | 50 |



Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206
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Orthogonal Tandem Catalysis Concurrent Construction of β -Lactams

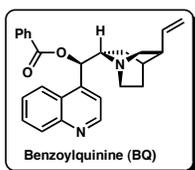
- Addition of an appropriate Lewis acid catalyst was expected to activate the imine:



- Most Lewis acids added actually decreased the observed yield.
- Lewis acids interaction with benzoylquinine prevents impedes catalysis by either.



- Certain lanthanide and pseudolanthanide triflates exhibit lower affinity to bind the organocatalyst, and are characterized by fast "on/off" rates.

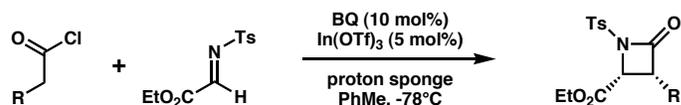


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| Cu(OTf) ₂ | 35 |
| Mg(OTf) ₂ | 36 |
| Sn(OTf) ₂ | 44 |
| Sm(OTf) ₃ | 45 |
| Yb(OTf) ₃ | 50 |
| La(OTf) ₃ | 63 |
| Al(OTf) ₃ | 78 |
| Sc(OTf) ₃ | 80 |
| In(OTf) ₃ | 95 |

Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206
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 Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831

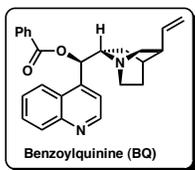
Orthogonal Tandem Catalysis Concurrent Construction of β -Lactams

- Addition of an appropriate Lewis acid catalyst was employed to activate the imine:



- Orthogonal catalysis by indium(III) triflate and benzoylquinine together provide higher yields than either catalyst alone.

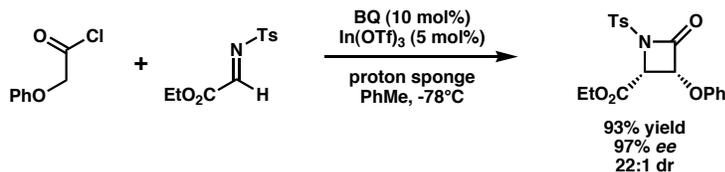
| R | Yield (%) Without In(OTf) ₃ | Yield (%) With In(OTf) ₃ | ee (%) | dr (cis:trans) |
|---------------------|---|--|--------|----------------|
| Ph | 65 | 95 | 98 | 60:1 |
| Bn | 60 | 94 | 98 | 9:1 |
| OPh | 45 | 93 | 97 | 22:1 |
| OAc | 56 | 98 | 98 | 34:1 |
| CH ₂ OPh | 53 | 93 | 96 | 12:1 |
| OBn | 56 | 98 | 96 | 11:1 |



Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206
 Lectka, T. *Org. Lett.* **2002**, *4*, 1603
 Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831

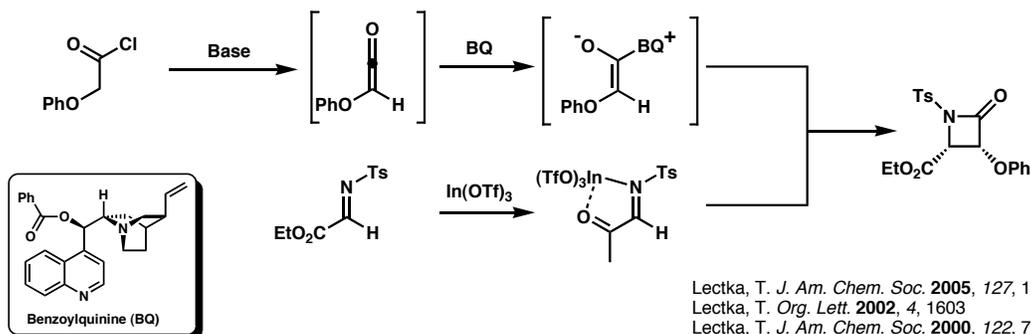
Orthogonal Tandem Catalysis Concurrent Construction of β -Lactams

- Addition of an appropriate Lewis acid catalyst was employed to activate the imine:



- Ketene generation followed by nucleophilic addition generates an acylammonium enolate which adds into the Lewis acid activated imine.

- Indium was found to be the most efficient Lewis acid. Other Lewis acid species simply bind to benzoylquinine, thus preventing nucleophilic catalysis.



Tandem Catalysis Summary and Conclusions

- **Tandem catalysis provides a rapid pathway toward synthetic elaboration:**

- All tandem catalytic processes save time and energy by eliminating workup and purification problems, sometimes increasing isolated yield as a result.
- Auto tandem catalysis and assisted tandem catalysis both maximize the use of the catalyst species.
- Orthogonal tandem catalysis and auto tandem catalysis have the potential to exploit high-energy intermediates.

- **Tandem catalysis is still new:**

- Concurrent tandem catalysis often suffers from unwanted detrimental interactions between catalysts. They can be difficult to design and problematic to optimize.
- Catalyst recovery for assisted tandem and orthogonal tandem catalysis can be difficult.
- Assisted tandem catalysis is operationally inefficient compared to auto and orthogonal cases.

