Ischia Advanced School of Organic Chemistry
IASOC 2012, Ischia, Naples

Palladium-catalyzed Domino Processes: Serendipity and Rational Design

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Reaction Discovery: Rational Design and Serendipity

Rational design: Working hypothesis, knowledge-based

Experimental Observation ↓ ↑ Understanding of reaction
Re-design (rational?)

Serendipity: Unexpected results, accidental discovery

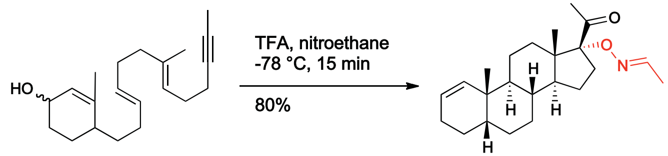
Domino Process in Organic Synthesis

Domino process: a combination of two or more bond-forming reactions under identical conditions *wherein the subsequent reactions result as a consequence of the functionality formed in the previous step*.

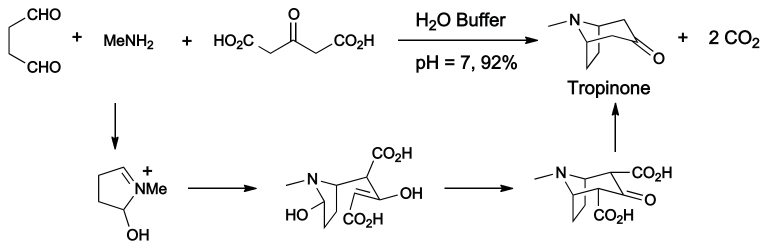
Could be: Uni-molecular (Intramolecular), Bi-molecular and Multi-component

a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136;
b) *Domino Reactions in Organic Synthesis*; L. F. Tietze, G. Brasche, K. Gericke, Eds.; Wiley-VCH, Weinheim, **2006**.
c) In natural product synthesis: Nicolaou, K. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134--7186.

Domino Reactions in Natural Products Syntheses: Classical Examples:

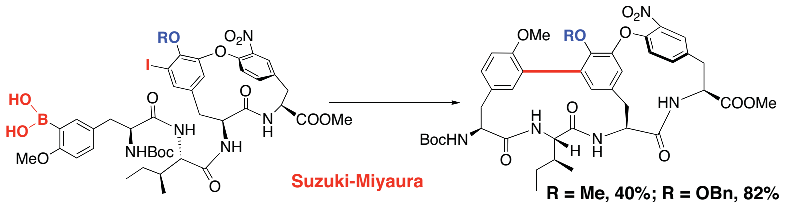


Johnson, W. S. *J. Am. Chem. Soc.*, **1973**, *95*, 4417

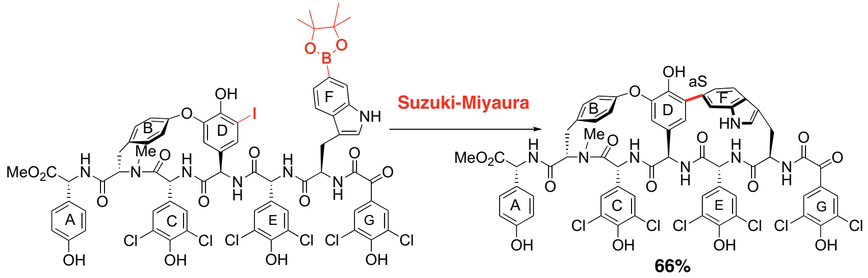


R. Robinson, *J. Chem. Soc.* **1917**, *111*, 762-768.

Intramolecular Suzuki-Miyaura Reaction

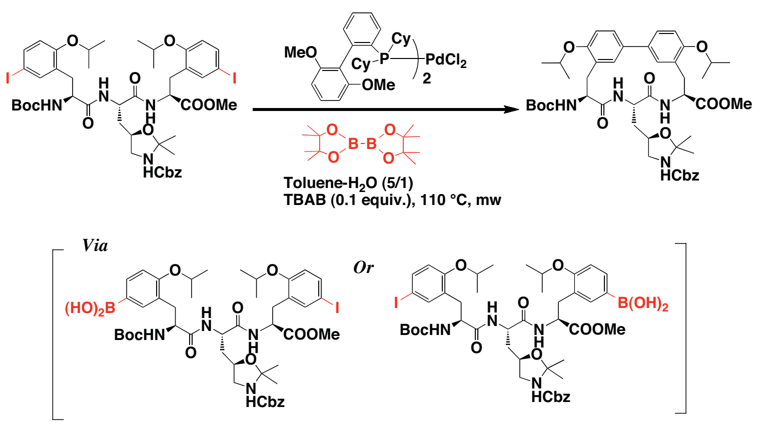


M. Bois-Choussy, P. Cristau, J. Zhu, *Angew. Chem. Int. Ed.* **2003**, 42, 4238-4241.



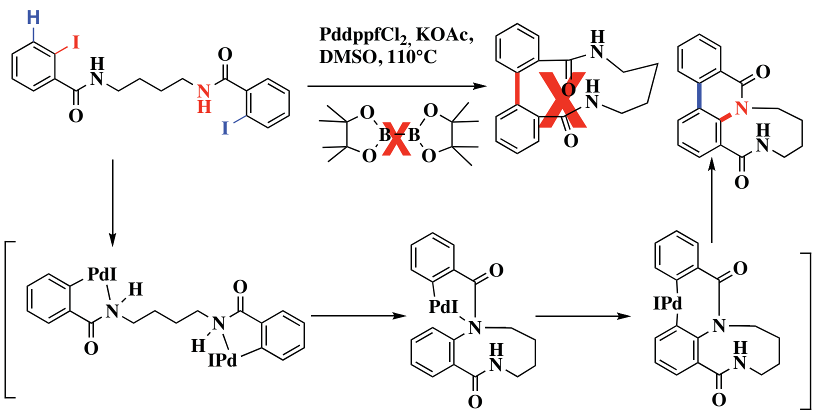
Y. Jia, M. Bois-Choussy, J. Zhu, *Angew. Chem. Int. Ed.* **2008**, *47*, 4167-4172.
Wang, Z. H.; Bois-Choussy, M.; Jia, Y.-X.; Zhu, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 2018-2022.

Total Synthesis of Biphenomycin B



Carbonelle, A.-C.; Zhu, J. *Org. Lett.* **2000**, *2*, 3477-3480; R. Lépine, J. Zhu, *Org. Lett.* **2005**, *7*, 2981-2984.
For application in diazonamide synthesis, see MacMillan, D. W. C. *Chem. Sci.* **2011**, *2*, 308-311.

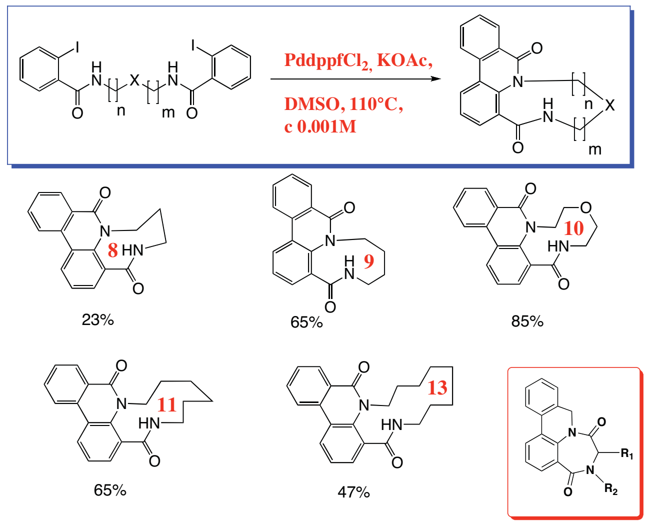
Palladium-Catalyzed Domino Process: Serentipity



Cuny, G.; Bois-Choussy, M.; Zhu, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 4774-4777.

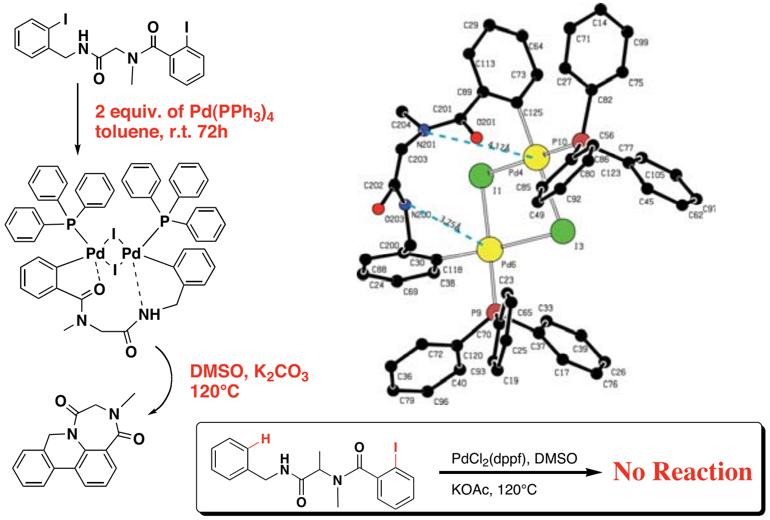
Rewiews on Domino process: L. Tietze, et al. *Chem. Rev.* **1996**, *96*, 115-136.
M. Lautens,et al. *Chem. Rev.* **2007**, *107*, 174-238.

Azaphenethrene Fused Macrocycle by Domino Intramolecular N-Arylation/C-H Functionalization



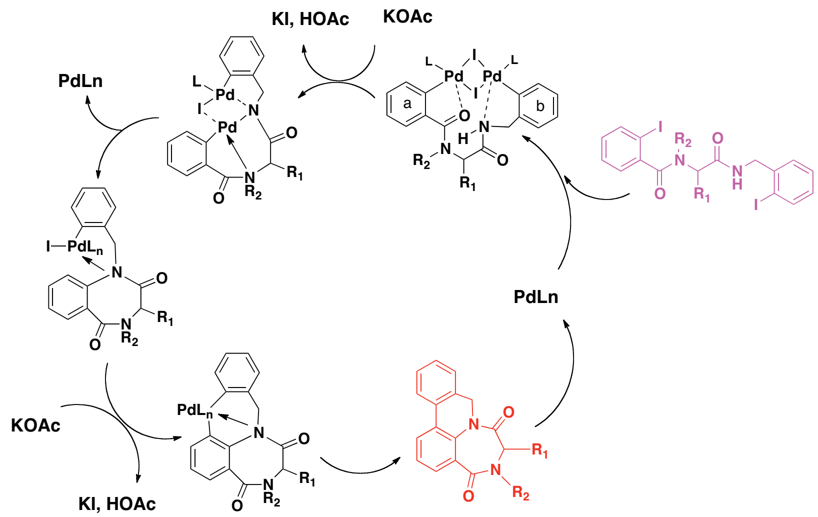
Cuny, G.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2004**, *126*, 14474-14484

Preparation and Isolation of a Bis-Palladacycle



Salcedo, A.; Neuville, L.; Rondot, C.; Retailleau, P.; Zhu, J. *Org. Lett.* **2008**, *10*, 857-860.
Cuny, G.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2004**, *126*, 14474-14484

Proposed Mechanism for the Domino Process



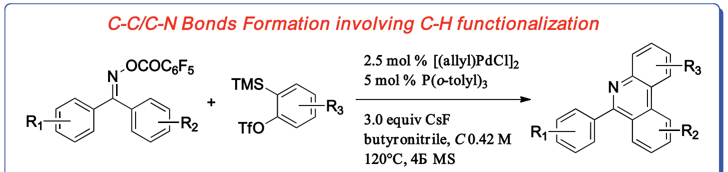
Metal-Catalyzed Domino Process By "*DESIGN (?)*"

Three key issues needed to be considered:

- **Initiation:**
  Carbometallation, Heteronucleomatallation are ideal
- **Propagation:**
  CO, isonitrile, olefin, allene… good relay
- **Termination: Any step involving reductive elimination**
  Cross coupling, Anion capture,
  β-hydride elimination
  C-H Functionalization…

…And Serendipity…

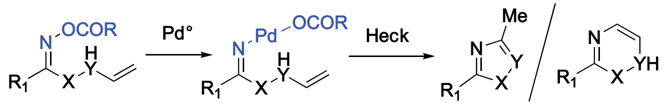
Expanding Narasaka's O-Acyloxime Chemistry



Gerfaud, T. Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 572-577.

Chemistry of Acyloxime: Synthesis of Isoquinolines and Phenanthridines

Narasaka's Chemistry

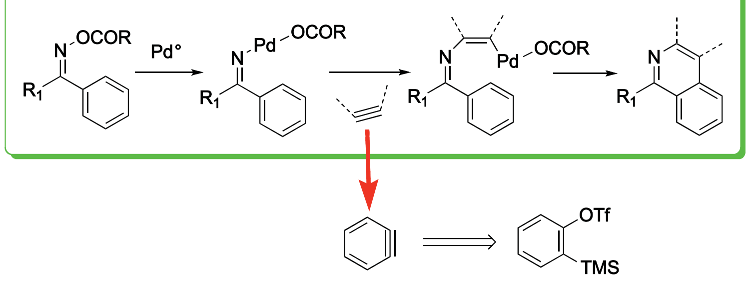


Observation: *Inter*molecular trapping of =N-Pd-PCOR didn't work

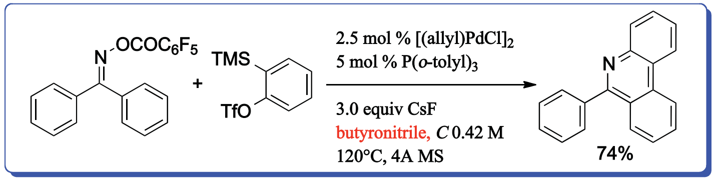
a) M. Kitamura, K. Narasaka, *Chem. Record* **2002**, *2*, 268-277;

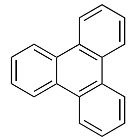
b) K. Narasaka, M. Kitamura, *Eur. J. Org. Chem.* **2005**, 4505–4519.

Domino Intermolecular aminopalladation/C-H functionalisation



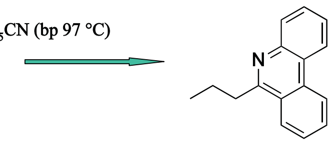
Domino C-C/C-N bonds formation: Condition survey





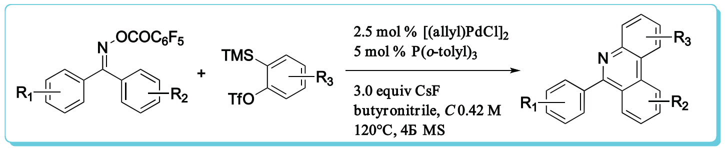
triphenylene

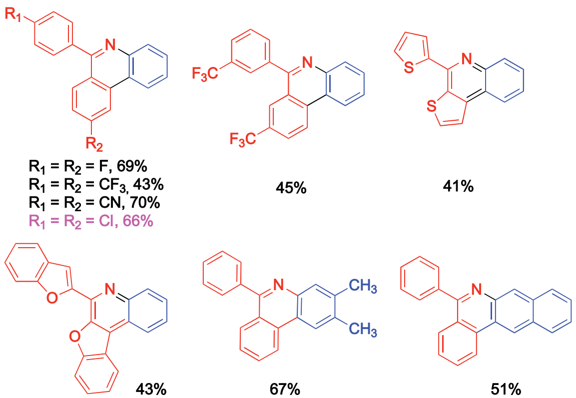
- Pd sources: $PdCl_2$ leading to trimerization of benzyne
- Floride source: **Tetrabutylammonium triphenyl difluorosilicate (TBAT), instead of CsF, led to the formation of triphenylene**
- Solvent: C_3H_7CN (bp 115-117 °C) is essential
- Temperature: Less efficient at 100 °C; 40% in C_2H_5CN (bp 97 °C)
- Ligands: $P(o\text{-tolyl})_3$ better than dppp and Xphos



Gerfaud, T. Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 572-577.

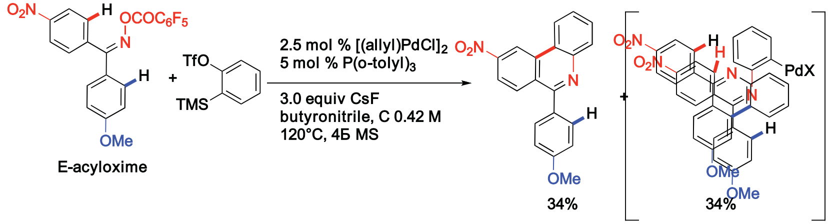
Synthesis of phananthridines: Selected Examples

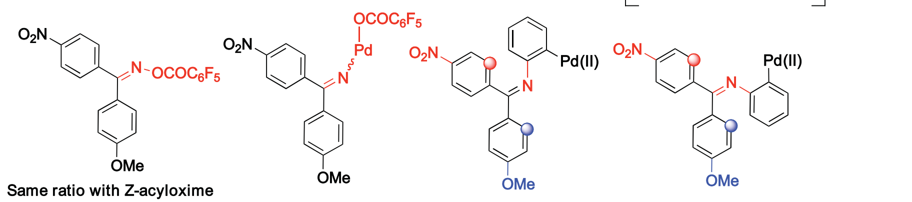




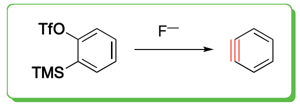
Gerfaud, T. Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 572-577.

Examples with Mechanistic Implication: Reaction is Insensitive to the Oxime Geometry

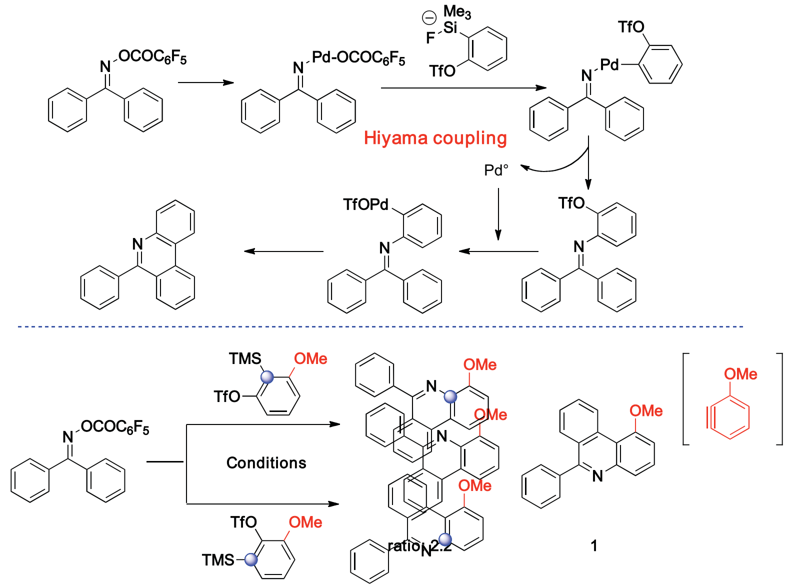




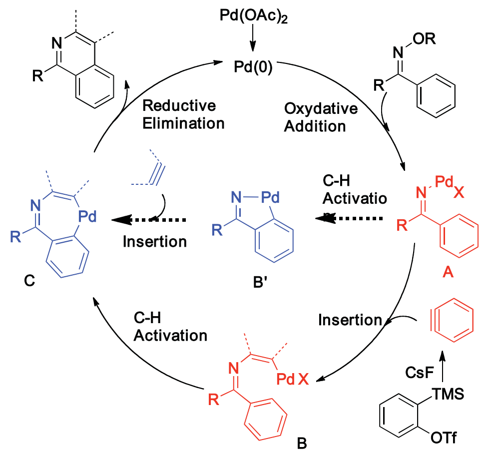
Gerfaud, T. Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 572-577.



Examples with mechanistic implication: Benzyne or not benzyne?



Mechanistic proposal

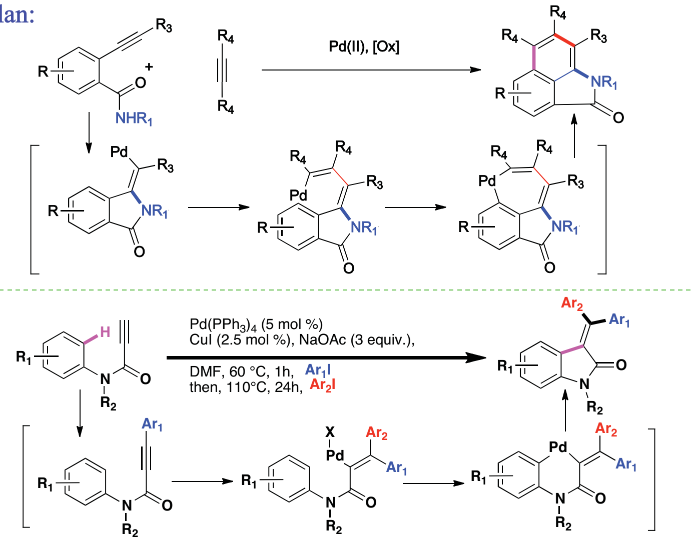


Key Conclusion: Intermolecular trapping of =N-PdX(II)X by a multiple bond is possible!

Gerfaud, T. Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 572-577.

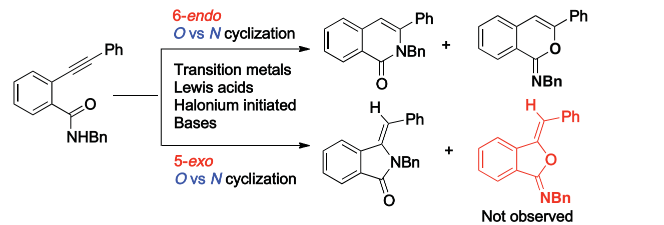
Amidopalladation Initiated Domino Process

Plan:

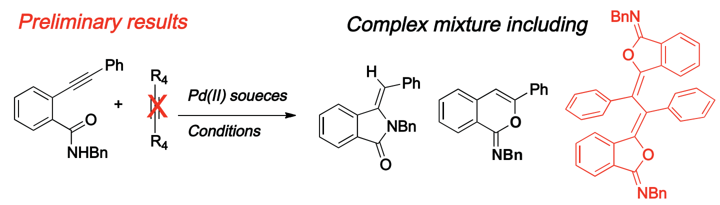


Pinto, A. Neuville, L. Zhu, J. *Angew Chem. Int. Ed.* **2007**, *119*, 3355-3359.

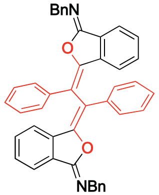
Chemistry of 2-Alkynylbenzamide: Serendipity

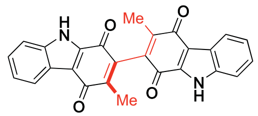


Reviews: a) G. Balme, *Eur. J Org. Chem.* **2003**, 4101-4111; b) P. Pale, *Chem. Rev.* **2008**, *108*, 3149-3173; c) S. F. Kirsch, *Synthesis* **2008**, 3183-3204.



Metal-catalyzed Syntheses of 1,3-Diene





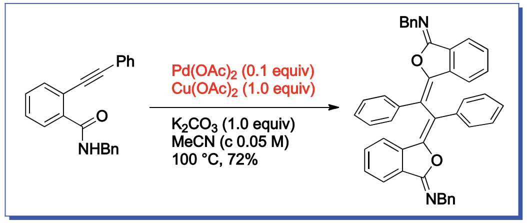
Bismurrayaquinone
R. J. Thomson, *at al*. *Angew. Chem. Int. Ed.* **2011**, *50*, 9931-9934

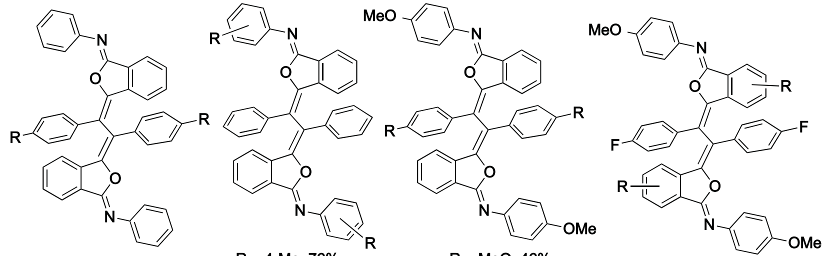
Metal-catalyzed cyclizative dimerization processes involving **alkynes:**
Au-catalyzed:
a) H. A. Wegner, S. Ahles, M. Neuburger, *Chem. Eur. J.* **2008**, *14*, 11310-11313;
b) K. H. Ahn, *Angew. Chem.* **2011**, *123*, 11648-11652; *Angew. Chem. Int. Ed.* **2011**, *50*, 11446-11450;
Pd-catalyzed:
N. Furuichi, H. Hara, T. Osaki, H. Mori, S. Katsumura, *J. Org. Chem.* **2004**, *69*, 7949-7959 (mentionned as side products)

Metal-catalyzed cyclizative dimerization processes involving **allenes**,

Pd-catalyzed: S. Ma, *Chem. Eur. J.* **2005**, *11*, 2351-2356;
Au-catalyzed: A. S. K. Hashimi, *Eur. J. Org. Chem.* **2006**, 1387-1389.

Cyclizative Dimerization: Conditions Survey





R = H, 65%
R = Me, 79%

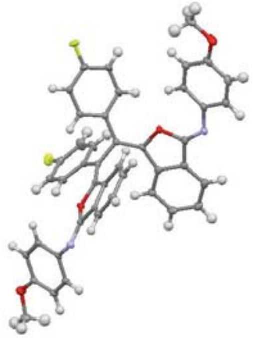
R = 4-Me, 76%
R = 4-Cl, 55%
R = 3-Cl, 42%

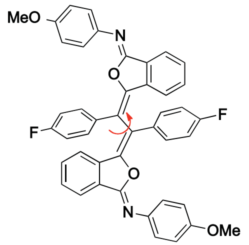
R = MeO, 46%
R = Me, 61%
R = F, 72%

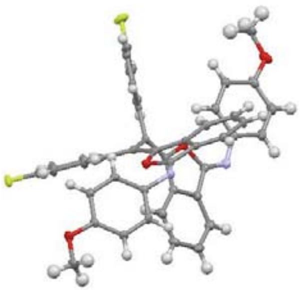
R = 6-Me, 52%
R = 4-OMe, 52%

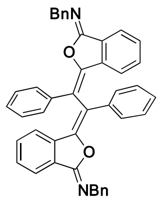
Yao, B.; Jaccod, C.; Wang, Q.; Zhu, J. *Chem. Eur. J.* **2012**, *18*, 5864-5868.

Axial chirality of the dimer





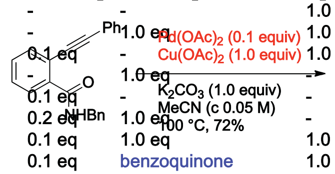


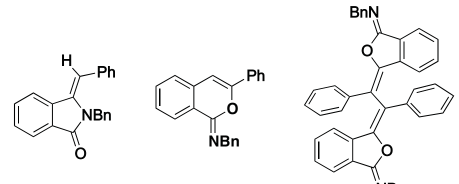


Two enantiomers were separated by analytic chiral HPLC (OJ-RH column)

Synergistic Effect of Pd and Cu

Entry	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	Yields
1	-	-	1.0 eq	92% of 1
2	-	1.0 eq	1.0 eq	<10% of 3 + 53% of 1
3	0.1 eq	-	1.0 eq	<10% of 3 + 63% of 1
4	-	1.0 eq	-	12% + 43% of 2
5	0.1 eq	-	-	11% + 35% of 2
6	0.2 eq	1.0 eq	-	48% of 3
7	0.1 eq	1.0 eq	1.0 eq	72% of 3
8	0.1 eq	benzoquinone	1.0 eq.	10% of 3 + 64% of 1



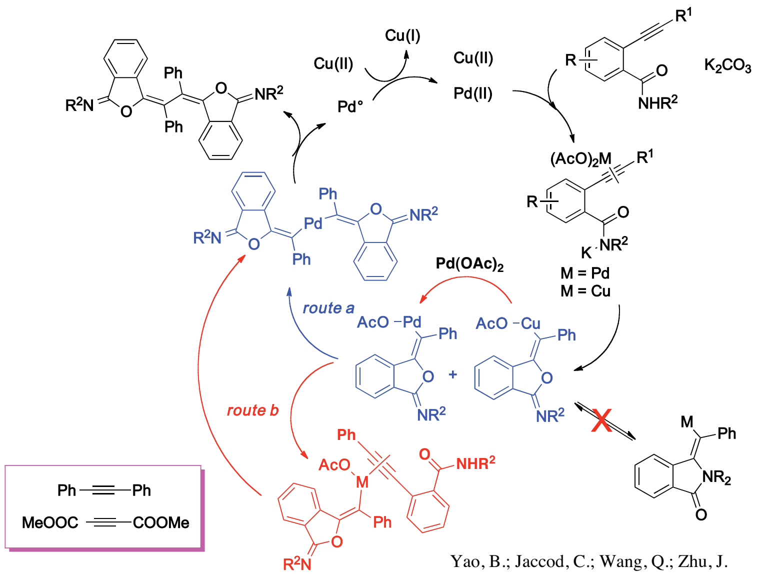


1 2 3

Conclusion:

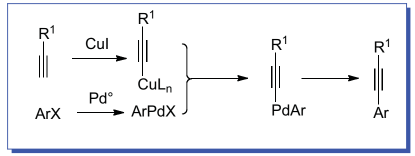
a) Cyclizative dimerization took place only in the presence of both Pd and Cu catalysts.
b) $Cu(OAc)_2$ is not merely acting as an oxidant to convert Pd° back to Pd^{II}.
c) Higher concentration produced lower yield of cyclic dimer (results not shown).

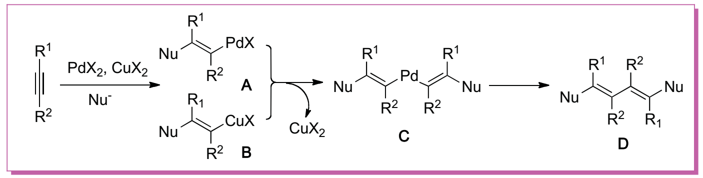
Possible Reaction Pathway: Cooperative Effects of Pd and Cu???



Yao, B.; Jaccod, C.; Wang, Q.; Zhu, J. *Chem. Eur. J.* **2012**, *18*, 5864-5868.

Synergestic Effects of Pd and Cu





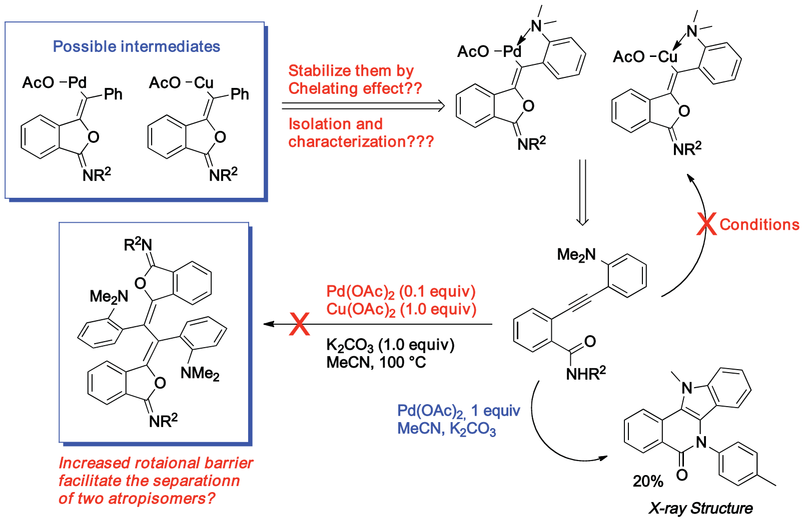
Pd-catalyzed cross coupling of vinylcuprate:

N. Jabri, A. Alexakis, J. F. Normant, *Tetrahedron* **1986**, *42*, 1369-1380.

CuI-accelerated Still coupling,

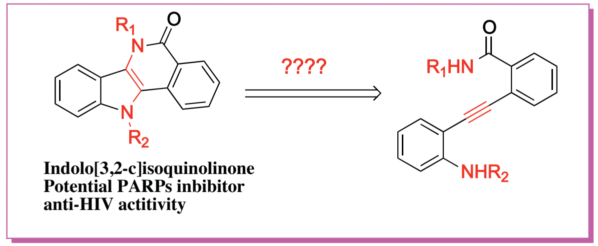
L. S. Liebeskind, R. W. Fengl, *J. Org. Chem.* **1990**, *55*, 5359-5364.

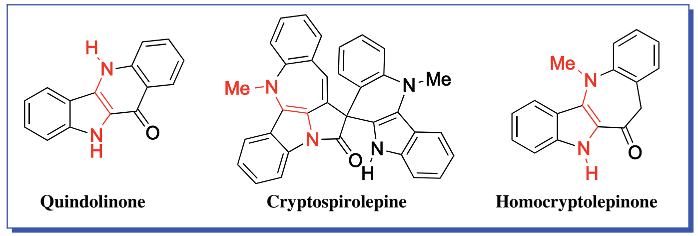
Serendipity from a "Rational" Experimental Design



Indolo[3,2-c]-isoquinolinone
Potential PARPs inhibitor, anti-HIV actitivity

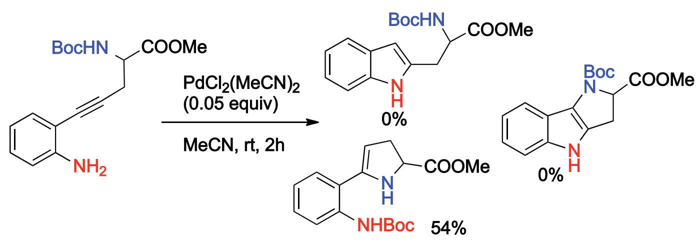
Explore the Serendipity: Diamination of Alkynes?



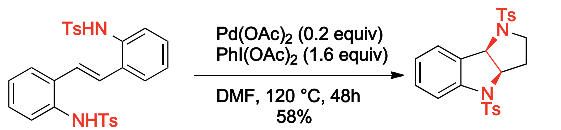


Indolo[3,2-c]isoquinolinone: C. Szabó, *Org. Lett.* **2005**, *7*, 1753 – 1756; L. Li, W. K. S. Chua, *Tetrahedron Lett.* **2011**, *52*, 1574 – 1577. Review : P. Jagtap, C. Szabó, *Nature Rev. Drug Discov.* **2005**, *4*, 421-440.

Diamination of Alkynes: Poorly Studied



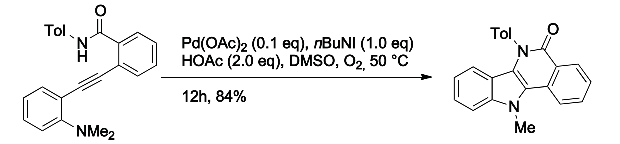
P. J. T. Rutjes, *Org. Lett.* **2003**, *5*, 1717-1720.



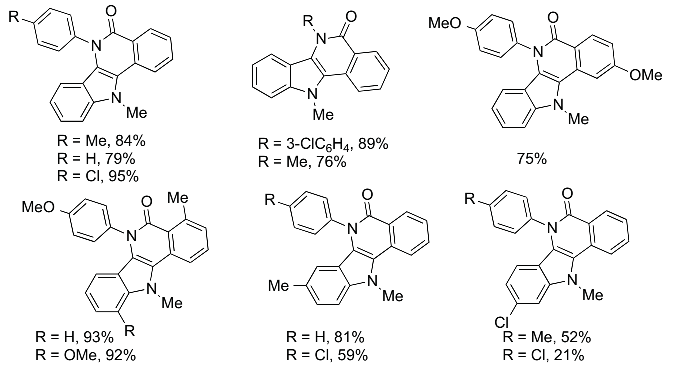
K. Muniz, *J. Am. Chem. Soc.* **2007**, *129*, 14542-14543

For a recent review on nucleopalladation, see: S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981-3019.
For a review on the transition-metal catalyzed diamination, see:
Cardona, F.; Goti A. *Nature Chemistry* **2009**, *1*, 269.

Diamination of Alkynes: Conditions and Scope



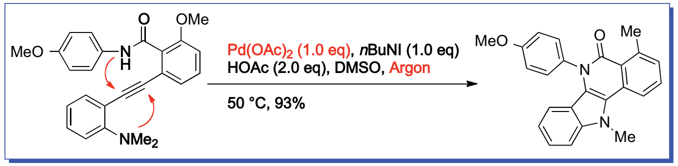
Key: a) The presence of HOAc is critical b) O_2 or air as terminal oxidant



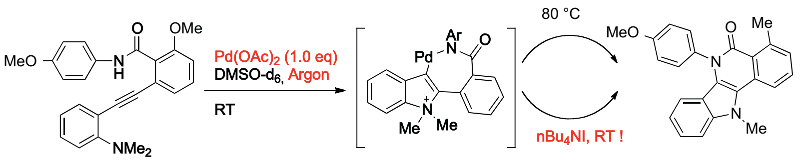
Yao, B.; Wang, Q.; Zhu, J. *Angew Chem. Int. Ed.* 2012, *51*, 5170-5174.

Diamination of Alkynes: Mechansitic Consideration

Question 1: Pd°/Pd^{II} or Pd^{II}/Pd^{IV} catalytic cycle



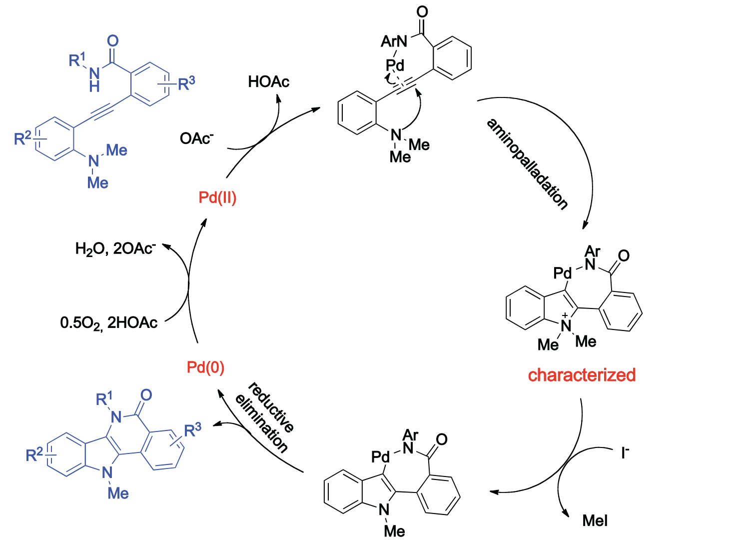
Question 2: Order of cyclization sequence and role of iodide



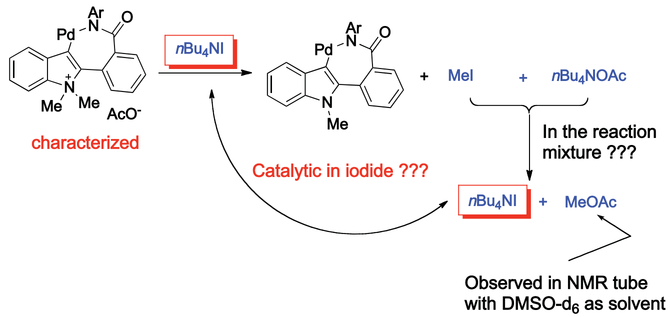
Identified spectroscopically
HRMS Calcd for $[C_{25}H_{23}N_2O_2Pd]^+$ 489.0804; found 489.0791

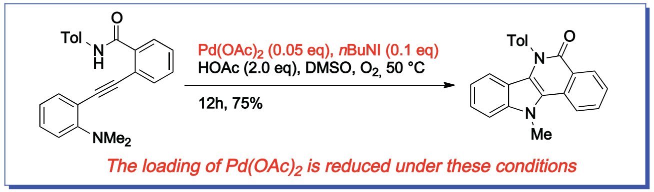
Conclusion: a) reaction went through a Pd°/Pd^{II} or Pd^{II}/Pd^{IV} catalytic cycle
b) Indole formation preceeded the quinolinone formation
c) AcO- can also effect the N-demathylation, but Iodide is much more efficient.

Diamination of Alkynes: A Possible Mechanism



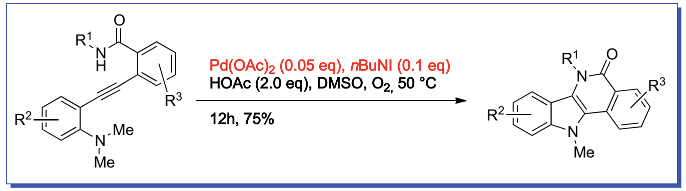
Diamination of Alkynes: Further Mechanistic Consideration

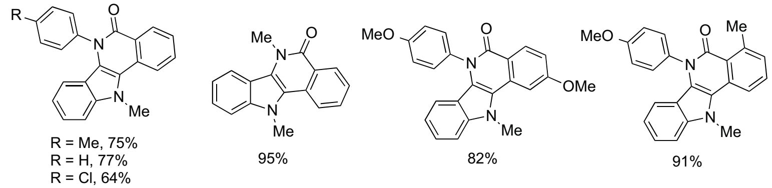




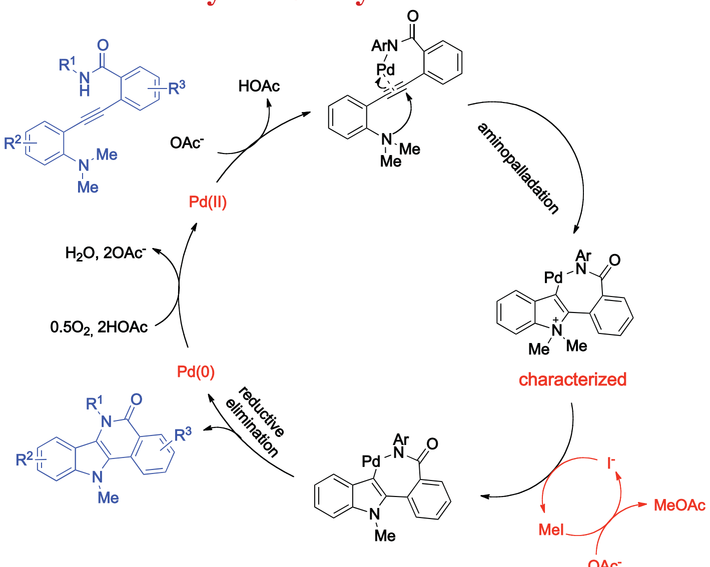
Yao, B.; Wang, Q.; Zhu, J. *Angew Chem. Int. Ed.* **2012**, *51*, 5170-5174.

Diamination of Alkynes with Catalytic Amount of Iodide: Examples



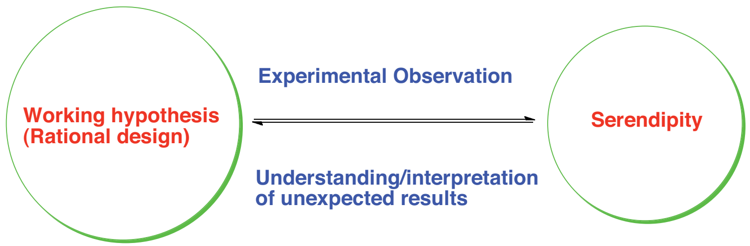


Diamination of Alkynes: Catalytic Turnover of Iodide Anion



Halide effect on metal-catalyzed transformation, see:
K. Fagnou, M. Lautens, *Angew. Chem. Int. Ed.* **2002**, *41*, 26-47.

Reaction Discovery: Rational Design and Serendipity



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