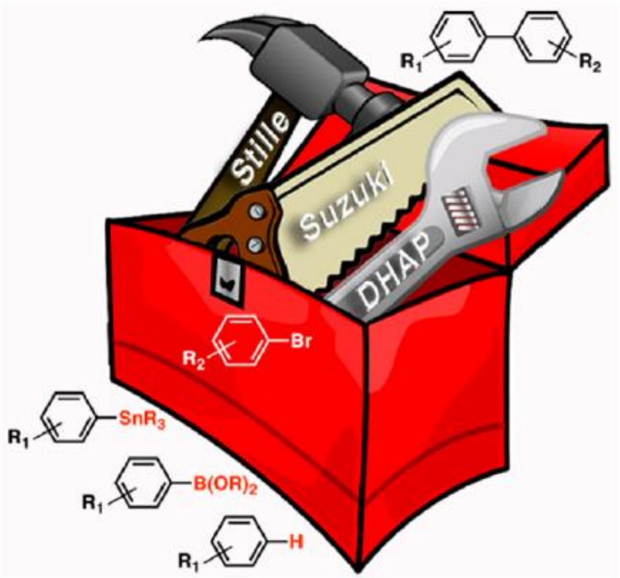
Frontiers in Chemical Synthesis I
Towards Sustainable Chemistry

Seminar Program
May 22, CH C3 30
May 23, BCH 4310

	Speaker	Title
May 22, 2014, CH C3 30		
Session I: (Antonin Clémenceau)		
13h30-14h45	Rahmanudin Aiman	*C-H Arylation for the Synthesis of Organic Materials*
14h45-16h00	Christopher Kourra	*Combinatorial Pd and Micellar Catalysis in Water*
16h00-17h15	Dylan Dagoneau	*Selected Examples of Domino Reactions in Total Synthesis*
May 23, 2014, BCH 4310		
Session II: (Christopher Kourra)		
13h30-14h45	Antonin Clémenceau	*Cinchona Alkaloids : Efficient Bifounctional Organocatalyts in Asymmetric Synthesis*
14h45-16h00	Fedor Zhurkin	*Iodonium Ylides in Organic Synthesis*
16h00-17h15	Ahmed Embaby	???

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

C-H Arylation: An Efficient & Sustainable Synthesis of π-Conjugated Organic Electronic Materials



Aiman Rahmanudin

Laboratory for Molecular Engineering of Optoelectronic Nanomaterials (LIMNO)

Supervised by Prof. Kevin Sivula

May 22nd 2014

Image taken from M. Leclerc. *Accounts of chemical research* 46.7 (2013): 1597-1605

Overview

Introduction

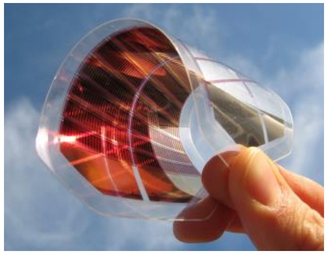
- Broader Context of Research Field - <u>Organic Electronic Materials</u>
- Types of Organic Semiconductors (OSCs) – Oligomer and Polymer

Main

- Discuss the Challenges of synthesizing OSCs
    - Brief Comparison with conventional Cross Coupling reactions
    - Discuss the Importance of Direct Arylation reactions for OSCs
    - Highlight the pioneering and important works

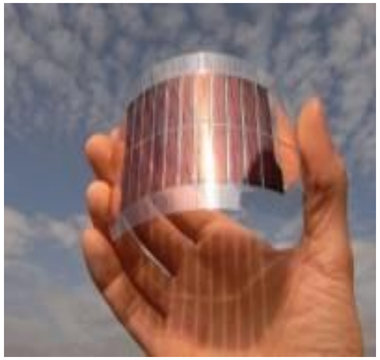
Future development

Conclusion

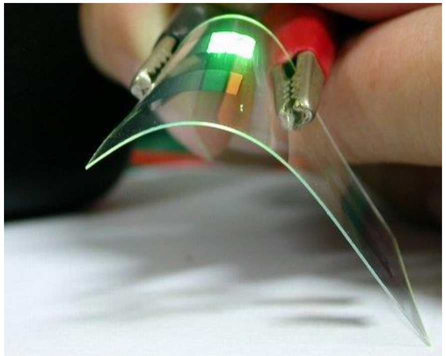


Broader Context – Organic Electronics Materials

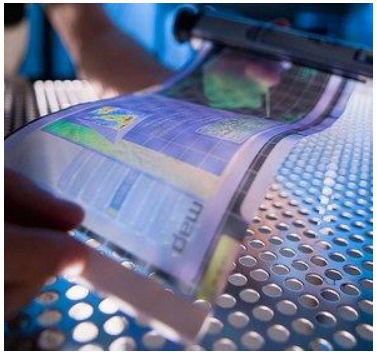
Organic semiconductors (OSCs) are viable candidates for **inexpensive** semiconductor devices



Photovoltaic Cells **(OPVs)**



Light-Emiting-Diodes **(OLEDs)**

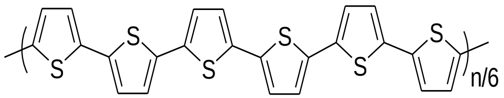


Field-Effect-Transistors **(OFETs)**

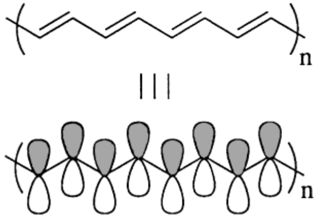
Promising Prospects over Inorganic semiconductors

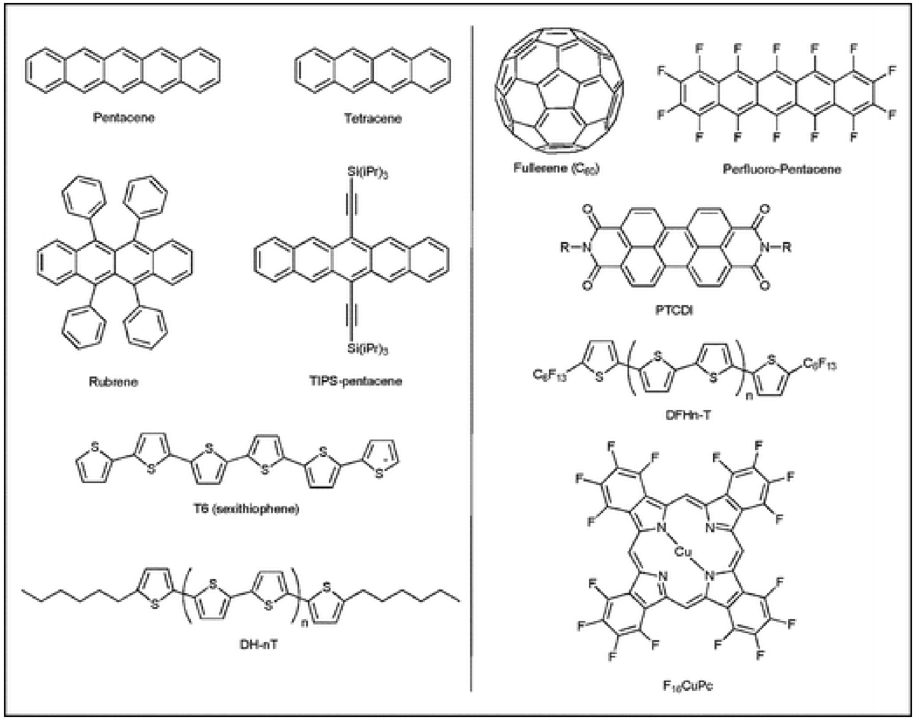
- **Cheaper** manufacturing costs
- **Solution Processable** in thin films at low temperatures - For device fabrication
- Allow for **roll-to-roll printing** of OSCs – Beneficial for **large scale production**
- "**Easier**" synthesis of molecular architecture
- Allow for **precise tuning** of **electronic properties** and **Improve solubility**
- Potentially **Environmentally benign**

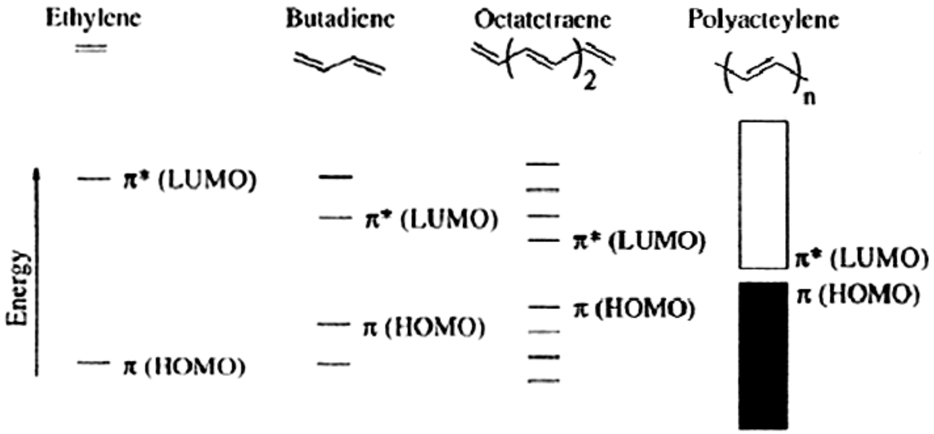
The Electronics of Organic Semiconductors



Conductivity first reported in 1980

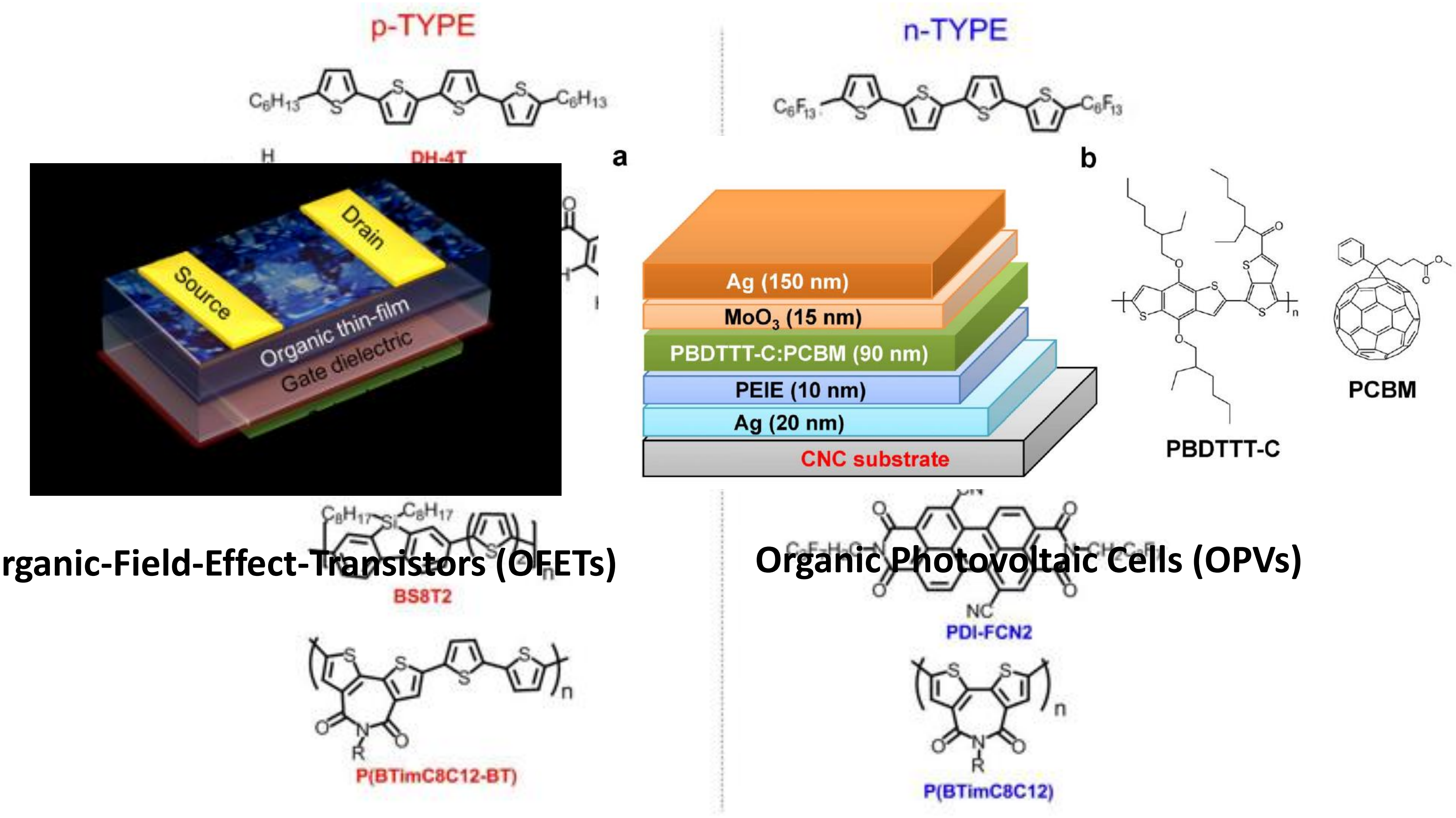






J. Roncali, *Chem. Rev.* **1997**, 97, 173-205; Reddinger, J. L.; Reynolds, J. R. *Advances in Polymer Science*, Vol 145, Springer-Verlag: Berlin, 1999, pp. 57-122. Handbook of Conducting Polymers, 2nd ed.; Skotheim, T. A.; Elsenbaumer, R. L.; Reynolds, J. R., Eds.; Marcel Dekker: New York, 1998.

Types of Organic Semiconductors (OSCs) – Oligomer and Polymer



Organic-Field-Effect-Transistors (OFETs)

Organic Photovoltaic Cells (OPVs)

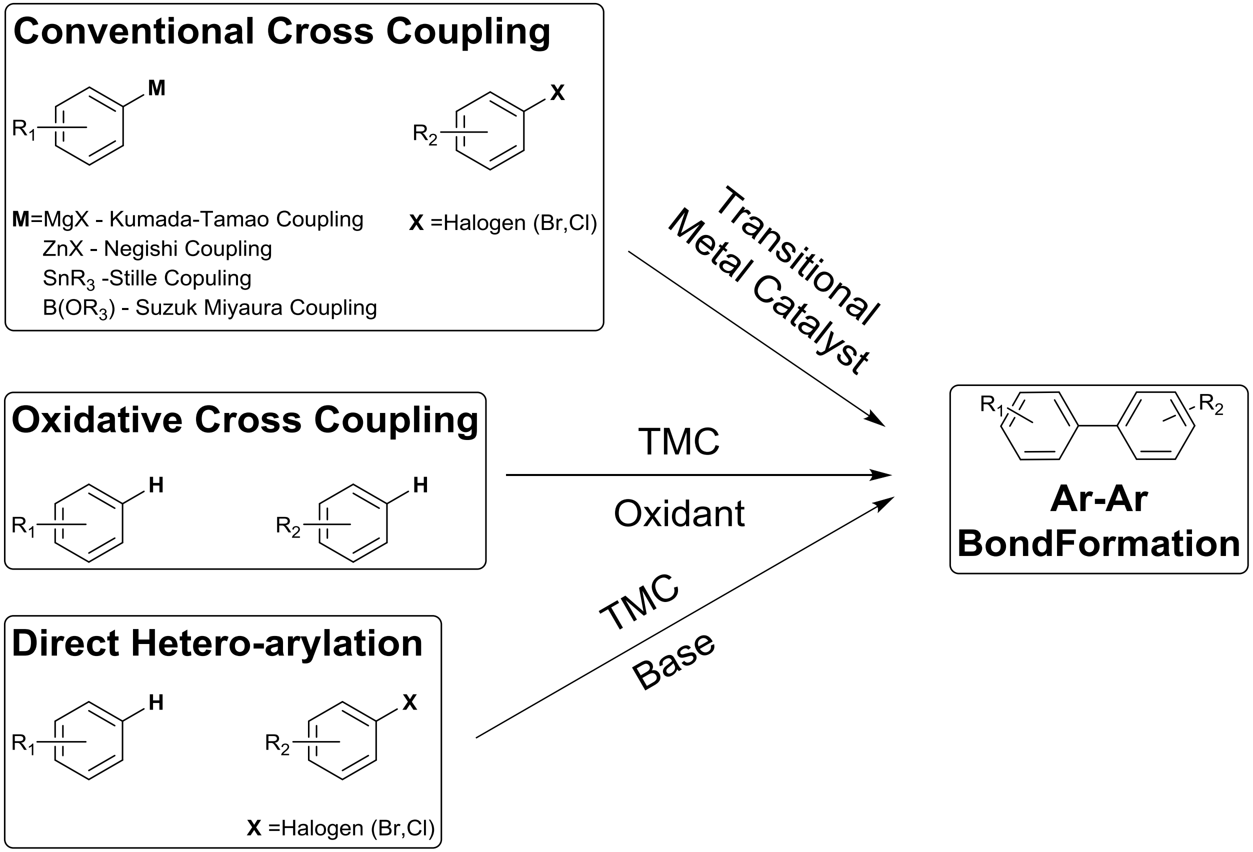
Roncali, Jean, Philippe Leriche, and Philippe Blanchard. "Molecular Materials for Organic Photovoltaics: Small is Beautiful." *Advanced Materials* (2014).;Ameri, Tayebeh, et al. "Organic ternary solar cells: a review." *Advanced Materials* 25.31 (2013): 4245-4266.; Kippelen, Bernard, and Jean-Luc Brédas. "Organic photovoltaics." *Energy & Environmental Science* 2.3 (2009): 251-261.

Synthetic Methods of making Organic Semiconductors

Aryl-Aryl bond formation Reaction

is one of the most **important synthetic tool** for the development of

π-Conjugated Organic Electronic Materials



Conventional Cross Coupling

M=MgX - Kumada-Tamao Coupling
ZnX - Negishi Coupling
SnR_3 -Stille Copuling
$B(OR_3)$ - Suzuk Miyaura Coupling

X =Halogen (Br,Cl)

Transitional Metal Catalyst

Oxidative Cross Coupling

TMC
Oxidant

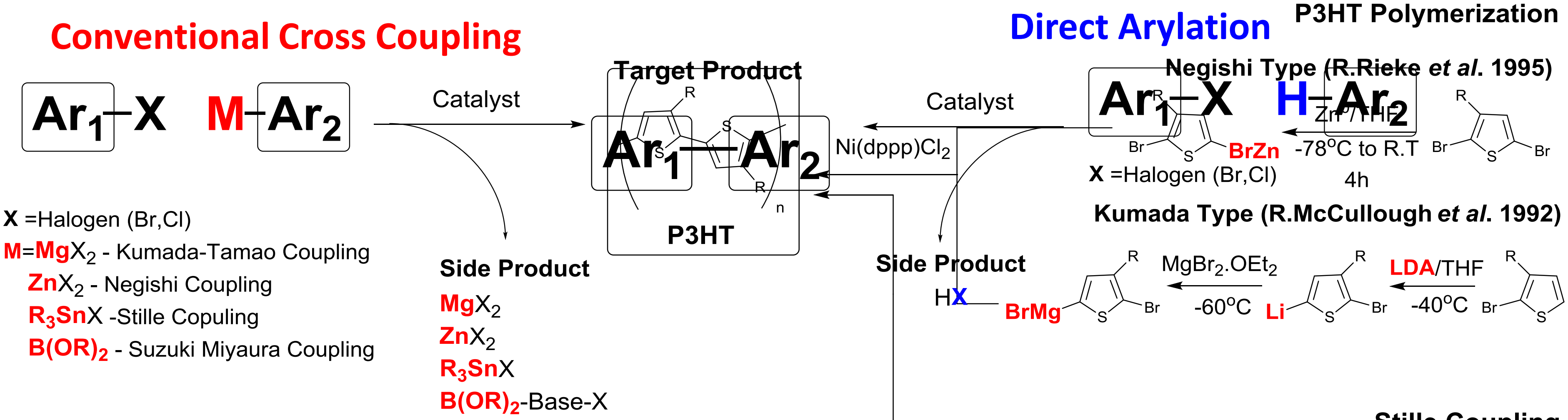
Direct Hetero-arylation

X =Halogen (Br,Cl)

TMC
Base

Ar-Ar BondFormation

Comparison of Synthetic Routes



Conventional Cross Coupling

Ar$_1$–X M–Ar$_2$

Catalyst

Target Product

Ar$_1$–Ar$_2$

P3HT

X =Halogen (Br,Cl)
M=MgX$_2$ - Kumada-Tamao Coupling
ZnX$_2$ - Negishi Coupling
R$_3$SnX -Stille Copuling
B(OR)$_2$ - Suzuki Miyaura Coupling

Side Product
MgX$_2$
ZnX$_2$
R$_3$SnX
B(OR)$_2$-Base-X

Direct Arylation

Ar$_1$–X H–Ar$_2$

Catalyst

X =Halogen (Br,Cl)

Side Product
HX

P3HT Polymerization

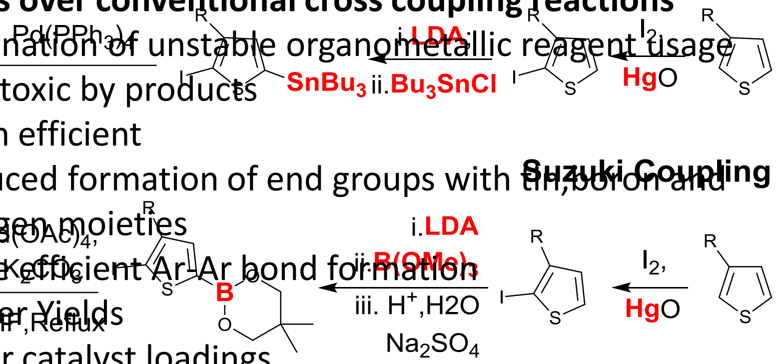
Negishi Type (R.Rieke *et al.* 1995)

Kumada Type (R.McCullough *et al.* 1992)

Stille Coupling

Main Features

- Widely studied and used
- Halogenated or pseudo-halogenated aromatics
- Lithiation reaction to add SnR$_3$ and B(OR)$_2$
- Numerous steps in the preparation and purification
- Instability of reagents
  (Organostanne and Boronic ester monomers)
- Stoichiometric amounts of Toxic of reagents and side-products



Advantages over conventional cross coupling reactions

- Elimination of unstable organometallic reagent usage
- Less toxic by products
- Atom efficient
- Reduced formation of end groups with tin,boron and halogen moieties
- More efficient Ar-Ar bond formation
- Higher Yields
- lower catalyst loadings

Suzuki Coupling

DHAR Review: Okamoto, Ken, et al. *Macromolecules* 46.20 (2013): 8059-8078; M. Leclerc. *Accounts of chemical research* 46.7 (2013): 1597-1605.
Negishi:R.D.Rieke. *Journal of the American Chemical Society* 117.1 (**1995**): 233-244. **Kumada:R.** McCullough J. Chem. Soc., Chem. Commun., 1992, 70-72.
Stille: Iraqi, A.; Barker, G. W. *J. Mater. Chem.* **1998**, 8, 25 **Suzuki:** Guillerez, S.; Bidan, G. *Synth. Met.* **1998**, 93, 123

Challenges in Synthesizing Organic Semiconductors: Importance of developing a sustainable synthetic strategy

- Organic Electronic Materials are applied in various applications in **OPVs**, **OFETs** & **OLEDs**
- **Syntheses** of increasingly **complex π-conjugated molecules**
- **Designing efficient OSCs** and **devices** for **optimum optoelectronic performance**
  - Quantum effici

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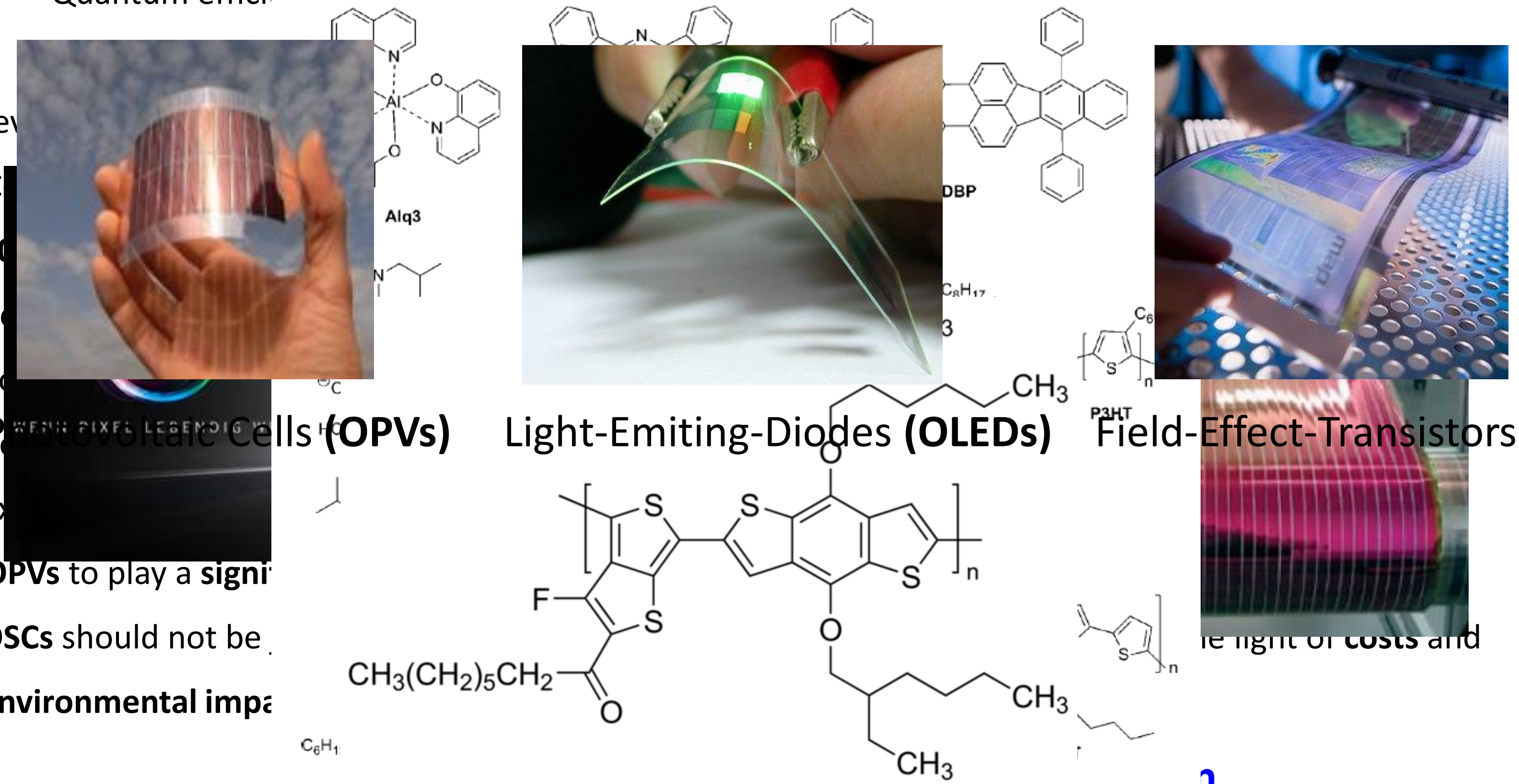
- **OPVs** to play a **signi**
- **OSCs** should not be ... **ie light of costs and**

environmental impa

One such strategy is the **Direct Arylation Reaction**



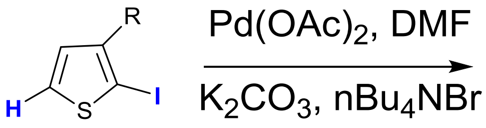
Photovoltaic Cells **(OPVs)** Light-Emiting-Diodes **(OLEDs)** Field-Effect-Transistors **(OFETs)**

OLED: Sasabe, H.; Kido, J. *Chem. Mater.* **2011**, 23, 621; Thejo Kalyani, N.; Dhoble, S. J. *Renewable Sustainable Energy Rev.* **2012**, 16, 2696; **OPV**: Yang, Y. *Nat. Photonics* **2009**, 3, 649; Yang, Y. *Nat. Commun.* **2013**,4, 1446; **REVIEW Synthesis Accesibility of OPVs :** Osedach, T. P.; Andrew, T. L.; Bulović, V. *Energy Environ. Sci.* **2013**, 6, 711

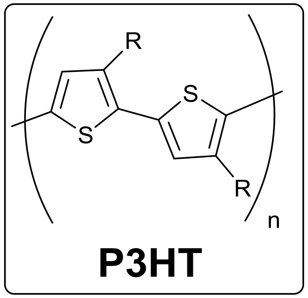
C-H Direct Arylation Reactions: Pioneering Works

Initial attempts at Direct Arylation of P3HT Organic Semiconductors

Lemaire (1999)

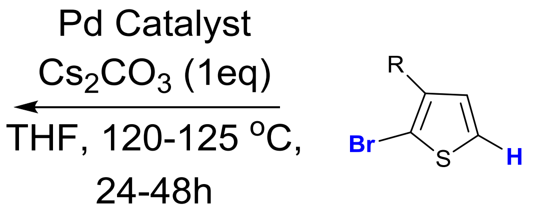


M$_w$ = 3000
Polydispersity Index(PDI) =2
Regioregularity = 88%
Yield= 93%



P3HT

Ozawa (2010)



M$_w$ = 30000
Polydispersity Index(PDI) =1.61
Regioregularity = 98%
Yield= 99%

- Decade long Gap to develop a sustainable Direct Arylation Method
- **Stille** and **Suzuki Coupling** were widely studied and used during this period

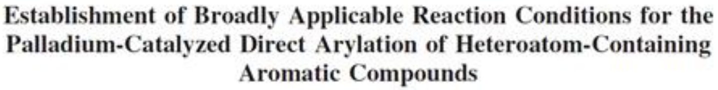
M. Lemaire & co-workers *Tetrahedron letters* 40.32 (**1999**): 5873-5876.; Ozawa & co-workers, *Journal of the American Chemical Society*132.33 (**2010**): 11420-11421. ;
Thompson et al. *Macromolecules* 44.6 (**2011**): 1242-1246.

C-H Direct Arylation Reactions:
Pioneering Works in Optimizing Direct Arylation Reactions by Fagnou & co-workers

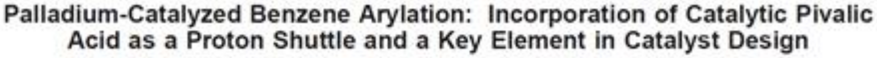
- Optimized reaction conditions for Aryl-aryl bond formation with a wide range of Aryl groups

- Versatile Application with the use of **Carboxylate** (Pivalic Acid) as a **Co-catalyst**

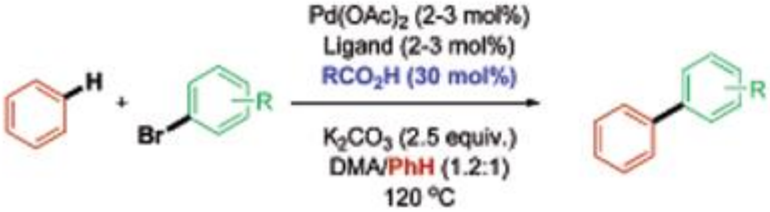
- **C-H bond activation** proceeds via Concerted-Metalation Deprotonation **(CMD)** pathway

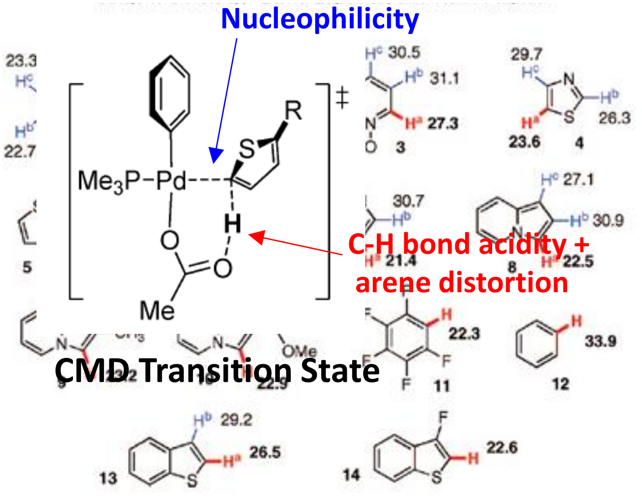


Establishment of Broadly Applicable Reaction Conditions for the Palladium-Catalyzed Direct Arylation of Heteroatom-Containing Aromatic Compounds



Palladium-Catalyzed Benzene Arylation: Incorporation of Catalytic Pivalic Acid as a Proton Shuttle and a Key Element in Catalyst Design





Nucleophilicity

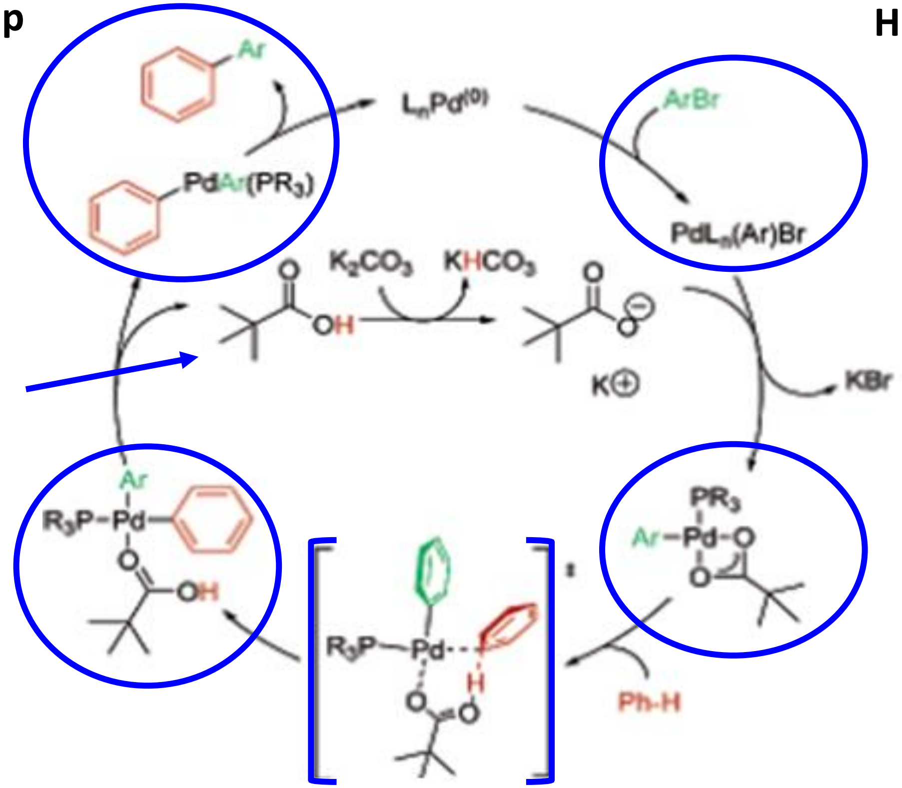
C-H bond acidity + arene distortion

CMD Transition State

Figure 1. Free energy of activation ($\Delta G^{\ddagger}_{298K}$, kcal mol^{-1}) for direct arylation via the CMD pathway involving an acetate ligand. Red bonds indicate the experimentally observed sites of arylation.

K.Fagnou & co-workers : Catalytic Intermolecular Direct Arylation of Perfluorobenzenes *J. Am. Chem. Soc.*, 2006, *128* (27), pp 8754–8756; "Palladium-catalyzed benzene arylation: incorporation of catalytic pivalic acid as a proton shuttle and a key element in catalyst design." *J. Am. Chem. Soc* 128.51 (2006): 16496-16497. "Establishment of broadly applicable reaction conditions for the palladium-catalyzed direct arylation of heteroatom-containing aromatic compounds." *J. Org. Chem* 74.5 (2009): 1826-1834. *J. Am. Chem. Soc* 130.33 (2008): 10848-10849; *J. Org. Chem* 77.1 (2011): 658-668.

Catalytic Cycle using <u>Carboxylate</u> additive by Fagnou & co-workers



Oxidative addition of Halogenated-Ar

Reductive elimination step for the Aryl-Aryl bond formation

Carboxylate Acid acts as a Proton Shuttle

De-halogenation then carboxylate anion exchange

Deprotonation then Carboxylate Ligand Dettaches

Activation of C-H bond assisted by carboxylate
H-Bonding interaction via a
Concerted-Metallation-Deprotonation
Transition State

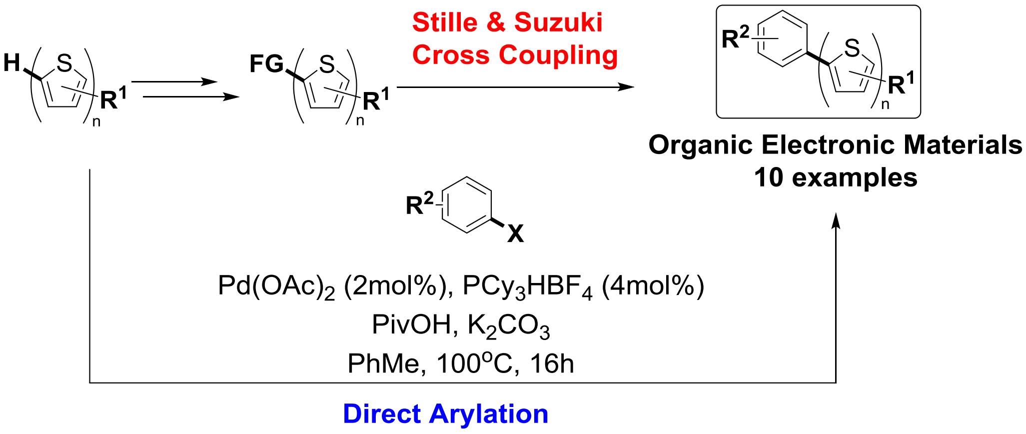
"Palladium-catalyzed benzene arylation: incorporation of catalytic pivalic acid as a proton shuttle and a key element in catalyst design." Fagnour & co-workers *J. Am. Chem. Soc* 128.51 (**2006**): 16496-16497.

C-H Direct Arylation Reactions:
Selected Key Examples

- **Successful examples of Oligomers**
  - Oligothiophene
  - Diketopyrrolopyrrole Derivatives
- **Highlight the Problem of Regioselectivity during Polymerization**
  - P3HT
- **Controlling Regioselectivity**
  - Controlling Regioselectivity via Protecting Groups
  - Directing group on Thiophene unit
  - Controlling Polymer Purity and Molecular Weight via Reaction Conditions

C-H Direct Arylation Reactions: Oligothiophene based Organic Electronic Materials

Direct Arylation using Fagnou's conditions

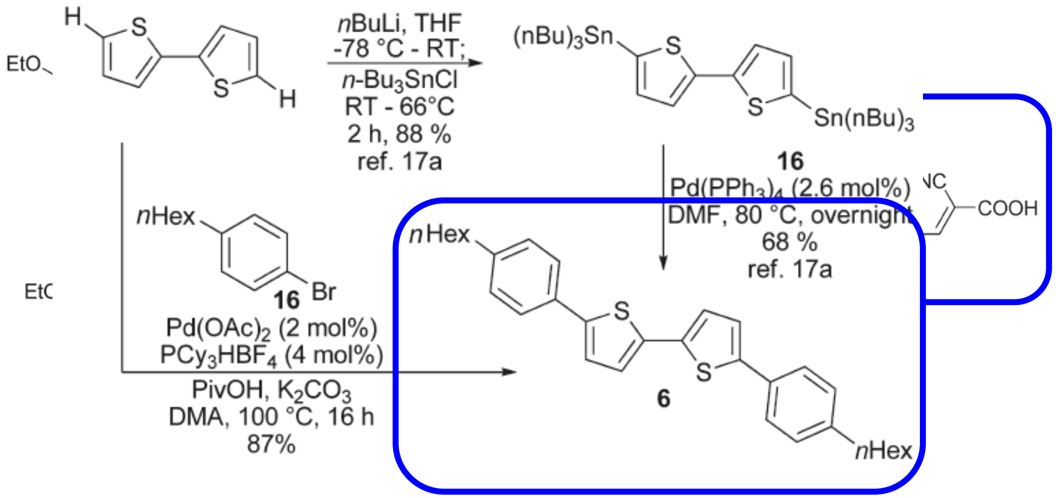


Comparison between Conventional Cross Coupling and Direct Arylation Reactions

- Versatile Reaction Condition
- Higher Yields
- Fewer synthetic steps
- Lower Catalyst Loadings
- No organometallic Intermediates

Organic Field Effect Transistors

Organic Dye Sensitized Solar Cells

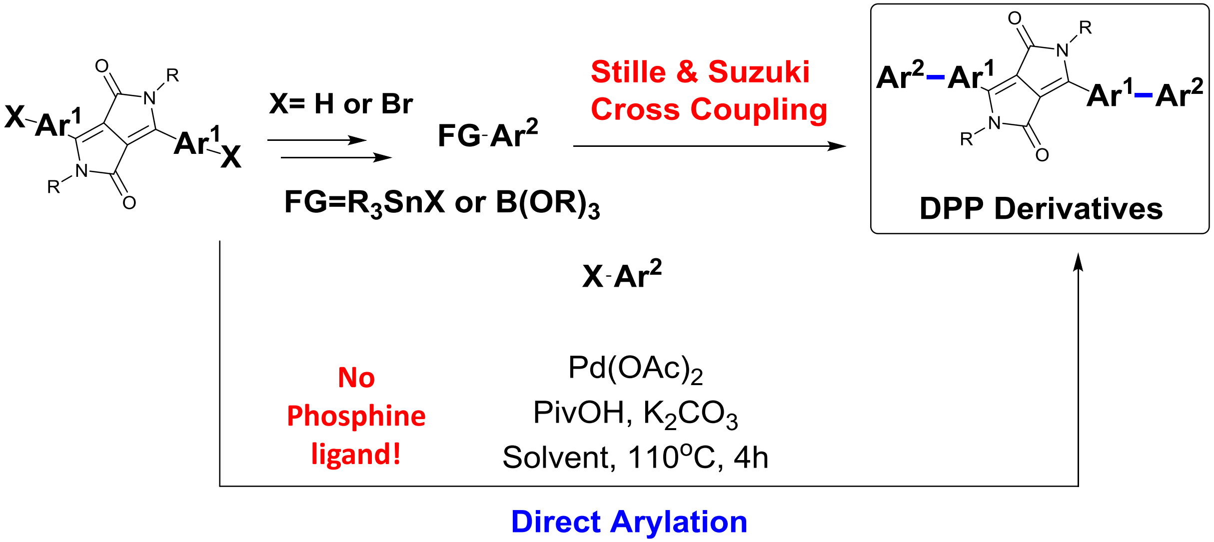


- Direct Arylation Yield = 87%
- Stille Coupling Yield = 68%
- Lesser Steps
- Avoid the use of BuLi and OrganoTin intermediates
- Higher Yields

- Direct Arylation Yield = 99%
- Suzuki Coupling Yield = 89%
- Almost quantitative Yield
- No Chromatography required

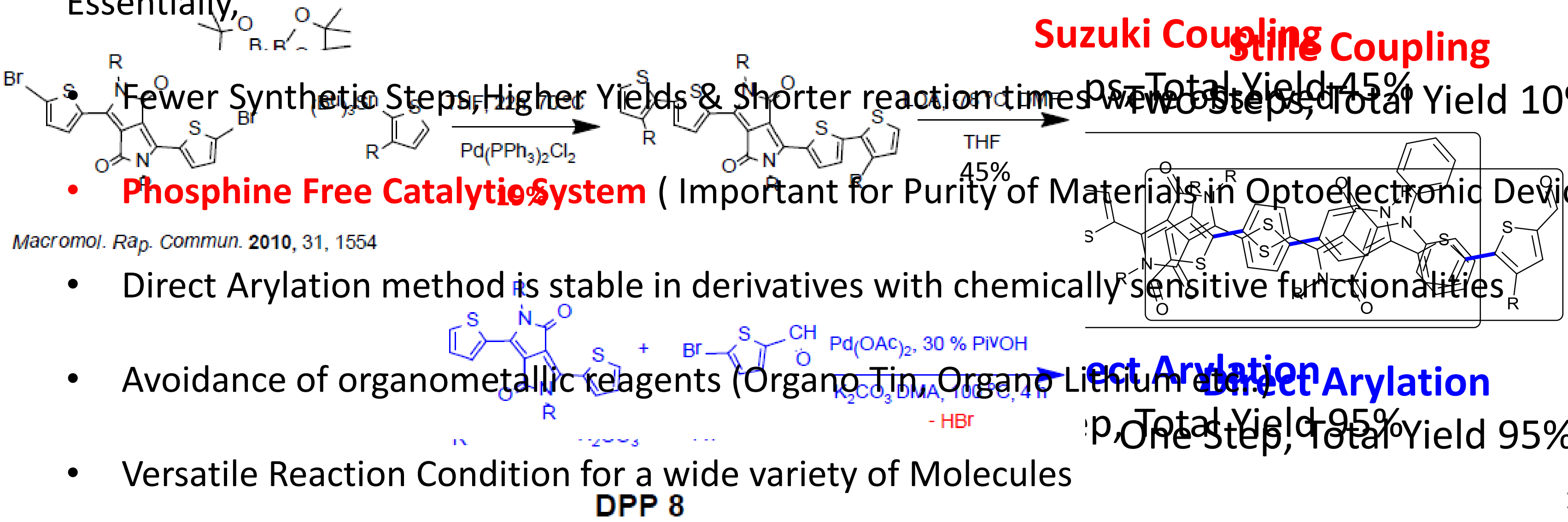
Schipper, Derek J., and Keith Fagnou; *Chemistry of Materials* 23.6 (2011): 1594-1600.

C-H Direct Arylation Reactions: Diketopyrrolopyrrole (DPP) Derivatives



- **DPP** - Important class of High performance pigment used in inks, paints and now **Organic Electronics**
- **17 DPP** derivatives synthesized via Direct Arylation and **compared** with **Conventional Cross coupling**
- Based on Fagnou's conditions but **Free** of **phosphine ligands**

Essentially,



- Fewer Synthetic Steps, Higher Yields & Shorter reaction times were observed
- **Phosphine Free Catalytic System** (Important for Purity of Materials in Optoelectronic Devices)
- Direct Arylation method is stable in derivatives with chemically sensitive functionalities
- Avoidance of organometallic reagents (Organo Tin, Organo Lithium etc.)
- Versatile Reaction Condition for a wide variety of Molecules

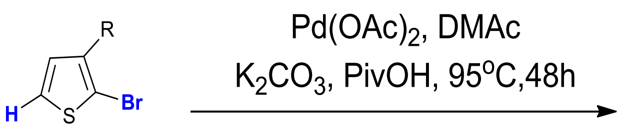
Macromol. Rap. Commun. **2010**, 31, 1554

Liu, Shi-Yong & co-workers. "C–H activation: making diketopyrrolopyrrole derivatives easily accessible." *Journal of Materials Chemistry A* 1.8 (**2013**): 2795-2805.

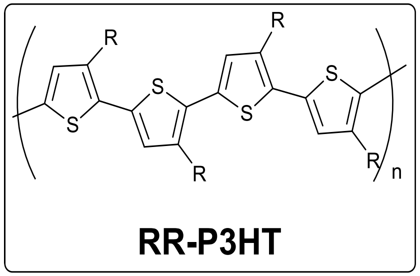
C-H Direct Arylation Reactions: Polymer Organic Semiconductors

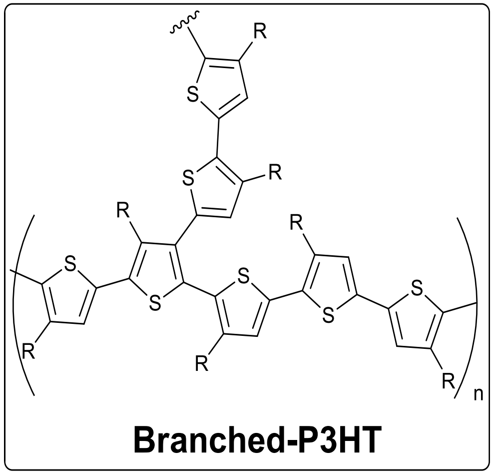
Problems with Regioselectivity

Thompson *et al.* (2012)



α-position

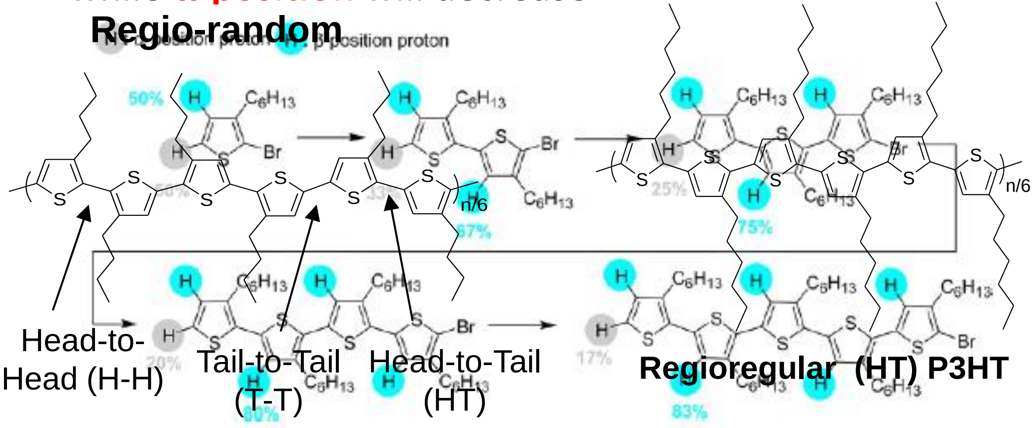


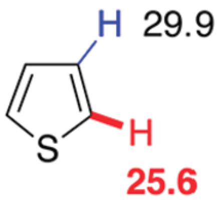


β-position

- Low Yield & Regioselectivity
- Regio random & Branched-P3HT formed
- **α-position** coupling is more selective than **β-position** as shown by Fagnou *et al.*
- But as Polymer Chain Grows, % of **β-position** will increase while **α-position** will decrease

M_w = 15000
Polydispersity Index(PDI) =2.9
Regioregularity = 88%
Yield= 39%



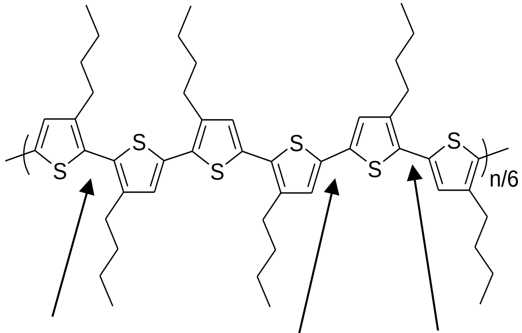


Luscombe & co-workers *Polymer Chemistry* 4.12 (2013): 3499-3506. Thompson & co-workers " *Journal of Polymer Science Part A: Polymer Chemistry* 50.18 (2012): 3691-3697;

K.Fagnou & co-workers. *J. Org. Chem* 77.1 (**2011**): 658-668; *J. Chem. Soc. Chem. Commun.* **1986**, 1346-1347. Rieke, R. D. *et al J. Am. Chem. Soc.* **1992**, 114, 10087-10088.

Regioregular Poly(3-alkylthiophene)

Regio-random P3AT

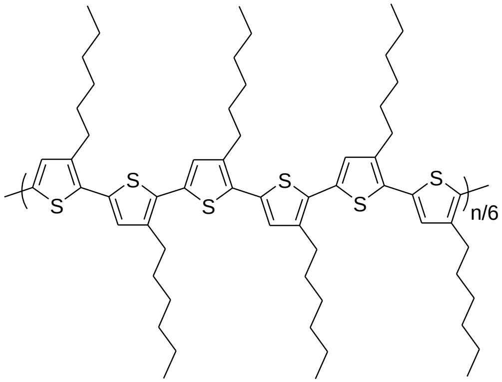


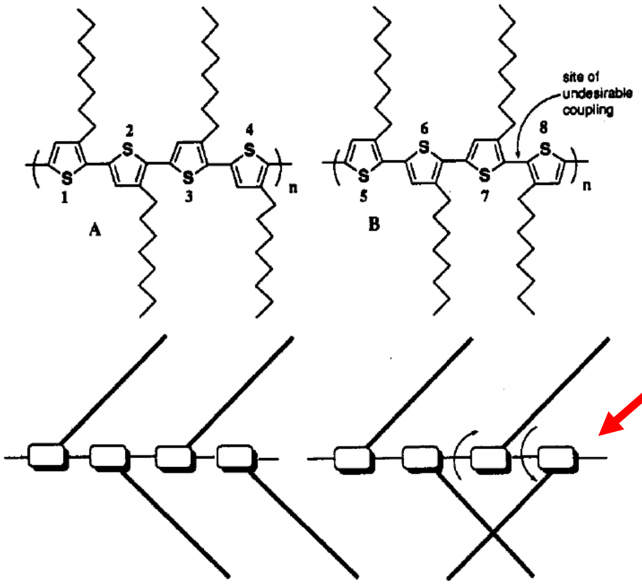
Head-to-Head (H-H)

Tail-to-Tail (T-T)

Head-to-Tail (HT)

Regioregular <u>(HT) P3AT</u>





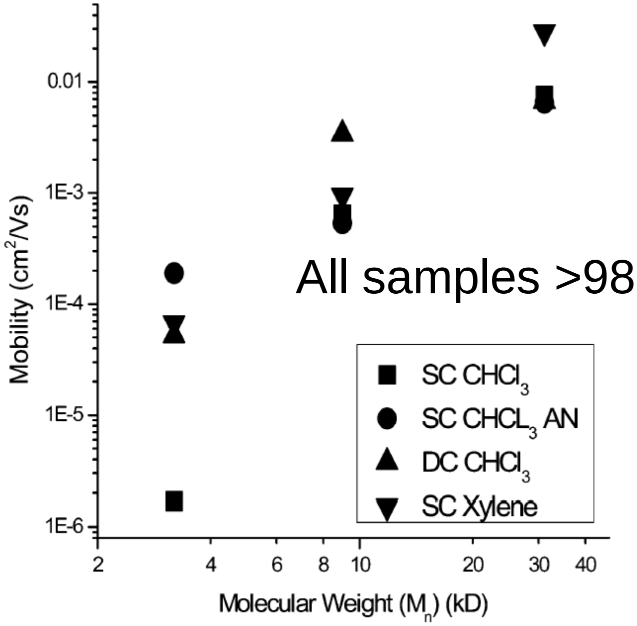
Unfavorable interaction reduces effective conjugation length

μ = <u>1 x 10^{-4} cm^2/(Vs) Regiorandom</u> (70 % HT-HT)

μ = <u>0.1 cm^2/(Vs) Regioregular</u> (> 96% HT content)

McCullough *et al* *J. Org. Chem.* **1993**, *58*, 904-912.;*Phys Rev B* **2003**, *67*, 064203.; *Nature* **1999**, *401*, 685-688.

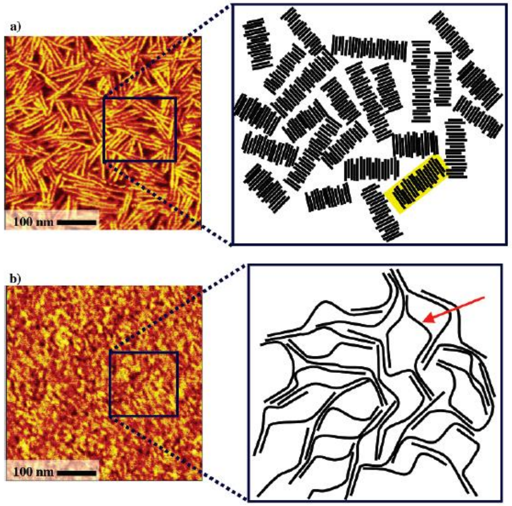
Effect of P3HT Molecular Weight on FET Mobility



All samples >98% RR

3.2 kD

31.1 kD



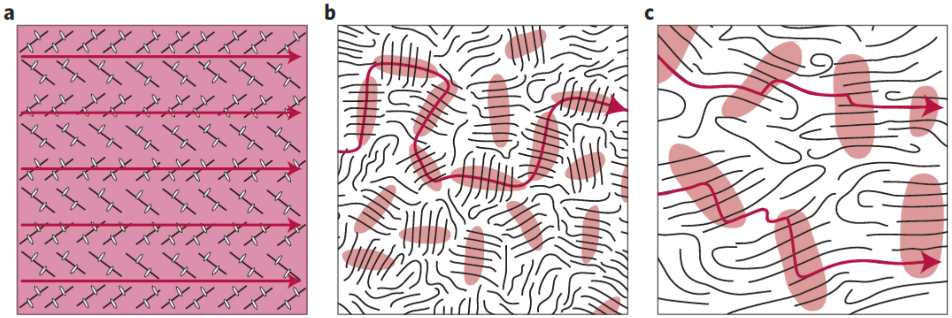
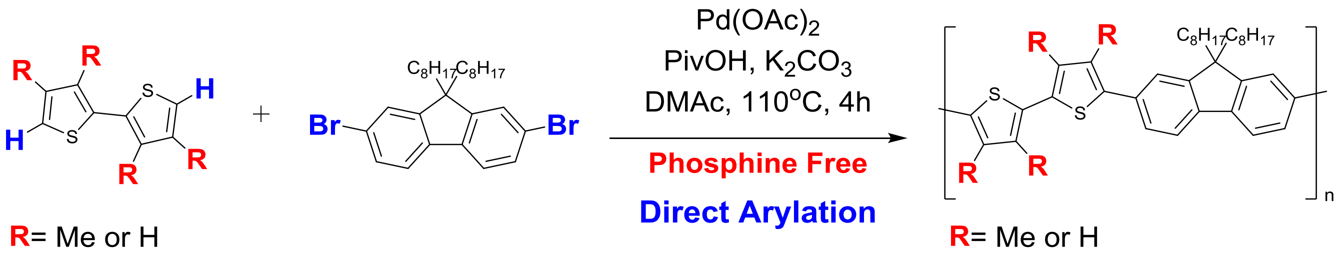


Figure 1 | Order and charge transport in organic semiconductors. **a**, Tight packing of molecules (black) in organic crystals may result in macroscopically long-range structural order and charge delocalization (red background). **b**, The packing of small-to-medium molecular weight conjugated polymers can be sufficiently good on the nano- and microscale to form small ordered domains, but these domains are not well connected, resulting in transport bottlenecks at the grain boundaries. **c**, The packing order in the novel, high-molecular-weight polymers is usually poor, but the long and semirigid chains ensure domain interconnectivity, thus effectively increasing the charge mobility in these materials. The charge-motion paths are shown by the red arrows. The red shaded regions in **b** and **c** indicate charge delocalization occurring in ordered domains.

Himmelberger, Scott, et al. "Effects of confinement on microstructure and charge transport in high performance semicrystalline polymer semiconductors."*Advanced Functional Materials* 23.16 (2013): 2091-2098; **VitalyPodzorov,** *Nature Materials* **12**,947–948 (2013); Fréchet, J. M. J. *et al Macromolecules* **2005**, *38*, 3312-3319.

C-H Direct Arylation Reactions: Polymer Organic Semiconductors (Controlling Regioselectivity via Protecting Groups)

Work by Kanbara & co workers – Reactivity of Bi-thiophene Unit



Polymer (R=H) Exhibit High performance in OFETs
R. Friend *et al*

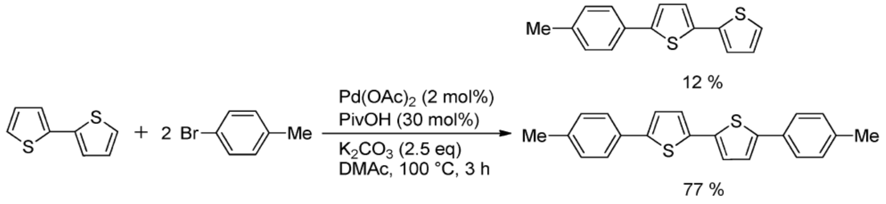
Polycondensation for monomer R=H

- Insoluble product was obtained due to Cross linking structure of polymer

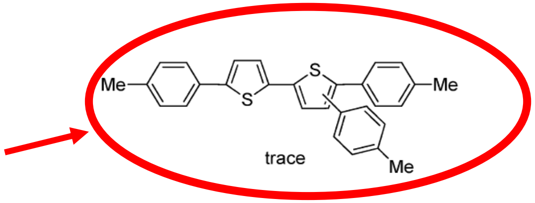
Polycondensation for monomer R=Me

- Obtained High M_n= 31800 ,PDI=2.46 & Yield=91%
- ^{1}H NMR indicated no branching, and no terminal unit was observed
- Indicates no branching the fluorene unit

Model Reaction with 2,2-Bithiophene



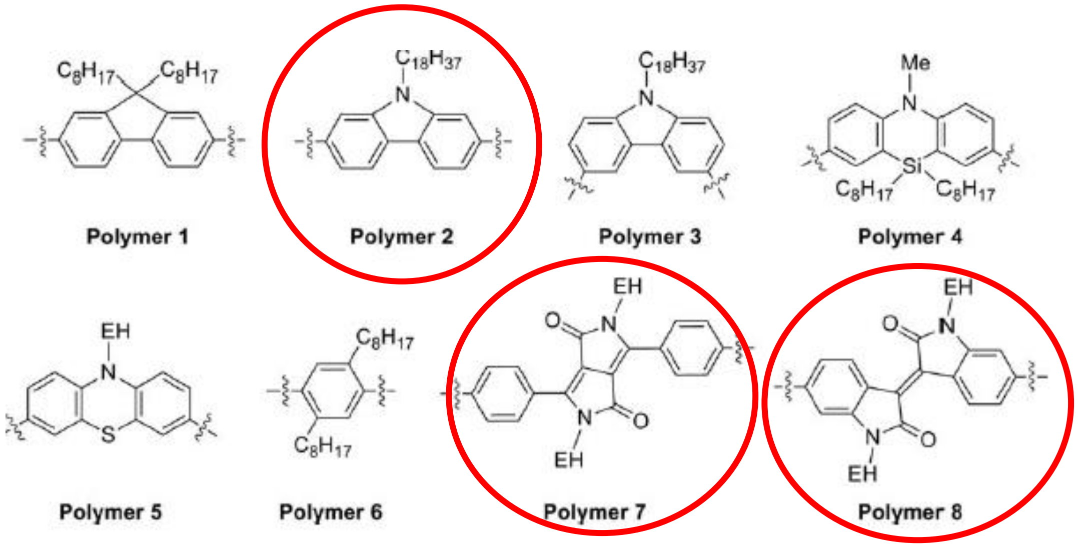
- **β-position Cross-linked** structure confirmed by MS
- Induced cross-linking during polymerization



R. Friend & co-workers. Science 21 March 2003: Vol. 299 no. 5614 pp. 1881-1884 ; Kanbara et al. "Synthesis of thiophene-and bithiophene-based alternating copolymers via Pd-catalyzed direct C–H Arylation." *ACS Macro Letters* 1.1 (**2011**): 67-70.

C-H Direct Arylation Reactions: Polymer Organic Semiconductors (Controlling Regioselectivity via Protecting Groups)

Further investigation by Kanbara & co workers



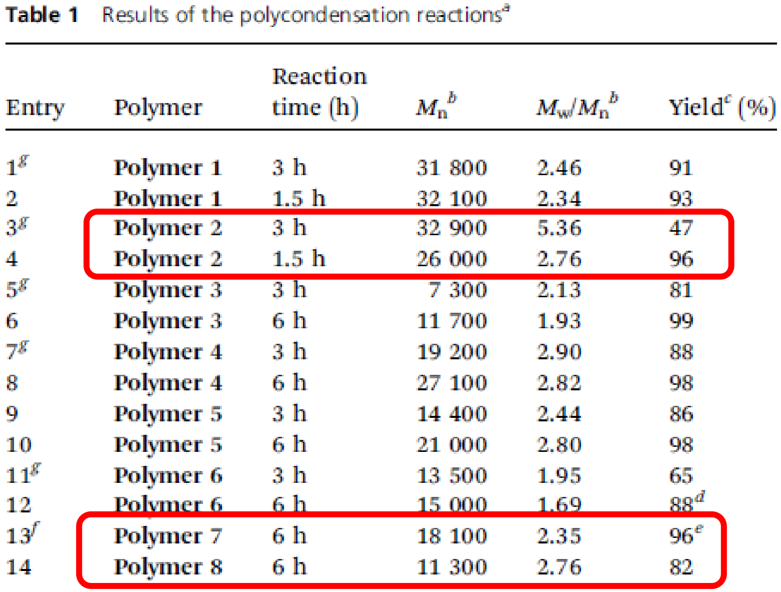
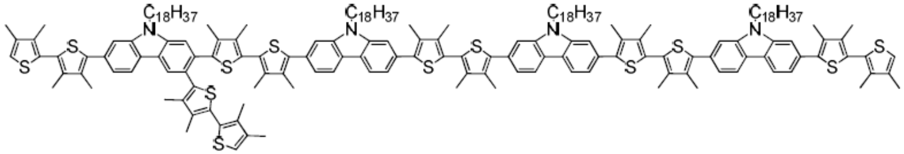


Table 1 Results of the polycondensation reactions[a]

Entry	Polymer	Reaction time (h)	M_n[b]	M_w/M_n[b]	Yield[c] (%)
1[g]	Polymer 1	3 h	31 800	2.46	91
2	Polymer 1	1.5 h	32 100	2.34	93
3[g]	Polymer 2	3 h	32 900	5.36	47
4	Polymer 2	1.5 h	26 000	2.76	96
5[g]	Polymer 3	3 h	7 300	2.13	81
6	Polymer 3	6 h	11 700	1.93	99
7[g]	Polymer 4	3 h	19 200	2.90	88
8	Polymer 4	6 h	27 100	2.82	98
9	Polymer 5	3 h	14 400	2.44	86
10	Polymer 5	6 h	21 000	2.80	98
11[g]	Polymer 6	3 h	13 500	1.95	65
12	Polymer 6	6 h	15 000	1.69	88[d]
13[f]	Polymer 7	6 h	18 100	2.35	96[e]
14	Polymer 8	6 h	11 300	2.76	82

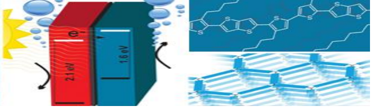
Reactivity of the other monomer

- Formation of largely insoluble product indicated presence of cross linked structures
- Due to high reactivity of C-H bonds on the 3 and 6 positions of the carbazole derivative
- Large polydispersity index M_w/M_n = > 5
- Soluble fraction low M_n showed cross linked structures as detected by MALDI-TOF-MS
- Reducing reaction time impedes the formation of Cross linked structures



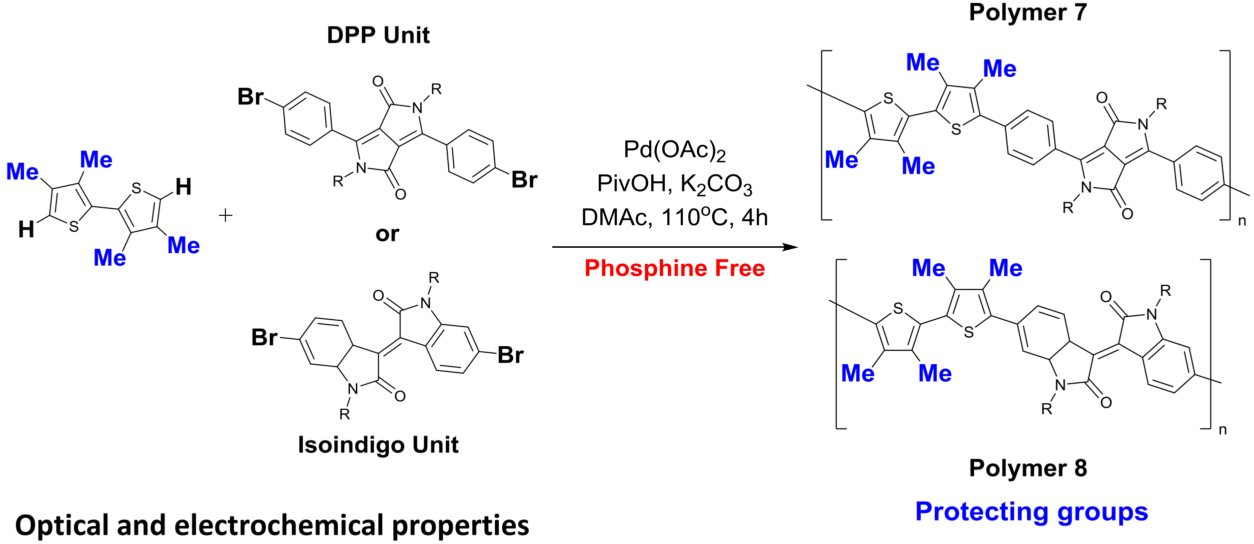
Calculated mass: **2993.60880**

Kanbara et al. "Direct arylation polycondensation for the synthesis of bithiophene-based alternating copolymers." *Polymer Chemistry* 4.4 (**2013**): 947-953.

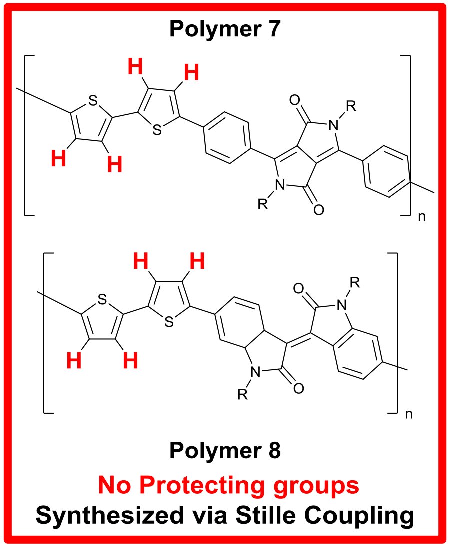


C-H Direct Arylation Reactions: Polymer Organic Semiconductors (Controlling Regioselectivity via Protecting Groups)

Further investigation by Kanbara & co workers



Protecting groups



No Protecting groups

Synthesized via Stille Coupling

Optical and electrochemical properties

- **Polymer with Protecting groups as compared to no Protecting groups**
  - **λ_{max}** in thin films at **shorter wavelengths**
  - CV measurements also indicated **larger band gaps**
  - **PCE%** are also **significantly lower**
- **Methyl groups** on the bithiophene units induced a **twisted structure** due **to steric hindrance**
- **Decrease** in **coplanarities** and **conjugation lengths** on the polymer backbone
- Affecting **charge carrier transport** and **morphology in solid-state**

Power conversion Efficiency %

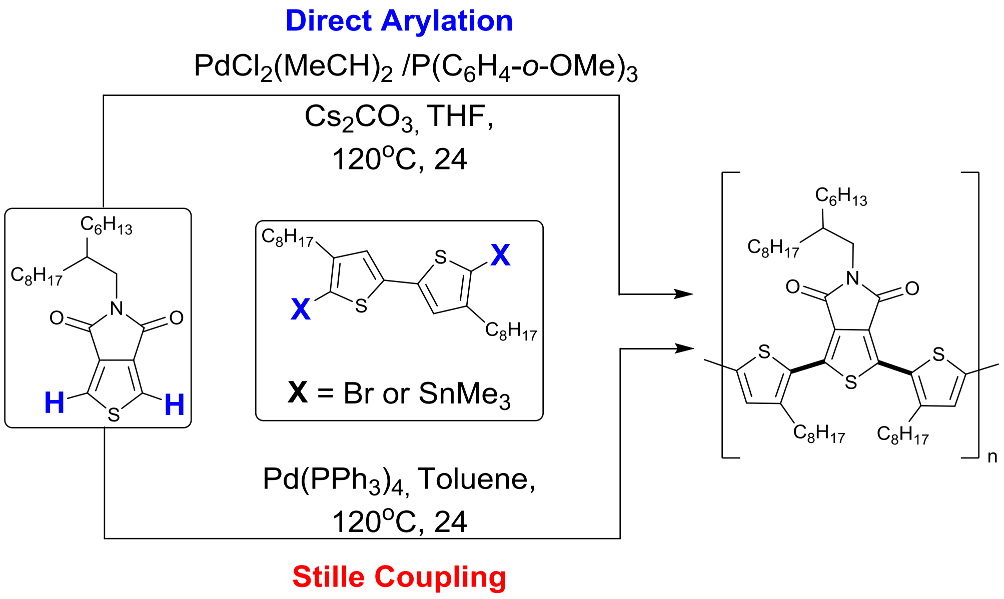
Polymer 7	**0.89**	**1.67**
Polymer 8	**0.39**	**6.3**

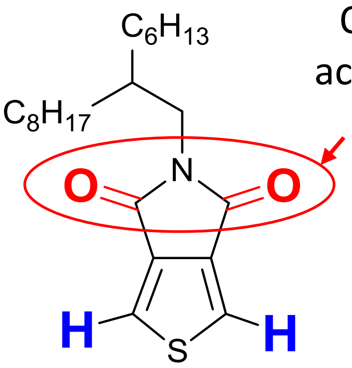
- Strategy of placing protecting groups severely affects PCE%
- Indicating the need to develop high regioselectivty for direct arylation polycondensation reactions

C. R. Kagan, *ACS Appl. Mater. Interfaces*, **2011**, **3**, 3874–3883; M. R. Anderson, *J. Am. Chem. Soc.*, **2011**, **133**, 14244–14247; Kanbara & co-workers *Polymer Chemistry* 4.4 (**2013**): 947-953.

C-H Direct Arylation Reactions:
Controlling Polymer Regioselectivity via Orienting Group

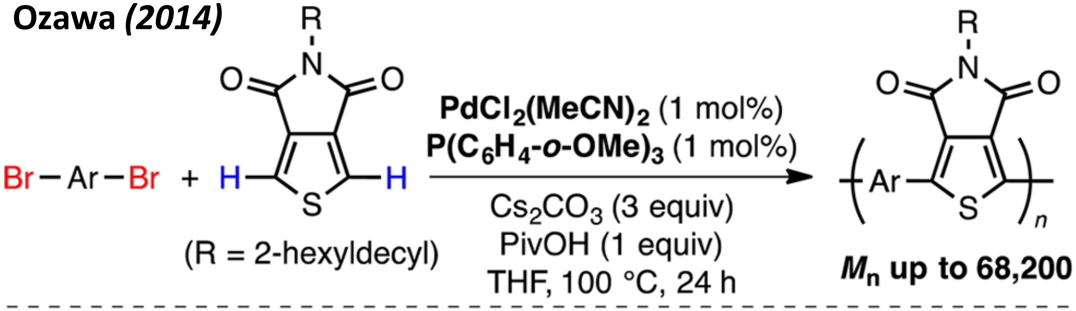
Work by Leclerc and Co-Workers





Orienting and activation Group for the **C-H**

- Record PCE of 7.3% for OPVs
- **Ozawa *(2014)***



Catalyst /Ligand Loadings

PdCl$_2$(MeCH)$_2$	**1%**	**8%**
P(C$_6$H$_4$-o-OMe)$_3$	**1%**	**16%**
M$_n$ (kDa)	**68**	**56**
PDI	**2.2**	**2.6**
Yield	**99**	**96**

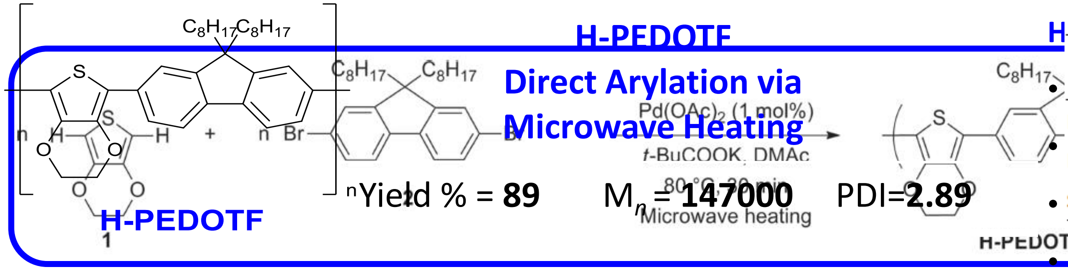
Polymerization Results

M$_n$ (kDa)	**56**	**9**
PDI	**2.6**	**1.5**
Yield	**96**	**71**

PCE efficiency: K.-H. Wei, *Adv. Mater.* **2011**, **23**, 3315–3319; M. Leclerc, *J. Am. Chem. Soc.* **2010**, **132**, 5330–5331; **Synthesis:** Leclerc, M. (**2012**). *Angewandte Chemie*, *124*(9), 2110-2113; Ozawa *et all. Macromolecules*, **2014**, *47* (2), pp 626–631

C-H Direct Arylation Reactions:
Controlling Polymer Regioselectivity, Purity & Molecular Weight via Reaction Conditions

Kanbara *et al.*

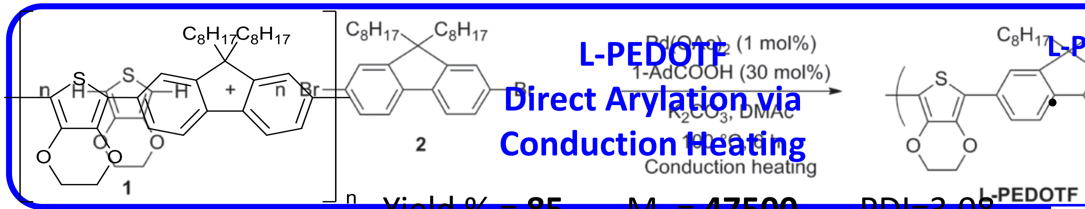


H-PEDOTF

Direct Arylation via Microwave Heating

Yield % = **89** M_n = **147000** PDI=**2.89**

H-PEDOTF

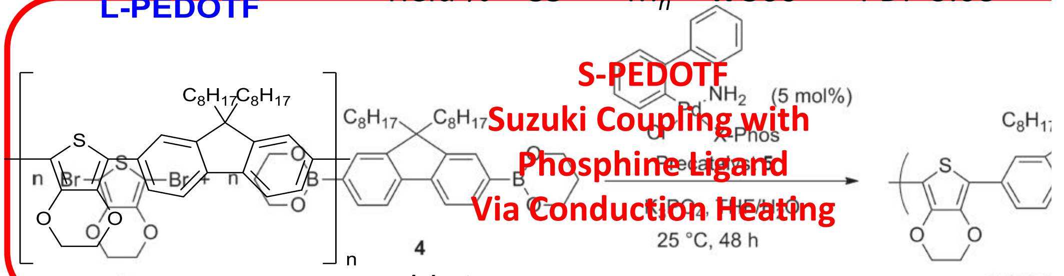


L-PEDOTF

Direct Arylation via Conduction Heating

Yield % = **85** M_n = **47500** PDI=3.08

L-PEDOTF



S-PEDOTF

Suzuki Coupling with Phosphine Ligand Via Conduction Heating

Yield % = **85** M_n = **17100** PDI=**2.08**

S-PEDOTF

Table 3. OFET[a)] characteristics.

Polymer	μ_h[b)] [$cm^2\,V^{-1}\,s^{-1}$]	on/off ratio	V_{th}[c)] [V]
H-PEDOTF	$1.2 \pm 0.1 \times 10^{-3}$	$1.6 \pm 0.4 \times 10^4$	−18 ± 1
L-PEDOTF	$7.7 \pm 0.4 \times 10^{-4}$	$9.2 \pm 0.2 \times 10^3$	−21 ± 1
S-PEDOTF	$3.2 \pm 0.2 \times 10^{-5}$	$4.3 \pm 1.0 \times 10^2$	−30 ± 1

- Efficient C-C bond Formation
- L-PEDOT & S-PEDOT
- **H-PEDOTF** mobility is by **two orders of magnitude higher** than **S-PEDOTF**
- Br terminated units and Non-alternating Polymer Structures

L-PEDOTF Direct Arylation via Conduction Heating

- Impurities in materials act as carrier traps
- Defects on terminal unit and non-alternating structures affect OFETs performance

Table 2. Results of elemental analysis and ICP-AES.

	Elemental analysis [%]			ICP-AES [ppm]	
	C	H	Br	Pd	P
Calculated value[a)]	79.50	8.39	0		
H-PEDOTF	79.44	8.33	0	1590	nd[b)]
L-PEDOTF	78.52	[illegible]	0.34	2300	nd[b)]
S-PEDOTF	77.48	8.42	0.08	4390	470

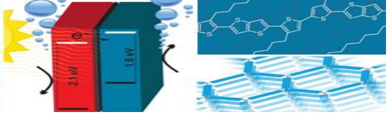
[a)] The values were calculated from the formula of the constituting repeating unit; [b)] Not detected.

	PCE%
H-PEDOTF	**4.08**
L-PEDOTF	**2.55**
S-PEDOTF	**0.48**

Direct Arylation Strategy

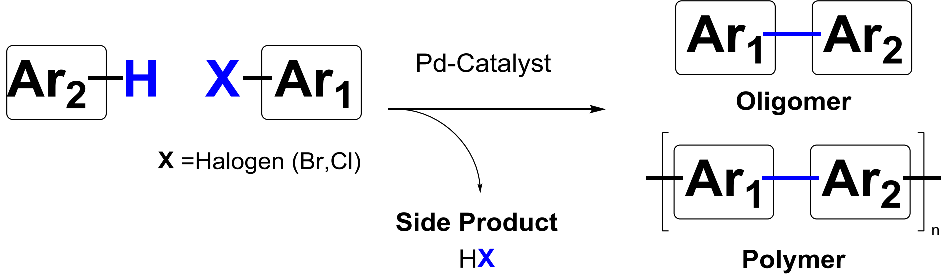
- Reduces number of Purification Steps
- High Purity and Molecular weight Polymer
- Improves Optoelectronic device performance

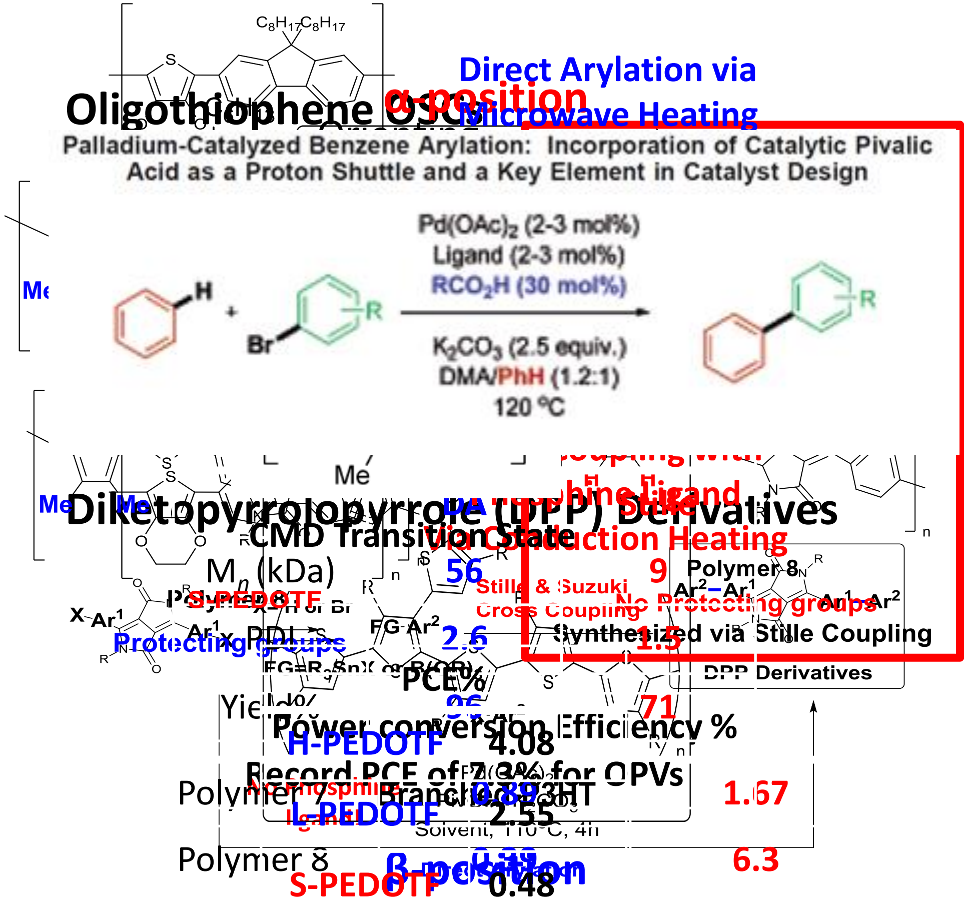
Kanbara, & co-workers *Advanced Functional Materials* (2014).



Overview

Direct Arylation Reaction





Palladium-Catalyzed Benzene Arylation: Incorporation of Catalytic Pivalic Acid as a Proton Shuttle and a Key Element in Catalyst Design

Pd(OAc)$_2$ (2-3 mol%)
Ligand (2-3 mol%)
RCO$_2$H (30 mol%)
K$_2$CO$_3$ (2.5 equiv.)
DMA/PhH (1.2:1)
120 °C

- Pd Catalyzed Reactions
  - Proceeds via Concerted-Metallation-Deprotonation
  - Carboxylate acid (PivOH) aids in C-H activation
  - Phosphine-Free Conditions
  - Versatile Reaction Conditions
  - Reduce Synthetic Steps
  - No Toxic Organometallic reagents
  - Less Toxic by-products
- Small molecule Direct Arylation Reaction show very good yields and obtain high purity products
- Problems of regioselectivity during C-H Activation for Polymerization reactions
- Lack of regiocontrol on C-H activation
  - Producing Branched & Cross linked polymer
  - (Monomer Dependent)
  - Protection of active C-H sites reduces side reactions
  - Affects optoelectronic properties in devices

Improved Device Performance

- Orienting Group aids in C-H Activation
- High Purity and Molecular Weight

C-H Direct Arylation Reactions:
Future developments & Main Challenges

- Many Challenges for both the catalytic design & materials synthesis community
- Most Arylation reaction proceed sufficiently well for small molecule OSCs
- Improvements still needed for Direct Arylation Polymerization Reactions
  - Higher yields and Molecular weight

    (>30000 Da for better OFET and OPV performance)
  - Better understanding and control of Regioselectivity
  - Develop pathways for living polymerizations

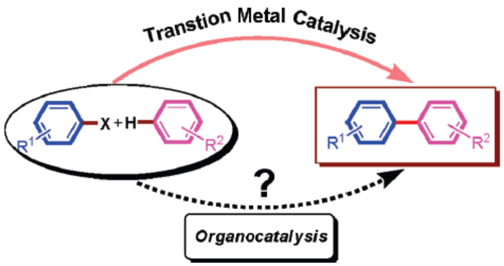
    (Currently based on Polycondensation reactions)
    - Constant Chain Length – Low PDI
    - Predictable Molecular Weight
    - Better Control of morphology of materials in Solid-state
    - Better Optoelectronic performance
- Wider range of monomers not just thiophenes
- Development of Metal Free Direct Arylation Reactions for Organic Semiconductors

Future developments:
Metal-Free Direct Arylation Reaction

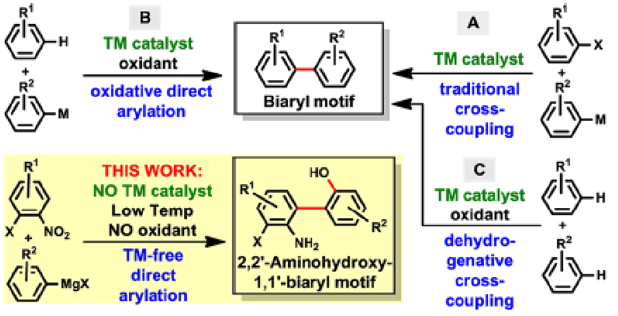
Organocatalysis in Cross-Coupling: DMEDA-Catalyzed Direct C−H Arylation of Unactivated Benzene

Wei Liu,† Hao Cao,† Hua Zhang,† Heng Zhang,† Kin Ho Chung,§ Chuan He,† Haibo Wang,†
Fuk Yee Kwong,*,§ and Aiwen Lei*,†,‡

Scheme 1. Approaches for Direct Arylation



Transition-Metal-Free Direct Arylation: Synthesis of Halogenated 2-Amino-2′-hydroxy-1,1′-biaryls and Mechanism by DFT Calculations



TM = transition metal, **X** = halides, pseudohalides, sulfonates; **M** = organomet. grp.

igure 2. Methods for the intermolecular construction of Ar–Ar bonds,
ncluding our novel *transition-metal-free direct arylation* process.

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Metal-Free, Visible-Light-Mediated Direct C−H Arylation of Heteroarenes with Aryl Diazonium Salts

Durga Prasad Hari, Peter Schroll, and Burkhard König*

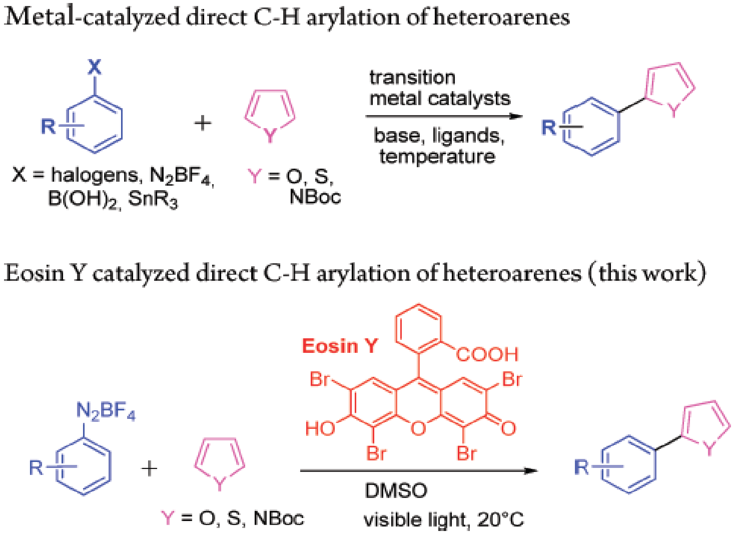


Figure 1. Metal-catalyzed and photocatalytic approaches for direct C−H arylation of heteroarenes.

Conclusion

- **Direct Arylation** is an Important tool for Chemist to synthesize Organic Semiconductors
  - Applying synthetic strategies that is **Efficient** & **Sustainable**
  - Highly useful for reactions without **toxic** and **stoichiometric** Organometallics
- Problems with regioselectivty and control for polymerization needs to be solved
- Other aspects of sustainable synthesis of Organic Electronics Materials
  - Metal free catalyzed Arylation reactions
  - Oxidative Homo-Coupling Reactions
  - Flow Reactor Synthesis
  - Use Cheap and abundant materials (Natural Dyes, Isoindingo, DPP etc.)

Energy &
Environmental Science

Effect of synthetic accessibility on the commercial viability of organic photovoltaics†

Timothy P. Osedach,[*a] Trisha L. Andrew[b] and Vladimir Bulović[c]

Energy Environ. Sci., 2013, **6**, 711

Green chemistry for organic solar cells

Daniel J. Burke and Darren J. Lipomi*

Energy Environ. Sci., 2013, **6**, 2053

Macromolecules

C–H Arylation Reaction: Atom Efficient and Greener Syntheses of π-Conjugated Small Molecules and Macromolecules for Organic Electronic Materials

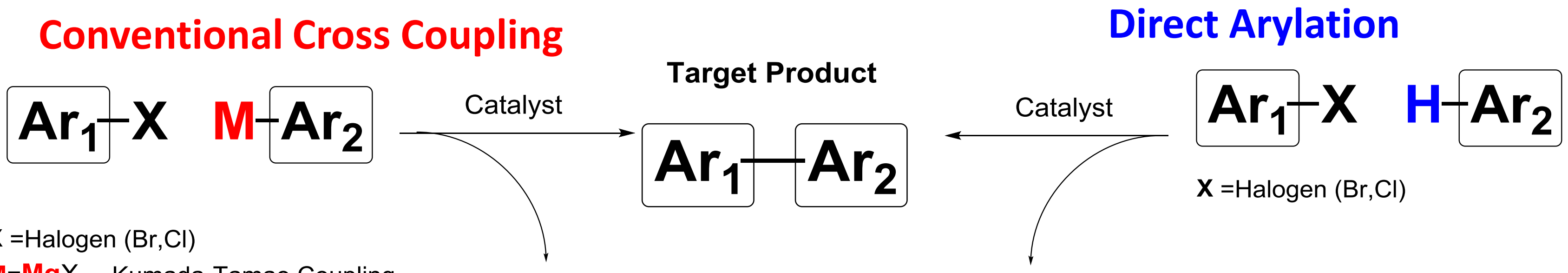
Ken Okamoto,[†,‡] Junxiang Zhang,[§] Jeremy B. Housekeeper,[‡,∥] Seth R. Marder,[*,§] and Christine K. Luscombe[*,†,‡]

Thank You for Listening!

1. What are the Key advantages of Direct Arylation over Cross Coupling Aryl-Aryl bond formation in the synthesis of π-Conjugated Organic Electronic Materials?

2. Why is it important to develop a green & sustainable synthetic stratergy for the synthesis of π-Conjugated Organic Electronic Materials?

What are the Key advantages of Direct Arylation over Cross Coupling Aryl-Aryl bond formation in the synthesis of π-Conjugated Organic Electronic Materials?



Conventional Cross Coupling

Ar_1-X $M-Ar_2$ Catalyst → **Target Product** Ar_1-Ar_2 ← Catalyst Ar_1-X $H-Ar_2$

Direct Arylation

X =Halogen (Br,Cl)

X =Halogen (Br,Cl)

M=**Mg**X_2 - Kumada-Tamao Coupling
ZnX_2 - Negishi Coupling
R_3SnX -Stille Copuling
$B(OR)_2$ - Suzuki Miyaura Coupling

Side Product
MgX_2
ZnX_2
R_3SnX
$B(OR)_2$-Base-X

Side Product
H**X**

Main Features

- Widely studied and used
- Halogenated or pseudo-halogenated aromatics
- Lithiation reaction to add SnR_3 and $B(OR_3)$
- Numerous steps in the preparation and purification of monomers
- Instability of reagents
  (Organostanne and Boronic ester monomers)
- Toxicity of reagents and side-products
- Stoichiometric amounts of by toxic-Products

Advantages over conventional cross coupling reactions

- Elimination of unstable organometallic reagent usage
- Less toxic by products
- Atom efficient
- Reduced formation of end groups with tin,boron and halogen moieties
- More efficient Ar-Ar bond formation
- Higher Yields
- lower catalyst loadings

Why is it important to develop a green & sustainable synthetic stratergy for the synthesis of π-Conjugated Organic Electronic Materials?

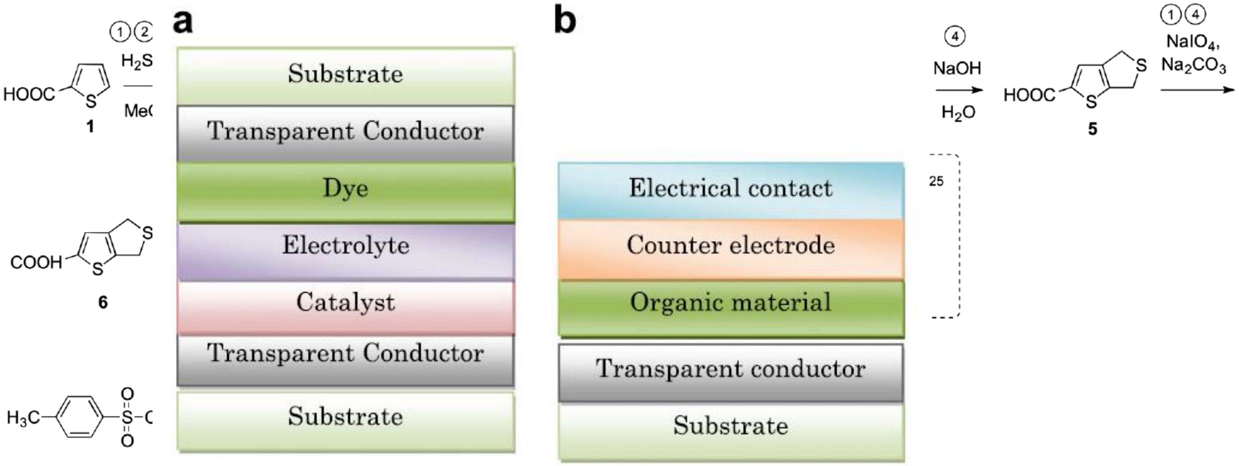


Table 1
Comparison of materials costs estimates for DSSC and OSC.

Cost Component	DSSC			OSC		
	Type used	Cost ($\$/m^2$)		Type used	Cost estimate ($\$/m^2$)	
		Low	High		Low	High
Semiconductor	TiO_2	0.04[*]	6.84[#]	C_{60}, CuPc & SnPc	3.30	5.00
Electrical contacts and interconnects	–	2.90[*]	6.84[#]	Aluminum, silver paint	3.40	5.00
Substrate[a]	PET glass	29.00	43.50[*,#]	Flexible Plastic, ITO	7.90	13.68
Protective cover	Glass cover	2.90[*]	45.58[#]	Flexible encapsulant	2.90	4.40
Sealant	Surlyn	2.90[*]	4.35[#]	Surlyn	2.90	4.40
Packaging material	N/A	N/A	N/A	–	2.00	3.00
Specialty chemicals	N/A	N/A	N/A	4 TBP	1.00	2.00
Other (absorbing dye; catalyst; electrolyte)	Ruthenium; platinum; tri-iodide	10.30[*]	14.50[#]	N/A	N/A	N/A
Total		45.14	121.61		23.40	37.48

[*] Smestad (1994), adjusted to 2008 values.

[#] Meyer (1996) adjusted to 2008 values.

[a] There are two substrates in DSSC devices hence the estimates are for the 2 substrates and not just one. For this reason, we base our estimate on $10/m2, which is the cost of one substrate.

Estimating the manufacturing cost of purely organic solar cells, Volume 83, Issue 8, August 2009, Pages 1224–1231 http://dx.doi.org/10.1016/j.solener.2009.02.003

Importance of developing a sustainable synthetic strategy

- Organic Electronic Materials are applied in various applications in OPVs, OFETs & OLEDs
- Great progress in Organic electronics is largely driven by the syntheses of increasingly complex **π-conjugated molecules**
- A lot of focus has been on designing efficient OSCs and device architecture for optimum optoelectronic performance
- Quantum efficiencies of OLEDs have outperform inorganic LEDs
- Power Conversion Efficiency (PCE) for OPVs have pass the 10%
- For example, for OPVs to play a significant role in the production of carbon-neutral energy, and to make solar energy more affordable than current technologies.
- The merit of high performance OSCs should not be judged only by highest demonstrated efficiency but also in the light of costs and environmental impact in the production of such materials , especially in large scale
- Cost of synthesizing the OSCs eg PBTTT-CF is estimated to cost around $400/g and requires 10 steps to synthesize
- For Organic Electronic devices to be economically viable
- Developing efficient syntheses is needed lower cost of materials in a manner that is eco friendly
- Fewer steps, fewer toxic reagents & by products
- One such stratergy in the Direct Arylation Reaction

DHAR Review: Okamoto, Ken, et al. *Macromolecules* 46.20 (2013): 8059-8078; M. Leclerc. *Accounts of chemical research* 46.7 (2013): 1597-1605.
Negishi:R.D.Rieke. *Journal of the American Chemical Society* 117.1 (**1995**): 233-244. **Kumada:R.** McCullough J. Chem. Soc., Chem. Commun., 1992, 70-72.
Stille: Iraqi, A.; Barker, G. W. *J. Mater. Chem.* **1998**, 8, 25 **Suzuki:** Guillerez, S.; Bidan, G. *Synth. Met.* **1998**, 93, 123

CH-707: Frontiers in Chemical Synthesis-Towards Sustainable Chemistry

Combinatorial Pd and Micellar Catalysis in Water

Christopher M.B.K Kourra

Contents for Sustainable Chemistry Presentation

- Brief introduction to sustainable chemistry

- Introduction to micelles and the purpose of their usage

- Design of surfactant molecules
  → ASIDE: More exotic surfactant molecules

- Pd catalysed cross coupling reactions with micelles in water:
    - Suzuki-Miyaura
    - Heck
    - Sonogashira
    - Stille
    - Negishi
    - Buchwald-Hartwig
    - Etc…….

- Summary and Outlook

Sustainable Chemistry Exercises

1) What are the key design features of a surfactant molecule?

2) Can you propose the major fragments for the synthesis of surfactant molecule “Nok”?

3) What are the advantages of Pd catalysed cross couplings in a water/micelle medium?

Introduction to Sustainable/Green Chemistry

The twelve principles of Green Chemistry:[1]

1) Waste minimisation and prevention

2) Atom economy

3) Design less hazardous chemical syntheses

4) Design and use of safer chemicals

5) Use of safer solvents and reaction conditions

6) Design for energy efficiency

7) Use of renewable feedstocks/raw materials

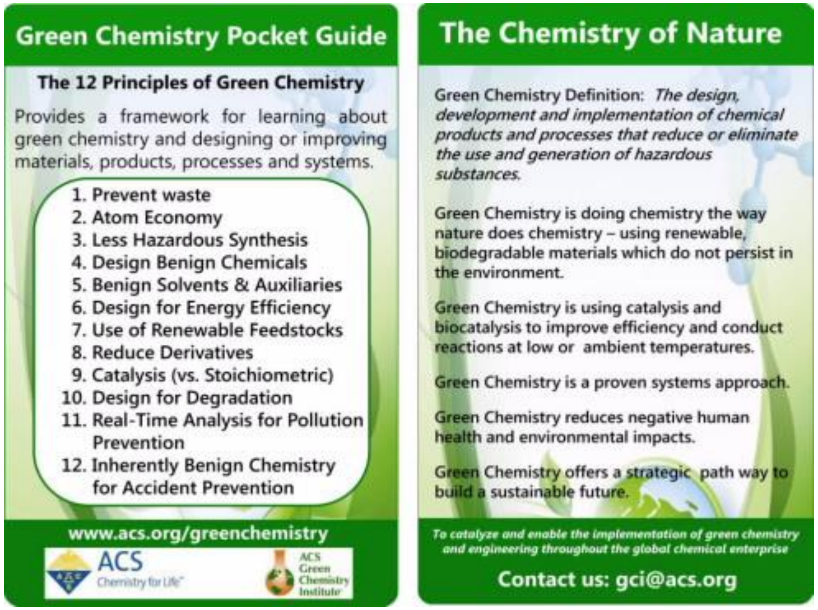
8) Reduce the use of chemical derivatives

9) Catalytic rather than stoichiometric reagents

10) Taking advantage of chemicals designed to degrade

11) Establishment of real-time controls for pollution prevention

12) Inherently safer chemistry for accident prevention



Green Chemistry Pocket Guide

The 12 Principles of Green Chemistry

Provides a framework for learning about green chemistry and designing or improving materials, products, processes and systems.

1. Prevent waste
2. Atom Economy
3. Less Hazardous Synthesis
4. Design Benign Chemicals
5. Benign Solvents & Auxiliaries
6. Design for Energy Efficiency
7. Use of Renewable Feedstocks
8. Reduce Derivatives
9. Catalysis (vs. Stoichiometric)
10. Design for Degradation
11. Real-Time Analysis for Pollution Prevention
12. Inherently Benign Chemistry for Accident Prevention

www.acs.org/greenchemistry

The Chemistry of Nature

Green Chemistry Definition: *The design, development and implementation of chemical products and processes that reduce or eliminate the use and generation of hazardous substances.*

Green Chemistry is doing chemistry the way nature does chemistry – using renewable, biodegradable materials which do not persist in the environment.

Green Chemistry is using catalysis and biocatalysis to improve efficiency and conduct reactions at low or ambient temperatures.

Green Chemistry is a proven systems approach.

Green Chemistry reduces negative human health and environmental impacts.

Green Chemistry offers a strategic path way to build a sustainable future.

To catalyze and enable the implementation of green chemistry and engineering throughout the global chemical enterprise

Contact us: gci@acs.org

ACS green chemistry pocket guides[2]

- Those in **blue** focus of reducing the risk in the laboratory
- Those in **green** are concerned with minimising the environmental footprint

[1] P. T. Anastas, J. C. Warner (eds.), *Green Chemistry: Theory and Practice*, **2000**, Oxford University Press (OUP), New York

[2] Green Chemistry and Engineering, ACS (www.acs.org/green chemistry); www.sigmaaldrich.com/chemistry/greener-alternatives.html

Introduction to Sustainable/Green Chemistry

Within chemistry there are several ways to work towards **sustainable chemistry**:

- Catalysis: Organocatalysis,
  - TM catalysis
  - Biocatalysis
- C-H activation
- Cascade reactions/ One-pot syntheses (Step economy- P. Wender)[1]
- Atom economy (B. Trost)[2]
- Flow chemistry
- **Chemistry in water (or "on-water")**

- In the past there was little serious consideration of water as a suitable reaction solvent - **fear of hydrolysis.**[3a]

- One of the original cases in which water was used as the reaction medium was Breslow's work describing how water enhances the Diels Alder reactions.[3b,c]

- Sharpless et al. conceived the concept of **"on-water" reactions** – instances where the reactants are insoluble in water.[3d]

Area of concern is the purification of the water used after these reactions

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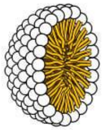
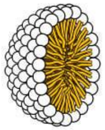
1. P. A. Wender, V. A. Verma, T. J. Paxton T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40-49.

2. a) B. M. Trost, *Science*, **1991**, *254*, 1471-1477; b) B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 259-281

3. a) R. N. Butler, A. G. Coyne, *Chem. Rev.* **2010,** *110*, 6302-6337; b) D. C. Rideout, R. Breslow, *J. Am. Chem. Soc.* **1980**, *102*, 7816- 7817; c) R. Breslow, *Acc. Chem. Rev.* **2004**, *37*, 471-478; d) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, B. K. Sharpless, *Angew. Chem. Int. Ed.* **2005**, *44*, 3275-3279.



What are micelles?

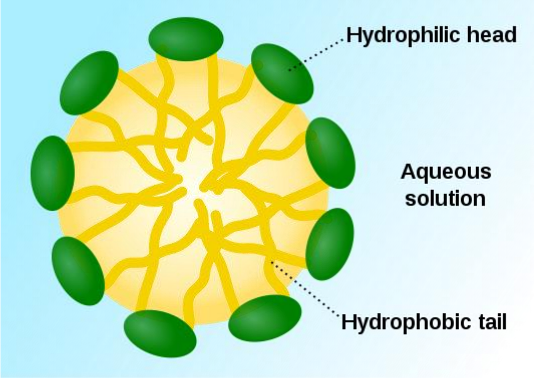


IUPAC definition: Micelle is a “particle of colloidal dimensions that exists in equilibrium with the molecules or ions in solution from which it is formed.”

Alan D. MacNaught, Andrew R. Wilkinson (eds.). Compendium of Chemical Terminology: IUPAC Recommendations (2nd ed.) (the "Gold Book“), ***1997****, Blackwell Scientific Publications, Oxford.*

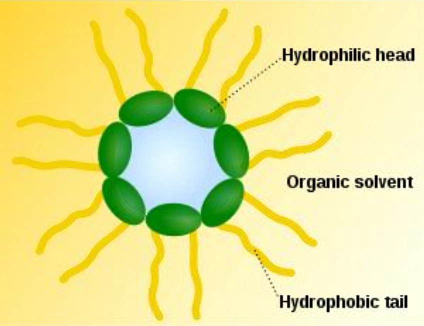
- A micelle is an aggregate of surfactant molecules dispersed in a liquid colloid.

Normal Phase Micelle



- **“Oil-in-water system”**
- The hydrophilic head is polar and can be charged (+ve or -ve)
- The tail of the surfactant molecule is hydrophobic
- The individual surfactant molecules are thus **amphiphilic**

Reverse/Inverse Micelle

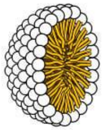


“Water-in-oil system”

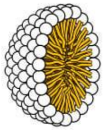
- Micelles act as **emulsifiers** and are thus capable of dispersing a liquid or solid into another immiscible liquid.

- The insoluble species is incorporated into the **micelle core**, which acts as the ***‘effective reaction solvent’***.

Source of pictures: Swiss-Prot.; Swiss Institute of Bioinformatics (SIB), Geneva



What are micelles?

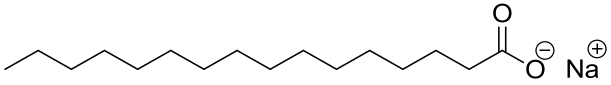


Brief History of their Discovery

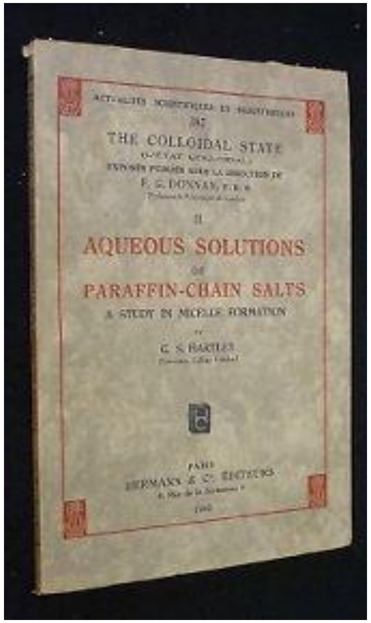
University of BRISTOL

- First scientific study into micelles was carried out in **1913** by **James William McBain** at the University of Bristol.[1]

- Postulation of the existence of 'colloidal ions' in order to rationalise the good electrolytic conductivity of aqueous solutions containing sodium palmitate (sodium hexadecanoate).



- The term **'micelles'** was popularised by G.S. Hartley book[2] entitled:
Aqueous Solutions of Paraffin Chain Salt: A Study in Micelle Formation



THE COLLOIDAL STATE
F. G. DONNAN
II
AQUEOUS SOLUTIONS
OF
PARAFFIN-CHAIN SALTS
A STUDY IN MICELLE FORMATION
BY
G. S. HARTLEY
PARIS
HERMANN & Cie, ÉDITEURS

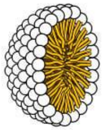
Some Physical-Organic Considerations:

- With ionic surfactants, (i.e. the hydrophilic heads are charged):
  - → the micelles are **evenly dispersed** in the solution due to mutual repulsion
  - → **electrolytic conductivity** of the aqueous solution
  - → significant **ordering** of the surrounding solvent molecules

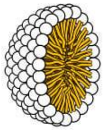
---

[1] J. W. McBain, *Trans. Faraday Soc.* **1913**, 9, 93-107

[2] G. S. Hartley, *Aqueous Solutions of Paraffin Chain Salts, A Study in Micelle Formation*, **1936**, Hermann et Cie, Paris.

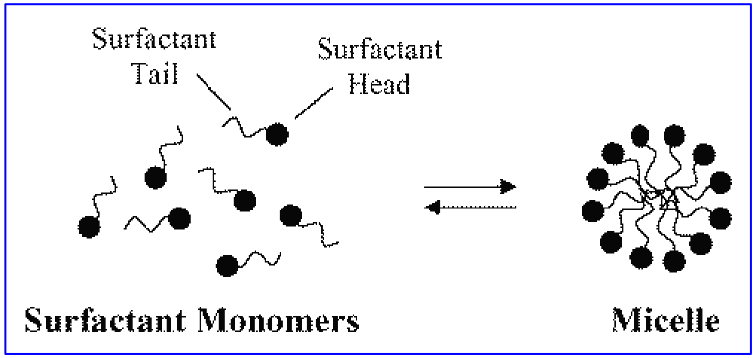


The Critical Micelle Concentration (CMC)[1]



- **IUPAC** definition: “the concentration of surfactants above which micelles will spontaneously form”
Alan D. MacNaught, Andrew R. Wilkinson (eds.), Compendium of Chemical Terminology: IUPAC Recommendations (2nd ed.) (the "Gold Book“), ***1997****, Blackwell Scientific Publications, Oxford.*

- **Krafft Temperature:** Temperature of the solution above which surfactants can form micellar aggregates[2]



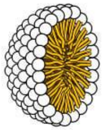
Reversible monomer-micelle thermodynamic equilibrium[3]

- The existence of micelles in solution does not mean that there are no individual surfactant molecules whatsoever in solution.

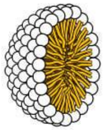
- The **Hydrophobic Effect** is the **energetic driving force** for the formation of micelles.[4]
- The lipophilic tails of the surfactant molecules **minimise unfavourable interactions** with water when they are part of a micelle as the oil-like core.

- Above the CMC, the **entropic penalty** of micellar assembly is outweighed by the entropic penalty of caging the individual surfactant monomers with water molecules.[4]

1. D. E. Kile, C. T. Chiou, *Environ. Sci Technol.* **1989**, *23*, 832-838
2. C. Vautier-Giongo, B. L. Bales, *J. Phys. Chem. B* **2003**, *107*, 5398-5403
3. *Scheme*: C. O. Rangel-Yagui, A. Pessoa-Jr., L. C. Tavares, *J. Pharm. Pharmaceut. Sci.* **2005**, *2*, 147-163
4. a) H.-J. Butt, K. Graf, M. Kappl, *Physics and Chemistry of Interfaces*, **2006**, Wiley-VCH: Weinheim, 269-277;
b) K. Esumi, U. Minoru *Structure-performance Relationships in Surfactants*. 2nd ed., Vol. 122, **2003**, New York: Marcel Dekker

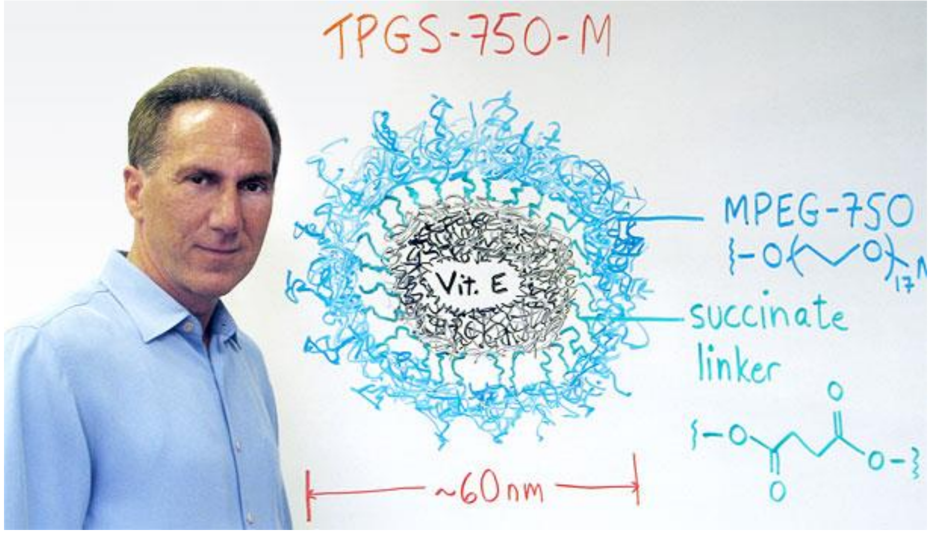


Using micelles as 'nanoreactors'[1]



- **Prof. Bruce Lipshutz** based at University of California- Santa Barbara (**UCSB**)
- Works on the **development of surfactant molecules**
- Investigates their **application to Pd, Ru, Rh, Au and Cu catalysis**

UCSB



> "Reactions in **alternative media** represent one approach to decreasing the huge amounts of organic waste generated by use of organic solvents in organic chemistry. ….. the **most likely and perhaps logical choice is water**."[2a]
>
> "Get organic solvents out of organic reactions"[2b]

This chemistry covers several key points of the green chemistry principles:

- Safer solvents - innocuous when used	(Only water is used; no need for a co-solvent)
- Waste minimisation of organic solvents	(80% of organic waste is estimated to be solvents)[3]
- Safer chemicals by design	(Surfactants)
- Employment of catalysts	(Catalytic amounts of TM's)

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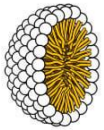
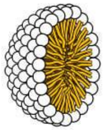
1. Review on **'Reactions in micellar systems'**: G. Oehme, E. Paetzold, T. Dewars, *Angew. Chem. Int. Ed.* **2005**, *44*, 7174-7199

2. a) S. Handa, J. C. Fennewald, B.H. Lipshutz, *Angew. Chem. Int. Ed.* **2014**, *53*, 3432-3435; b) N. A. Isley, F. Gallou, B. H. Lipshutz, *J. Am. Chem. Soc*. **2013**, *135* , 17707-17710.

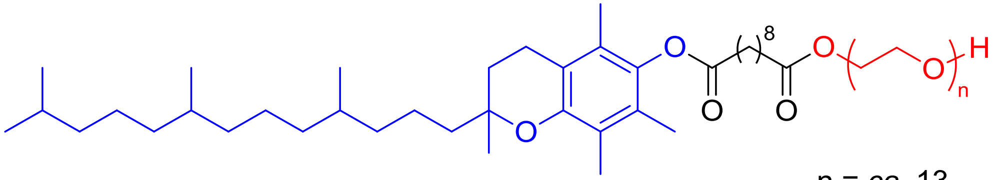
3. a) K. H. Shaughnessy, R. B. DeVasher, *Cur. Org. Chem.* **2005**, *9*, 585-604; b) R. A. Sheldon, I. W. C. E. Ardens, U. Hanefield, *Green Chemistry and Catalysis*, **2007**, Wiley-VCH: Weinheim, Germany.



The Design of Surfactant Molecules



First Generation: PTS-600 (Polyoxyethanyl α-tocopheryl sebacate)[1]



n = *ca.* 13

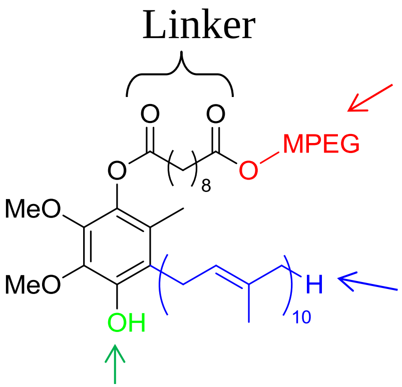
- **Vitamin E based**, non-ionic amphiphile were developed by Prof. Lipshutz

- PTS is commercially available *via* Sigma Aldrich (698717)

- The α-tocopheryl hydrocarbon chain acts as the 'effective reaction solvent.'

- PTS molecules form on average 24 nm diameter micelles.

PQS (Polyoxyethanyl ubiquinol sebacate)[2]



Hydrophilic head: solubilises PQS in pure water

Lipophilic tail: solubilises organic substrates

'Handle' to attach catalyst

PQS has three main components:

- Water soluble MPEG (polyethylene glycol) chain
- Sebacic acid (linker)
- Ubiquinol (fully reduced Coenzyme Q_{10})

All are totally safe for human consumption.

- The surfactant molecule is **environmentally benign by design.**

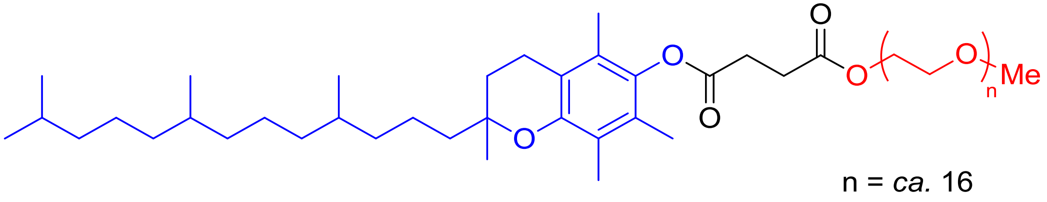
---

1. For reviews on 1st and 2nd generation surfactants and their uses see: a) B. H. Lipshutz, S. Ghorai, *Aldrichimica Acta.* **2008**, *41(3)*, 59-72; b) B. H. Lipshutz, S. Ghorai, *Aldrichimica Acta.* **2012**, *45(1)*, 3-16

2. R. Moser, S. Ghorai, B. H. Lipshutz, *J. Org. Chem.* **2012**, *77*, 3143-3148

The Design of Surfactant Molecules

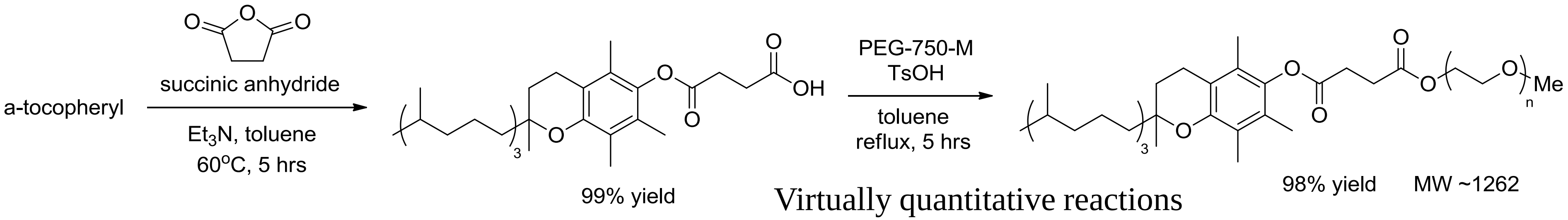
Second Generation: TPGS-750-M[1]



- Commercially available *via* Aldrich (733857)

- Like the 1st gen. surfactants, TPGS-750-M's lipophilic tail is racemic Vitamin E (**very costly component**).

Synthesis of TPGS-750-M



Virtually quantitative reactions

- For TPGS-750-M: **streamlined the surfactant synthesis** to make it **more economical**

(1) Shorter, significantly cheaper, four carbon, succinic acid linker

→ using succinic anhydride ensures only the **ring opened half acid ester is selectively formed**

(With PTS, lack of regiocontrol in esterification of sebacoyl chloride; extensive diester by-product formation)

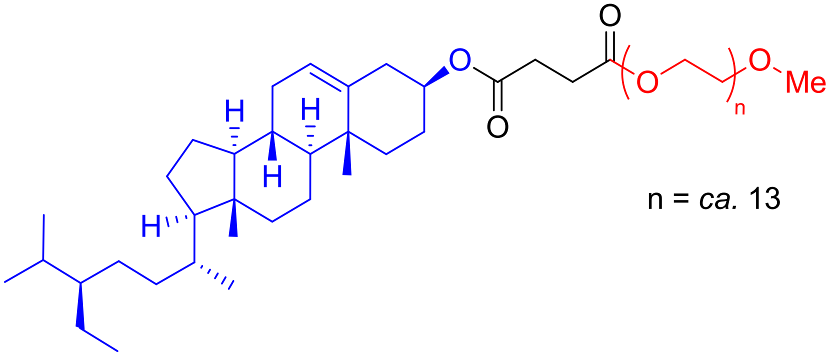
(2) The use of a mono-methylated PEG chain rather than a PEG diol **avoids double-ended diesterification** often seen with PTS

(3) Larger 53nm micelle (average diameter) determined by DLS

1. B. H. Lipshutz, S. Ghorai, A. R. Abela, R. Moser, T. Nishikata, C. Duplais, A. Krasovskiy, R. D. Gaston, R. C. Gadwood, *J. Org. Chem.* **2011**, *76*, 4379-4391

The Design of Surfactant Molecules

Third Generation: “Nok” (SPGS-550-M)[1]



n = *ca.* 13

- Recently developed in 2013/2014 and commercially available *via* Aldrich (776033)

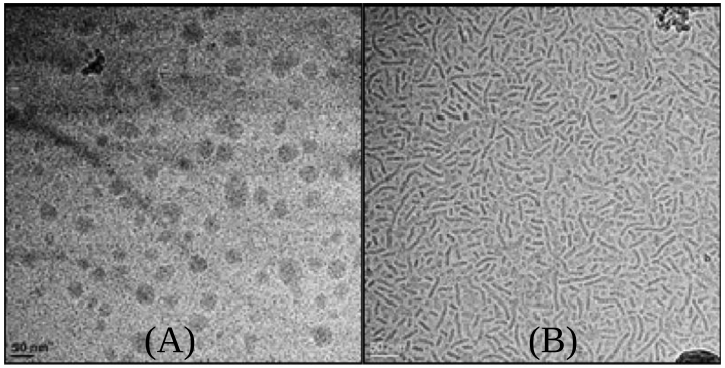
- **Prepared in two steps**: esterification of β-sitosterol with succinic anhydride and then a second esterification of the acid with MPEG-550.[1]

- **Same synthetic route** as for TPGS-750-M.[2]

- Nok is **significantly less expensive** and an equally effective substitute for TPGS-750-M. (Extensive side-by-side reactions showed **comparable yields and reaction rates** with TPGS-750-M.)[1]

- Smaller 550-MPEG gives rise to larger nanomicelles (dia. ~45–60 nm). **.: Greater surface area for reactions to occur**.

- Larger (M)PEG derivatives (750 or 1000) of Nok result in smaller nanomicelles (14-25 nm) and therefore lower levels of conversion and yields of desired products.



Cryo TEM image of (A) TPGS-750-M and (B) Nok

1. P. Klumphu, B. H. Lipshutz, *J. Org. Chem.* **2014**, *79*, 888-900
2. B. H. Lipshutz, S. Ghorai, A. R. Abela, R. Moser, T. Nishikata, C. Duplais, A. Krasovskiy, R. D. Gaston, R. C. Gadwood, *J. Org. Chem.* **2011**, *76*, 4379-4391

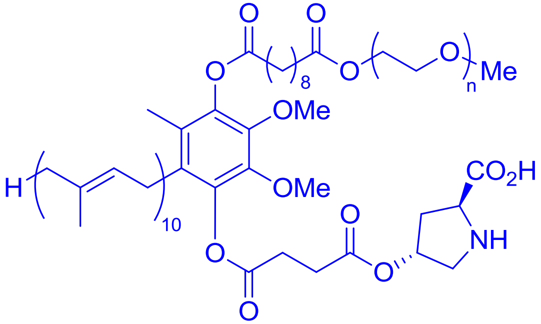
ASIDE: More Exotic Surfactant Molecules

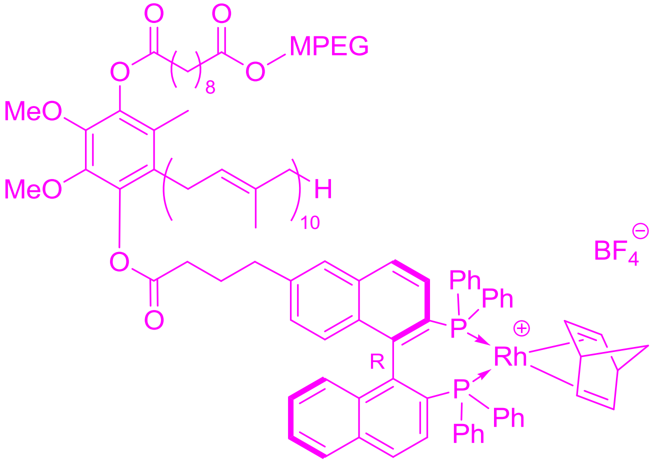
- The design of more complicated amphiphiles: catalyst is incorporated into the surfactant molecule.
- Concept of: "**In-flask catalyst recycling**" - catalyst can be recycled without being removed from the reaction vessel.

PQS-proline

- **Proline organocatalyst** covalently linked to the surfactant PQS molecule.[1]

- Water soluble MPEG-2000 component allows it to remain in solution upon in-flask extraction of the product.





PQS-BINAP-Rh(nbd)BF$_4$

- **First** non-racemically ligated transition metal catalyst tethered amphiphile.[2]

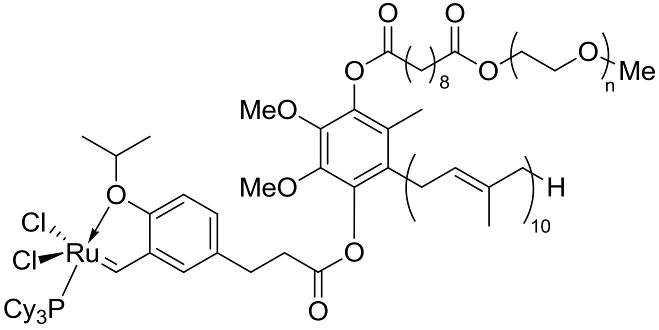
- Used for Rh catalysed asymmetric conjugate additions of arylboronic acids to cyclic and acyclic enones.

- Improvement in yield and ee of desired products compared with traditional organic solvents.

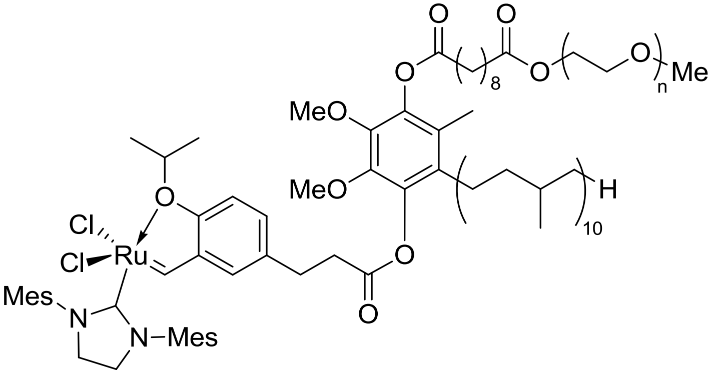
- ICP-MS revealed **catalyst bleeding** into the organic extract was **very low**; average Rhodium content of 17ppb prior to FCC.

1. B. H. Lipshutz, S. Ghorai, *Org. Lett.* **2012**, *14*, 422-425;
2. B. H. Lipshutz, N. A. Isley, R. Moser, S. Ghorai, H. Leuser, B. R. Taft, *Adv. Synth. Catal.* **2012**, *354*, 3157-3179

ASIDE: More Exotic Surfactant Molecules



PQS GH-1



PQS GH-2

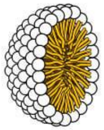
- Development of a PQS surfactant linked to GH-1 and GH-2 Ru catalysts.[1,2]

- Applied to both **RCM** and **Cross Metathesis** reactions performed **in water, at r.t. and open to air**.[1,2]

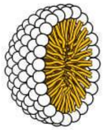
- PQS GH-2 requires the use of saturated lipophilic chain due to catalysts incompatibility with polypenoidal side chain

- PQS GH-2 catalyst was **recycled 7 times**; still providing acceptable isolated yields ~65%.
- Grubbs 2nd gen. and GH 2nd gen. gave <1% on second cycle.

1. B. H. Lipshutz, S. Ghorai, *Tetrahedron* **2010**, *66*, 1057-1063
2. B. H. Lipshutz, S. Ghorai, *Org. Lett.* **2009**, *11*, 705-708

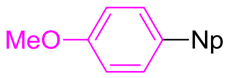


Pd. catalysed Suzuki-Miyuara cross couplings in water with the aid of micelles

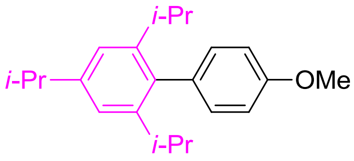


- Suzuki-Miyuara reaction is one of the most valued C-C bond forming reactions in organic chemistry.

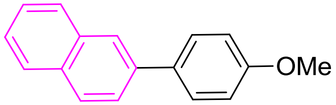
$$\underset{1.0\ \text{eq.}}{\text{(Het)ArX}} + \underset{1.5\text{-}2.0\ \text{eq.}}{\text{Ar'B(OH)}_2} \xrightarrow[\text{1-2 \% wt PTS/H}_2\text{O, RT}]{\text{2 mol\% Pd (dtbpf)Cl}_2 \quad 3.0\ \text{eq. Et}_3\text{N}} \text{HetAr-Ar'}$$



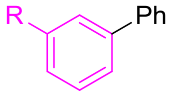
X= I, 7 hrs, 93%



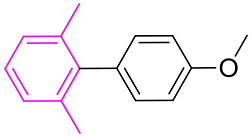
X = Br, 24 hrs, 76%



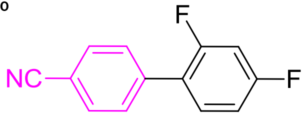
X = CF_3 2.5 hrs, 81%
n-C_8F_{17} 2.5 hrs, 95%



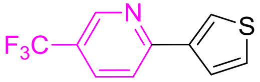
X = Br, R = CO_2Me, 0.25 hrs, 95%
Br CN 2 hrs, 78%



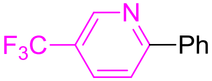
X = Cl, 50°C, 24 hrs, 82%
Cl, RT, 11 hrs, 99%^{a}



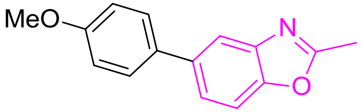
X = Cl, 22 hrs, 96%



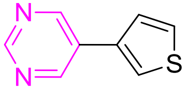
X = Cl, 19 hrs, 99%



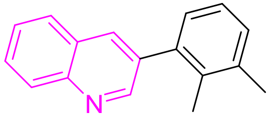
X = Cl, 24 hrs, 94%



X = Cl, 24 hrs, 95%^{b}



X = Br, 6 hrs, 99%



X = Br, 10 hrs, 86%

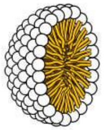
[a] Pd catalyst Neolyst™ CX31 (Umicore) was used instead; [b] 40°C

- Coupling of aryl halides and pseudohalides[1a)] or heteroaryl halides (bromides and chlorides)[1b)] with arylboronic acids in pure water and in most cases at **room temperature**.

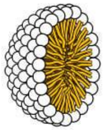
- The **absence of PTS was detrimental** to the yields of the reaction.
  → The corresponding "on-water" reactions do occur but to highly varying degrees and with lower yields.[2]

- A plethora of substrates and functional groups were tolerated by this reaction.

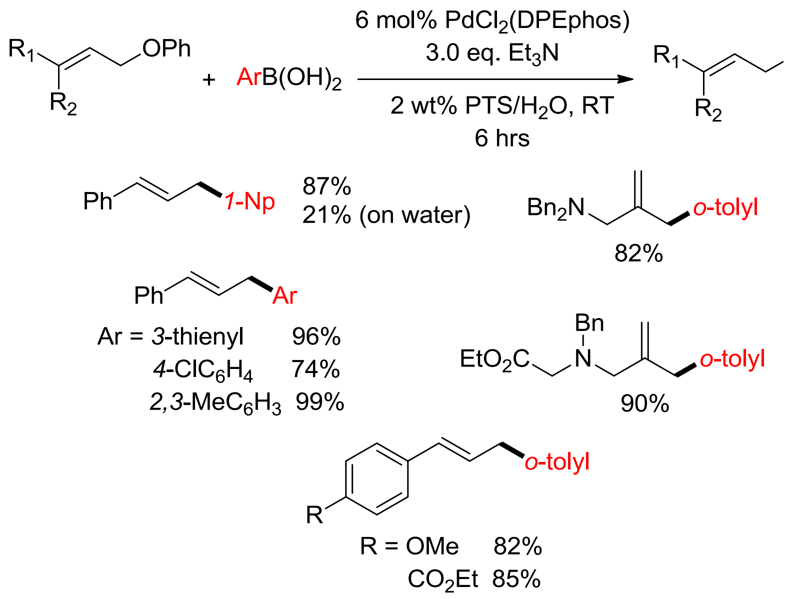
1. a) B. H. Lipshutz, T. B. Peterson, A. R. Abela, *Org. Lett.* **2008**, *10*, 1333-1336; b) B. H. Lipshutz, A. R. Abela, Org. Lett. **2008**, *10*, 5329-5332.
2. S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolib, B. K. Sharpless, *Angew. Chem. Int. Ed.* **2005**, *44*, 3275-3279

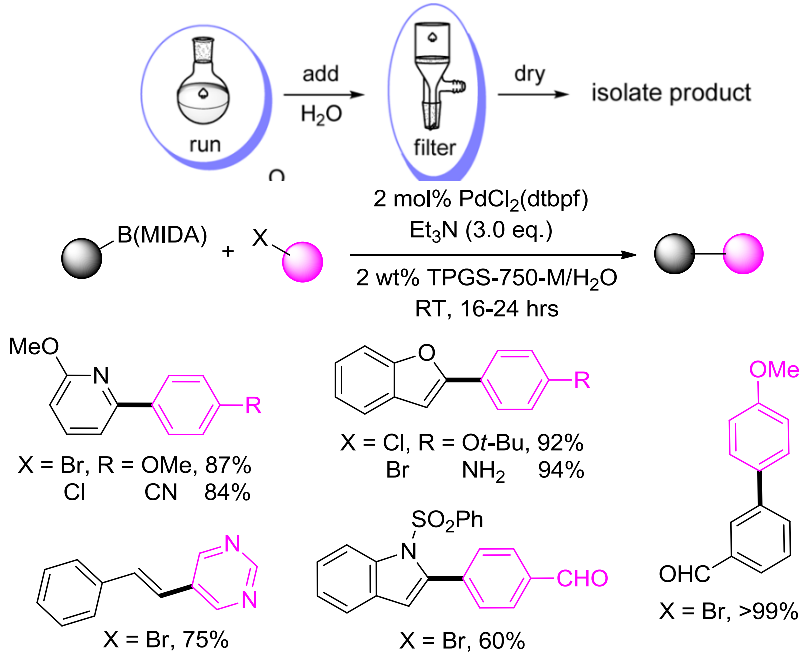


Pd. catalysed Suzuki-Miyuara cross couplings in water with the aid of micelles



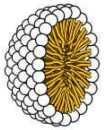
- **First** Suzuki-Miyuara reaction with **functionalised allylic ethers** at r.t, in water as only reaction medium made possible by combinatorial Pd and micellar catalysis.[1a)]
- Allylic ethers bearing various functional groups and electronic properties are tolerated by the reaction.

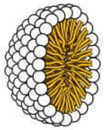




- Suzuki coupling of aryl/heteroaryl bromides and chlorides with air stable, crystalline **MIDA boronates** with release of the boronic acid occuring in water at r.t.[1b)]
- Normally product isolation involves extractive work-up with organic solvent to obtain the product. **No organic solvent is involved at any stage with this protocol with E factors approaching zero**.
  → Aqueous reaction medium was **recycled**.[1b]

1. a) T. Nishikata, B. H. Lipshutz, *J. Am. Chem. Soc*. **2009**, *131*, 12103-12105; b) N. A. Isley, F. Gallou, B. H. Lipshutz, *J. Am. Chem. Soc*. **2013**, *135* , 17707-17710.

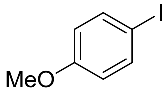
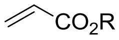
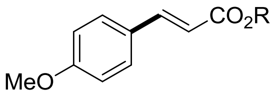
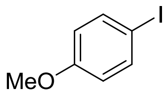
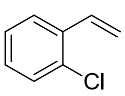
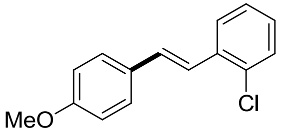
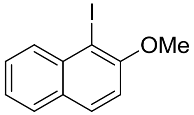
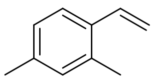
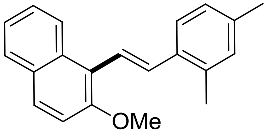
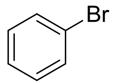
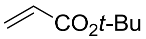
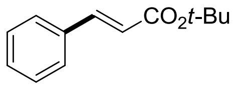




Pd cat. Heck couplings in water with the aid of micelles[1]

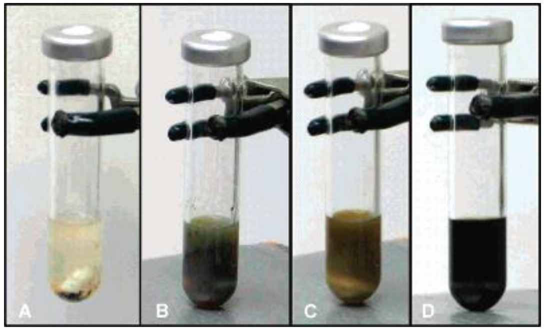
- **First** example of Heck reactions conducted **in only water** (no co-solvent) and **at room temperature**.[2a)]
  → The corresponding reactions in purely organic solvents do not occur at room temperature.[2a)]
- Comparative study of the three generations of surfactants showed slightly higher yields for the later two.[2b),c)]

Heck Reaction of acrylates and styrenes under micellar conditions

Aryl Halide (1 eq.)	Acrylate or styrene (2 eq.)	Product	Yield (%) PTS, TPGS-750-M, Nok
			R = *t*-Bu; 96, 97, 99 $CH_2CH(Et)$*n*-Bu; 84, 92, 93
			-, 99, 99
			92, 95, -
			-, 84[a], 79[a,b]

Reaction conditions: 2 mol% Pd(t-$Bu_3P)_2$, 3 eq. Et_3N, 2-5 wt% surfactant/H_2O, RT, 4-12 hrs

Appearance of a Heck Reaction



(A) *t* = 0 (*heterogeneous*); (B) *t* = 1 min, (C) *t* = 30 mins, (*pseudo-homogeneous*); (D) *t* = 3 hrs

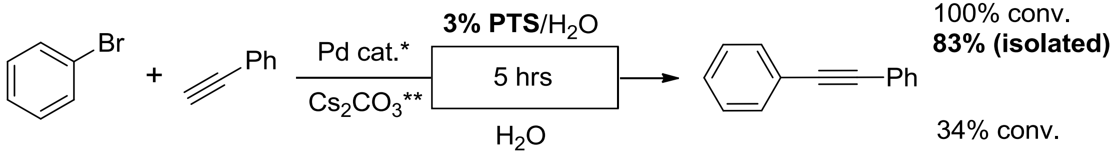
[a] Run for 72 hrs; [b] **19 hrs: 0M NaCl 29%; 1M NaCl 59%; 2M NaCl 76%; 3M NaCl 90%**

- Employment of "greasy" aryl iodides and acrylates emphasises the solublising power of these surfactants.
- Significant **enhancement of reactivity** of aryl bromides at r.t. was observed in the presence of **3M NaCl**.[3]

1. B. H. Lipshutz, N. A. Isley, J. C. Fennewald, E. D. Slack, *Angew. Chem. Int. Ed.* **2013**, *52*, 10952-10958.
2. a) B. H. Lipshutz, B. R. Taft, *Org. Lett.* **2008**, *10*, 1329-1332; b) B. H. Lipshutz, S. Ghorai, A. R. Abela, R. Moser, T. Nishikata, C. Duplais, A. Krasovskiy, R. D. Gaston, R. C. Gadwood, *J. Org. Chem.* **2011**, *76*, 4379-4391; c) P. Klumphu, B. H. Lipshutz, *J. Org. Chem.* **2014**, *79*, 888-900.
3. B. H. Lipshutz, S. Ghorai, W. W. Y. Leong, B. R. Taft, D. V. Krogstad, *J. Org. Chem.* **2011**, *76*, 5061-5073.

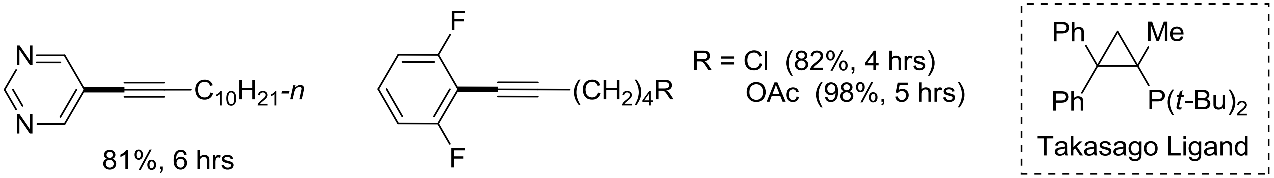
Pd catalysed Sonogashira cross couplings in water with the aid of micelles

- **First** Sonogashira coupling performed in the absence of copper[1] and organic solvents and **at r.t.**[2]
- Usually elevated temperatures and forcing conditions are required for Sonogashira couplings with aryl bromides.[3]



* 1 mol% $PdCl_2(CH_3CN)_2$, 2.5 mol% XPhos; ** 3.5 eq.

- Unprecedented, cross coupling of aryl bromide and terminal acetylene in water at ambient temperature.
- Bromobenzene + phenylacetylene in PTS/H_2O medium gave 100% conv. and 83% isolated yield in 5 hrs.
  → Whereas comparison with the “**on water**” reaction (i.e. *w/o* surfactant) gave 34% conv. in 5 hrs.



Reaction conditions: 1 mol% $Pd(OAc)_2$, 2.5 mol% Ligand, 3 eq. Et_3N, 3 wt% surfactant/H_2O, RT

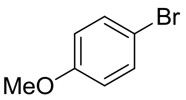
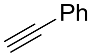
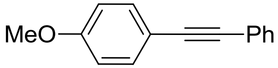
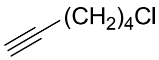
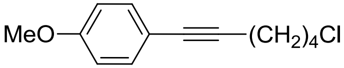
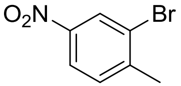
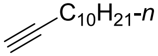
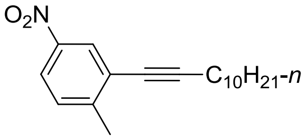
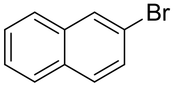
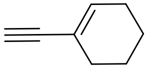
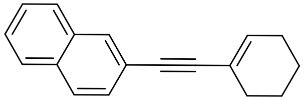
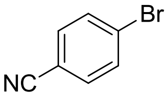
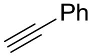
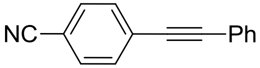
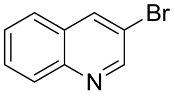
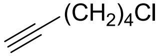
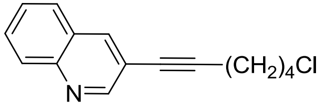
- Using **monodentate cyclopropylphosphine ligand (cBRIDP)** from Takasago Inc.[4] showed broad substrate scope and effectiveness (more rapid conversions) for more challenging substrates.

1. Absence of Cu: a) J.-F. Nguefack, V. Bolitt, D. Sinou, *Tett. Lett.* **1996**, *37*, 5527-5530
2. B. H. Lipshutz, D. W. Chung, B. Rich, *Org. Lett.* **2008**, *10*, 3793-3796
3. Z. Novak, A. Szabo, J. Répasi, A. Kotschy, *J. Org. Chem.* **2003**, *68*, 3327-3329
4. K. Suzuki, Y. Hori, T. Kobayashi, *Adv. Synth. Catal.* **2008**, *350*, 652-656

Pd catalysed Sonogashira cross couplings in water with the aid of micelles

- **Comparison** of effectiveness of Sonogashira reactions between the **three generations of surfactants** developed by Lipshutz et al.[1]

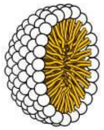
Comparative study for all three surfactant generations[1]

Aryl Bromide (1 eq.)	Alkyne (1.5 eq.)	Time (hrs)	Product	PTS yield (%)	TPGS-750-M yield (%)	Nok yield (%)
		28		89[a]	94	95
		25		55	66	-
		24		99	98	98
		21		84	99	-
		4		97[a]	97	90
		15		-	93	93

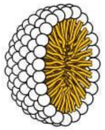
[a] 3 eq. of Cs_2CO_3 was used instead of Et_3N

Reaction conditions: 1-2 mol% $Pd(CH_3CN)_2Cl_2$, 2.5 mol% XPhos, 2-3 eq. Et_3N, 2-3 wt% surfactant/H_2O, RT

1. a) B. H. Lipshutz, S. Ghorai, A. R. Abela, R. Moser, T. Nishikata, C. Duplais. A. Krasovskiy, *J. Org. Chem.* **2011**, *76*, 4379-4391;
b) P. Klumphu, B. H. Lipshutz, *J. Org. Chem.* **2014**, *79*, 888-900; c) B. H. Lipshutz, D. W. Chung, B. Rich, *Org. Lett.* **2008**, *10*, 3793-3796



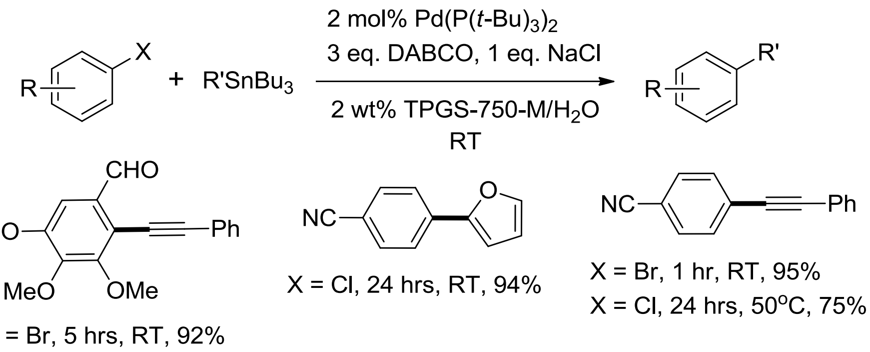
Pd cat. Stille cross couplings in water with the aid of micelles



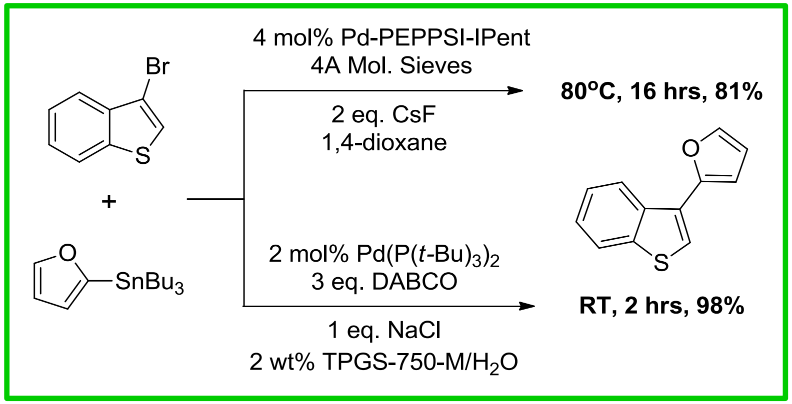
- Normally run at high temperatures in toxic organic solvents[1,4]

- Development of nanometal catalysts for reactions to be performed in water, under milder conditions[2]
  → suffer from poor substrate scope

Stille coupling with aryl halides under micellar conditions



Traditional vs Micellar Stille Coupling



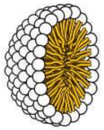
- **Stille cross couplings** carried out **in water, at room temperature using surfactants**[3]

- Pd(P(*t*-Bu)$_3$)$_2$ chosen as Palladium catalyst –reported as highly reactive for Stille couplings with Aryl bromides and chlorides[4]

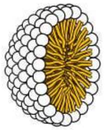
- In the absences of a surfactant, the so called “on-water” reaction, afforded lower conversion (39%).

- Stille couplings with **aryl chlorides** were more sluggish and required **gentle warming (50-60°C)**.

1. S. P. H. Mee, V. Lee, Sir J. E. Baldwin, *Chem. Eur. J.* **2005**, *11*, 3294-3308
2. J. C. Garcia-Martinez, R. Lezutekong, R. M. Crooks, *J. Am. Chem. Soc.* **2005**, *127*, 5097-5103
3. a) G. Lu, C. Cai, B. H. Lipshutz, *Green Chem.* **2013**, *15*, 105-109; b) P. Klumphu, B. H. Lipshutz, *J. Org. Chem.* **2014**, *79*, 888-900
4. A. F. Littke, L. Schwarz, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 6343-6348



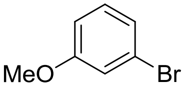
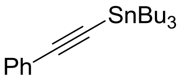
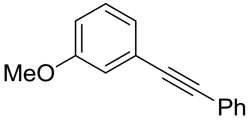
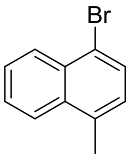
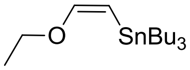
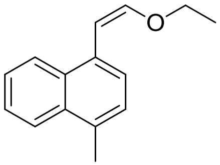
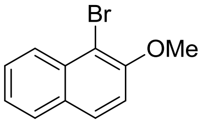
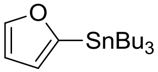
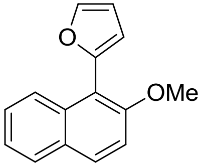
Pd catalysed Stille cross couplings in water with the aid of micelles



- **Presence of NaCl increased reaction conversion**[1]

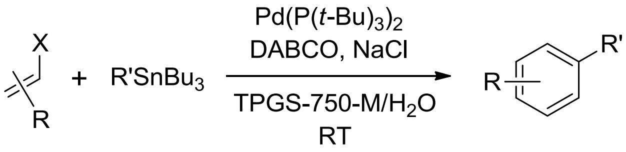
→ **enlarged, reorganised micelles** which provide **greater reaction surface area** and increased binding constants for substrates and catalyst.

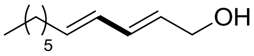
Side-by-side reaction comparisons between TPGS-750-M and 'Nok'[2]

Aryl Bromide (1 eq.)	Stannyl reagent (1.1 eq.)		TPGS-750-M yield (%)	Nok yield (%)	Time (hrs)
			98	99	2
			83	84	18
			94	97	4

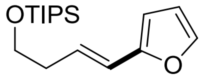
Reaction Conditions: 2 mol% $Pd(P(t\text{-}Bu)_3)_2$, 3 eq. DABCO, **1 eq. NaCl**, 2.0 wt% surfactant/H_2O, RT

Stille coupling with alkenyl halides under micellar conditions

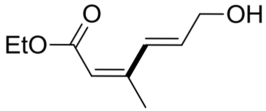




X = I, 6 hrs, 88%

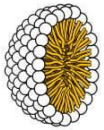


X = Br, 24 hrs, 89%

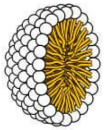


X = I, 2 hrs, 94% *(Z/E=99/1)*

1. G. Lu, C. Cai, B. H. Lipshutz, *Green Chem.* **2013**, *15*, 105-109
2. P. Klumphu, B. H. Lipshutz, *J. Org. Chem.* **2014**, *79*, 888-900



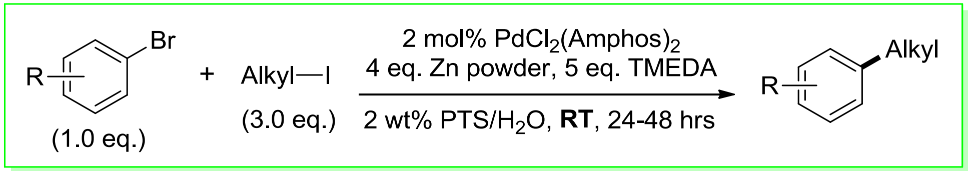
Pd catalysed Negishi-like cross couplings in water with the aid of micelles

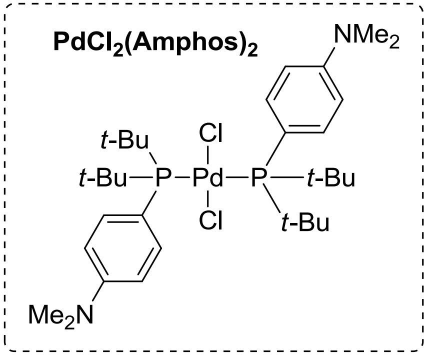


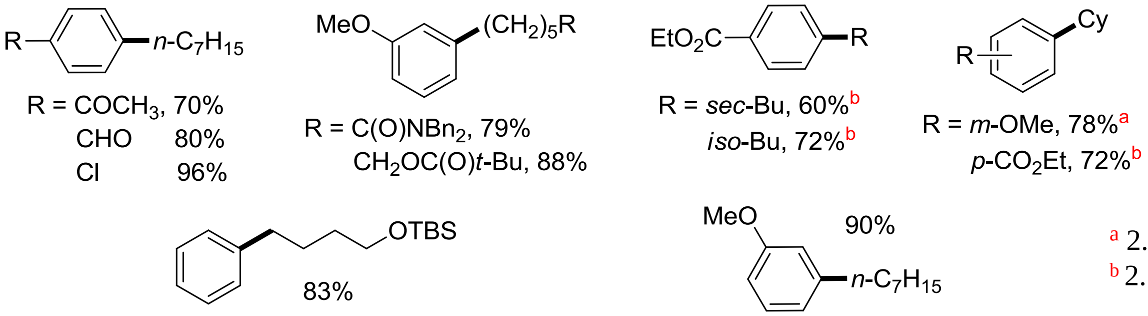
- As part of a new class of **air-stable catalysts**, $PdCl_2(Amphos)_2$[1] is employed in Negishi-like cross couplings to form sp^2-sp^3 C-C bonds between aryl bromides and 1° and 2° alkyl iodides.[2]

- **No prior formation of the organozinc reagents is required**; unprecedented **in-*situ* formation** of the organometallic coupling partner in the presence of zinc powder in **aqueous medium**.

- This approach relies on the simultaneous **chemoselective insertion** of Pd (**sp^2 C-X**) and Zn (**sp^3 C-X**) into two different types of C-Hal bonds.





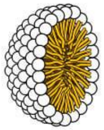


[a] 2.5 eq. of TEEDA was used;
[b] 2.5 eq. of $Et_2N(CH_2)_2NMe_2$ was used

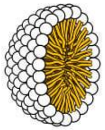
- Crucial importance of the **diamine base** as an activating agent for zinc insertion and as a stabilising ligand for the in-*situ* formed organozinc reagent.

- **Excess alkyl halide** is needed to compensate for protio-quenching of some of the organozinc reagent.

1. A. S. Guram et *al.* (Amgen Inc.), *Org. Lett.* **2006**, *8*, 1787-1789
2. A. Krasovskiy, C. Duplais, B. H. Lipshutz, *J. Am. Chem. Soc.* **2009**, *131*, 15592-15593



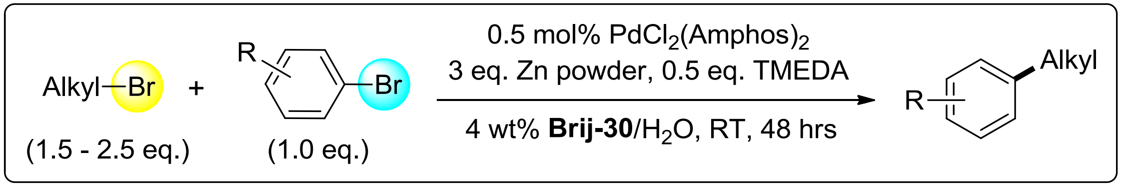
Pd catalysed Negishi-like cross couplings in water with the aid of micelles

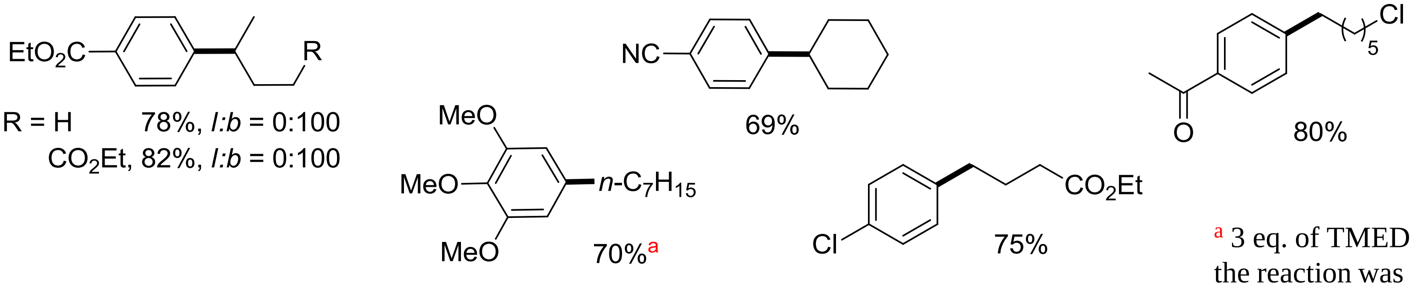


- Lipshutz et al. extended their aqueous micellar technology to Negishi-like cross couplings between **alkyl bromides** and **aryl bromides** at room temperature.[1]

- Once again, **moisture sensitive zinc reagents** are employed in aqueous micellar environment.

- This methodology is based on main group metals preference for sp^3 C-Hal bonds and TM's tendency to react quicker with sp^2 C-Hal bonds.



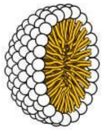


[a] 3 eq. of TMEDA were used and the reaction was stirred for 72 hrs

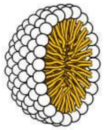
- Cheap, commercial surfactant **Brij 30** gave the cleanest and highest yielding reactions.
  → This surfactant was the best at **minimising the formation of byproducts** resulting from halogen reduction and Wurtz homo-coupling due to competitive Zinc insertion into the aryl substrate.

- A variety of substrates are tolerated, with halides, esters, ketones and nitriles all participating in the reaction.

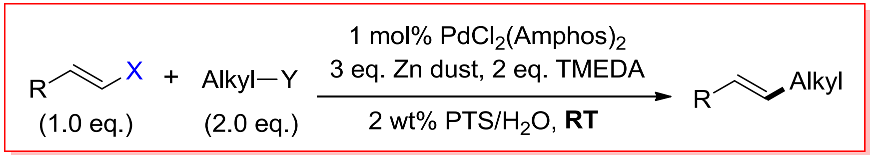
1. C. Duplais, A. Krasovskiy, B. H. Lipshutz, *Organometallics* **2011**, *30*, 6090-6097

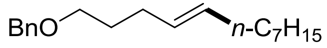


Pd catalysed Negishi-like cross couplings in water with the aid of micelles

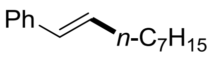


- Negishi-like stereoselective coupling between **alkenyl halides** and alkyl halides.[1]
- Crucial for the reaction's success are: more reactive **zinc dust**, TMEDA and the surfactant, PTS.
- Reactions proceeded with **high levels of retention** of both *E*- and *Z*-alkene geometry in the products.

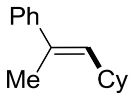




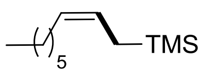
X = I, Y = I, 85%, *E:Z* = *>99:1*



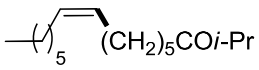
X = Br, Y = I
92%, *E:Z* = *91:9*



X = Br, Y = I, 66%
Br Br, 94%

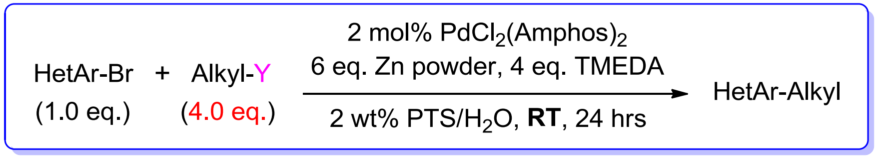


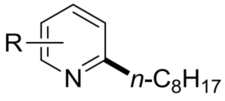
X = I, Y = Br, 94%, 99:1
I I 95%, 99:1



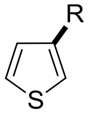
X = Br, Y = Br, 93%, 97:3

- Coupling of 1º and 2º alkyl halides and **heteroaromatic bromides**, with good functional group tolerance.[2]
- Water insoluble lipophilic substrates worked efficiently under these conditions whereas water soluble heteroaromatics provided only traces amounts of products.

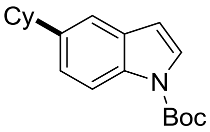




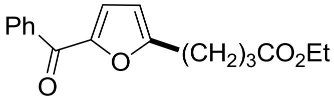
R = H, Y = I, traces
3-OMe, I, 62%
6-OMe, I, 99%



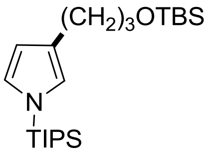
R = *n*-Bu, Y = I, 22%
n-heptyl I, 69%
n-decyl I, 78%



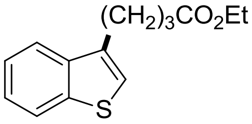
Y = Br, 97%



Y = I, 71%



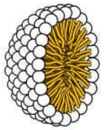
Y = I, 86%



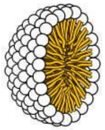
Y = I, 74%

1. A. Krasovskiy, C. Duplais, B. H. Lipshutz, *Org. Lett.* **2010**, *12*, 4742-4744

2. A. Krasovskiy, I. Thomé, J. Graff, V. Krasovskaya, P. Konopelski, C. Duplais, B. H. Lipshutz, *Tet. Lett.* **2011**, *52*, 2203-2205

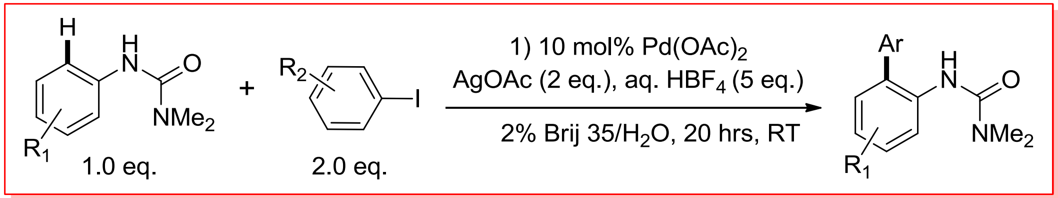


Pd catalysed C-H activation in water with the aid of micelles

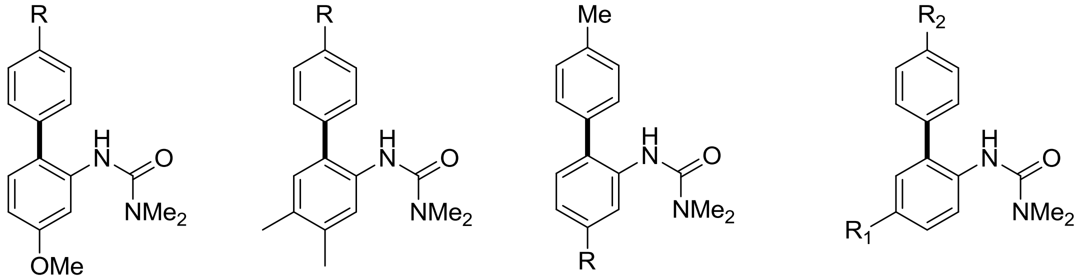


- **First room temperature** mono C-H *ortho*-arylation of urea derivatives with aryl iodides **in water.**[1,2]
- $Pd(OAc)_2$ catalyst in the presence of **AgOAc and HBF_4 additives** using the surfactant, Brij 35.
- **Absence of phosphine ligands**.

Sterically hindered aryl iodides with *o*-substituents (2-tolyl iodide, 2-anisyl iodide) were **not tolerated**.



Electron deficient ureas did not work.



R = OMe 76%
CO$_2$Et 42%[c]

R = OMe 81%[b]
Me 76%
H 97%[a]

R = OMe 87%
OBn 70%[b]
i-Pr 74%[a]
H 70%[b]

R_1 = *s*-Bu	R_2 = OMe	71%
s-Bu	Me	70%[a,d]
s-Bu	H	71%
OMe	Me	72%[a]

Effect on reactivity of EDG vs. EWG on the aryl iodide. ←

[a] Run for 48 hrs,
[b] Run for 72 hrs,
[c] Run for 96 hrs,
[d] 1.2 eq. of ArI

- Aniline derivatives lacking *ortho* or *meta* subsitutents which are prone to double arylation[3] but for this methodology were **highly selective** for the **singly arylated product**.

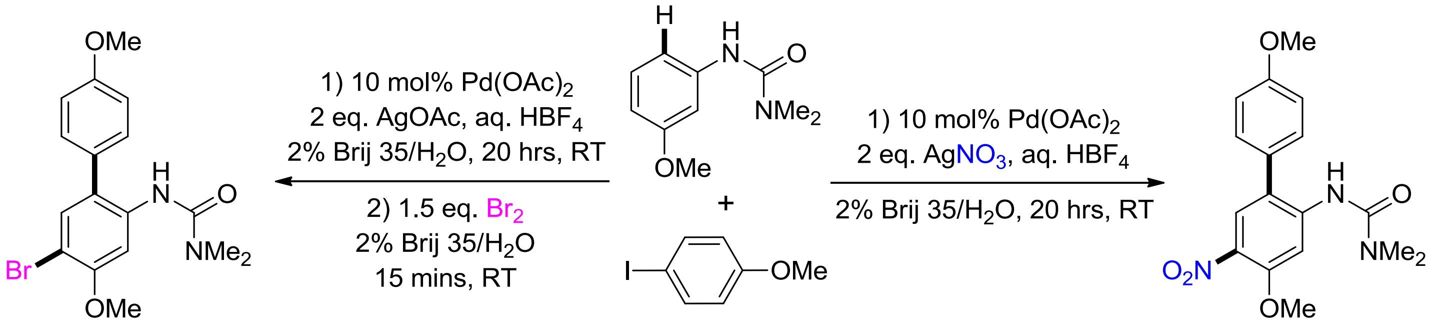
1. a) T. Nishikata, A. R. Abela, B. H. Lipshutz, *Angew. Chem. Int. Ed.* **2010**, *49*, 781-784; b) B. Lin, P. H. Dixneuf, *Chem. Soc. Rev.* **2013**,*42*, 5744 -5767.
2. For room temperature C-H arylations of indoles see: a) N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972-4973; b) N. Lebrasseur, I. Larrosa, *J. Am. Chem. Soc.* **2008**, *130*, 2926-2927; c) L.-C. Campeau, M. Bertrand-Laperle, J.-P. Leclerc, E. Villemure, S. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3276-3277.

Pd catalysed C-H activation in water with the aid of micelles

- **HBF_4** was essential for the formation of the biaryl product in good yield.

- Other surfactants, such as PTS and TPGS-705-M provided comparable yields (67% and 73% respectively) of the desired products with some other commercially available surfactants.
  → Brij-35 (polyoxyethylene (23) lauryl ether) gave the highest yield (76%).

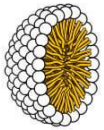
Tandem 'One-Pot' C-H activation and electrophilic trapping in water at RT

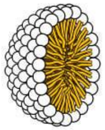


- **Tandem** C-H activation coupled with regioselective secondary electrophilic aromatic substitution (bromination or nitration) performed in water and at r.t.

- One example showed the use of a **$Pd(OAc)_2$-$AgBF_4$** catalytic system in water at r.t., which gave the mono C-H arylated product (moderate 40% yield), **without the assistance of an acid** or coordinating ligand.

1. T. Nishikata, A. R. Abela, B. H. Lipshutz, *Angew. Chem. Int. Ed.* **2010**, *49*, 781-784

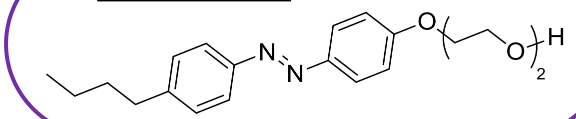




Pd catalysed Tsuji-Trost reaction in water with the aid of micelles

- Christophe Len et al. at Université de Technologie de Compiègne, France; employed the use of surfactant, C4-Azo-PEG in the **Tsuji-Trost reaction**.

C4-Azo-PEG

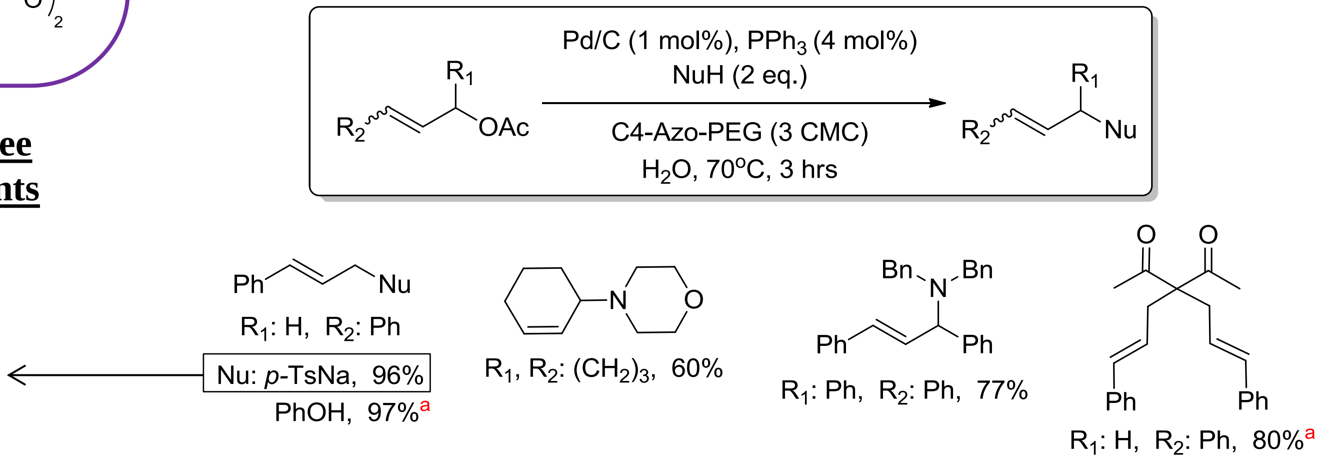


Comparison with three commercial surfactants

Surfactant	Yield
None	42
SDS	*26*
CTAB	80
Tween 20	71
C4-Azo-PEG	83
C4-Azo-PEG*	96

*Irradiation at 365 nm for 30 min just before extraction

Tsuji Trost reaction with allyl acetates under micellar conditions



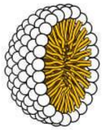
[a] Addition of 4 mmol of K_2CO_3 in the reaction

- Range of nucleophiles applicable to the Tsuji-Trost reaction under these aqueous, micellar conditions.

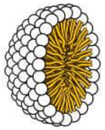
- **Irradiation** at 365 nm for 30 mins before EtOAc extraction affords higher yields due to the efficient breakdown of the emulsion enabling **greater product recovery**. *(Photochromic properties of C4-Azo-PEG)*

- **Recycling ability of the surfactant**; Four consecutive cycles gave high yields: 83, 99, 92 and 72%.

1. M. Billamboz, F. Mangin, N. Drillaud, C. Chevrin-Villette, E. Banaszak-Léonard, C. Len, *J. Org. Chem.* **2014**, *79*, 493-500

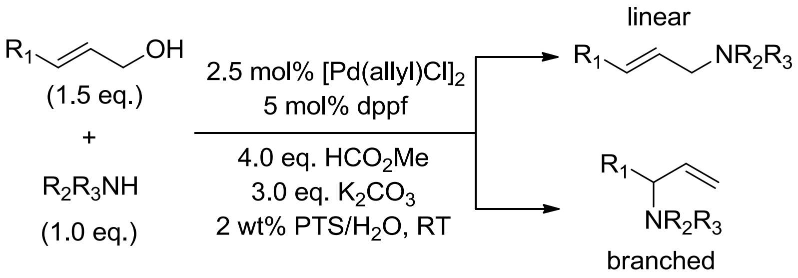


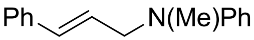
Pd catalysed Buchwald-Hartwig type aminations in water with the aid of micelles



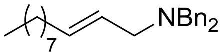
- **First** methodology for **allylic aminations** of 1°, 2° and 3° alcohols in water as the only solvent and **at r.t.**[1a)]
- Leaving group ability of the hydroxyl group is made possible be participation of methyl formate.

Aminations of allylic alcohols under micellar conditions

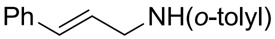




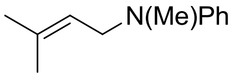
94%; l:b = 100:0; *E*:*Z* = 100:0
38% (on water)



84%; l:b = >25:1; *E*:*Z* = 16:1[a]



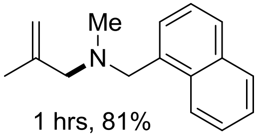
80%; l:b = 100:0; *E*:*Z* = 100:0



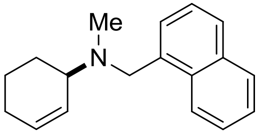
90%; l:b = 63:1

[a] biphep ligand was used instead of dppf

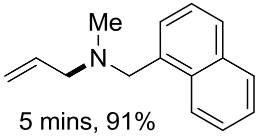
Aminations of allylic phenyl ethers under micellar conditions



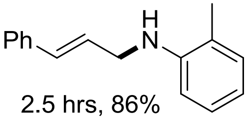
1 hrs, 81%



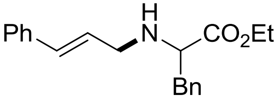
5 hrs, 80%



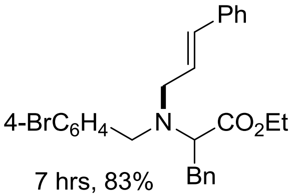
5 mins, 91%



2.5 hrs, 86%



2.5 hrs, 80%[a] (6%[b])



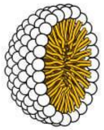
7 hrs, 83%

Reaction conditions: 0.5 mol% $[Pd(allyl)Cl]_2$, 1 mol% DPEphos, 1.0 eq. ether, 1.5 eq. amine, 1.5 eq. K_2CO_3, 4.0 eq. HCO_2Me, 2 wt% PTS/H_2O, RT, air

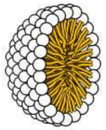
[a] 2.5 eq. of amine used,
[b] doubly allylated product

- **First** general method for Pd catalysed amination of **allylic phenyl ethers** in water, at r.t. and open to air.[1b)]
- For both protocols, the addition of **HCO_2Me is vital** in ensuring a fast reaction rate and the surfactant, PTS plays an important role for obtaining reliable, high yields vs "on-water" reactions.

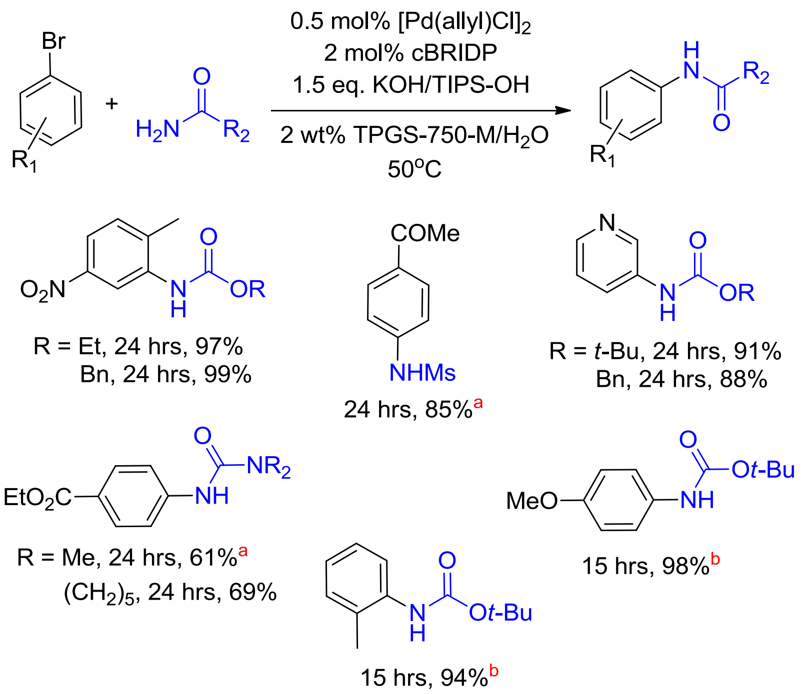
1. a) T. Nishikata, B. H. Lipshutz, *Org. Lett.* **2009**, *11*, 2377-2379; b) T. Nishikata, B. H. Lipshutz, *Chem. Commun.* **2009**, 6472-6474



Pd catalysed Buchwald-Hartwig type aminations in water with the aid of micelles



A single, general method for the amination of **protected ammonia equivalents** (carbamates, sulfonamides and ureas) with aryl/heteroaryl iodides, bromides and chlorides.[1a)]



0.5 mol% $[Pd(allyl)Cl]_2$
2 mol% cBRIDP
1.5 eq. KOH/TIPS-OH
2 wt% TPGS-750-M/H_2O
50°C

R = Et, 24 hrs, 97%
Bn, 24 hrs, 99%

24 hrs, 85%[a]

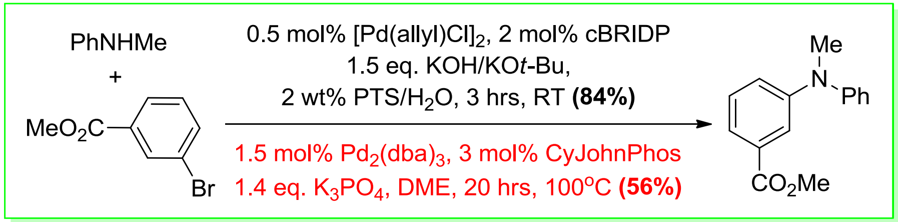
R = *t*-Bu, 24 hrs, 91%
Bn, 24 hrs, 88%

R = Me, 24 hrs, 61%[a]
$(CH_2)_5$, 24 hrs, 69%

15 hrs, 94%[b]

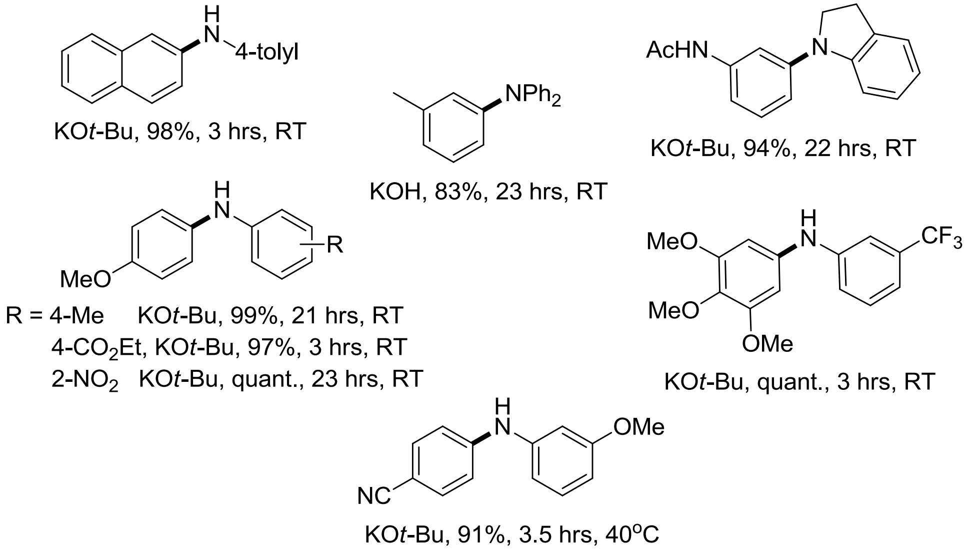
15 hrs, 98%[b]

[a] NaO*t*-Bu was used as the base instead; [b] RT



0.5 mol% $[Pd(allyl)Cl]_2$, 2 mol% cBRIDP
1.5 eq. KOH/KO*t*-Bu,
2 wt% PTS/H_2O, 3 hrs, RT **(84%)**

1.5 mol% $Pd_2(dba)_3$, 3 mol% CyJohnPhos
1.4 eq. K_3PO_4, DME, 20 hrs, 100°C **(56%)**



KO*t*-Bu, 98%, 3 hrs, RT

KOH, 83%, 23 hrs, RT

KO*t*-Bu, 94%, 22 hrs, RT

R = 4-Me KO*t*-Bu, 99%, 21 hrs, RT
4-CO_2Et, KO*t*-Bu, 97%, 3 hrs, RT
2-NO_2 KO*t*-Bu, quant., 23 hrs, RT

KO*t*-Bu, quant., 3 hrs, RT

KO*t*-Bu, 91%, 3.5 hrs, 40°C

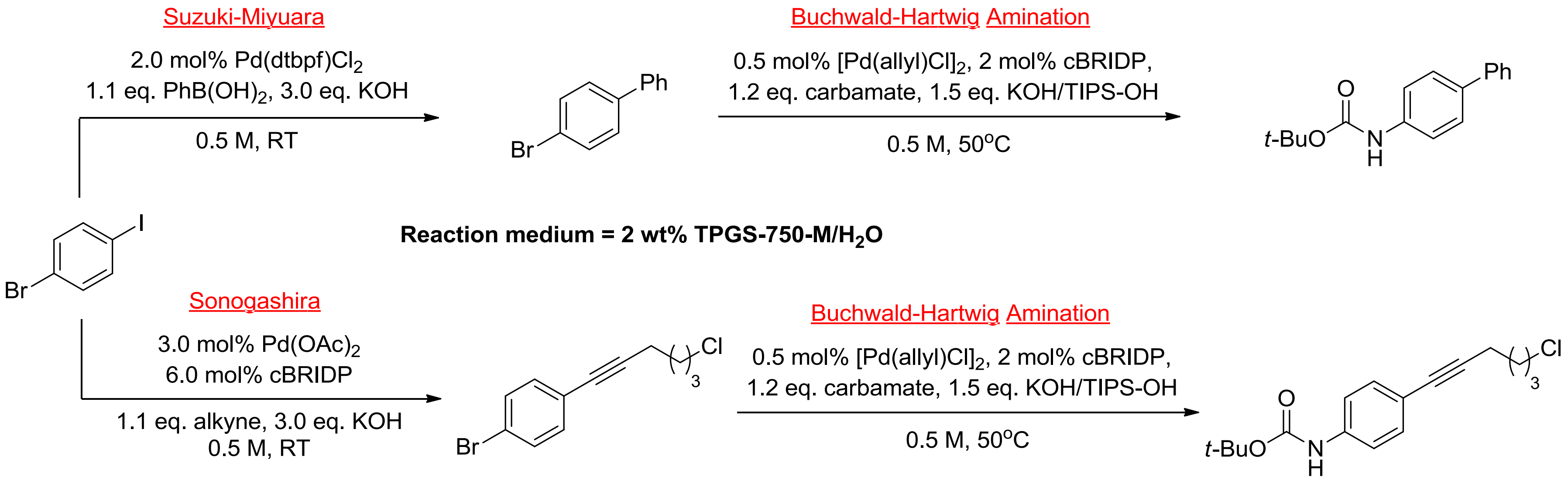
Unsymmetrical di- and triarylamines were prepared from aryl bromides and aryl amines under “green conditions” (water as only solvent and at **room temperature**) by utilising Pd and **micellar cataylsis.**[1b)]

1. a) N. A. Isley, S. Dobarco, B. H. Lipshutz, *Green Chem.* **2014**, *16*, 1480-1488; b) B. H. Lipshutz, D. W. Chung, B. Rich, *Adv. Synth. Catal.* **2009**, *351*, 1717-1721

Pd catalysed One-Pot Tandem Reactions in water with the aid of micelles

- Combining some of the methodologies we have already seen, the Lipshutz group developed elaborate tandem reactions to rapidly access complex aromatic products using **green chemistry**.

- **One-pot tandem sequence** involving an initial cross coupling, e.g. Suzuki-Miyuara or Sonogashira reaction followed by an amination reaction of a carbamate.[1]



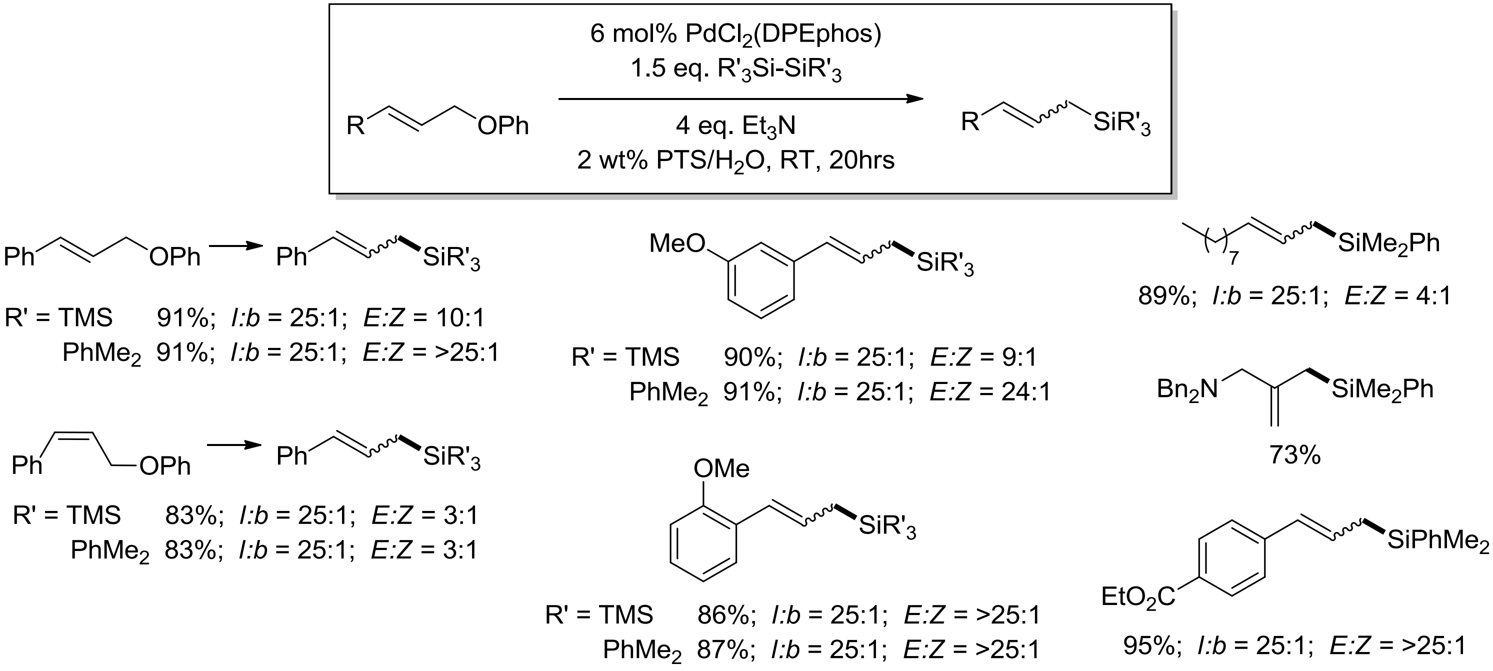
- The **more reactive iodide position is chemoselectively coupled first**.

- All reactions are performed in water with the aid of surfactant, TPGS-750-M, employing mild reaction temperatures ranging from r.t.-50°C.

1. N. A. Isley, S. Dobarco, B. H. Lipshutz, *Green Chem.* **2014**, *16*, 1480-1488

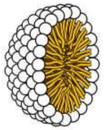
Pd catalysed Silylation reaction in water with the aid of micelles

- **Formation of allylic silanes** under very mild conditions due to Pd and micellar catalysis in water at r.t.
- Control experiments revealed the **importance of the surfactant** in providing the product in good yield.
- Catalytic Pd system with bidentate phosphine (DPEphos) ligand, with excess Et_4N (4 eq.) gave the best yields and the **excellent regio- and stereoselectivity** of the product.

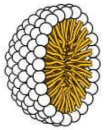


- Allylic dimethylphenyl silanes were both more efficient and more selective than the TMS derivatives.
- Electron-donating and electron-withdrawing groups readily underwent the silylation reaction.

1. R. Moser, T. Nishikata, B. H. Lipshutz, *Org. Lett.* **2010**, *12*, 28-31



Pd catalysed Fujiwara-Moritani reaction in water with the aid of micelles

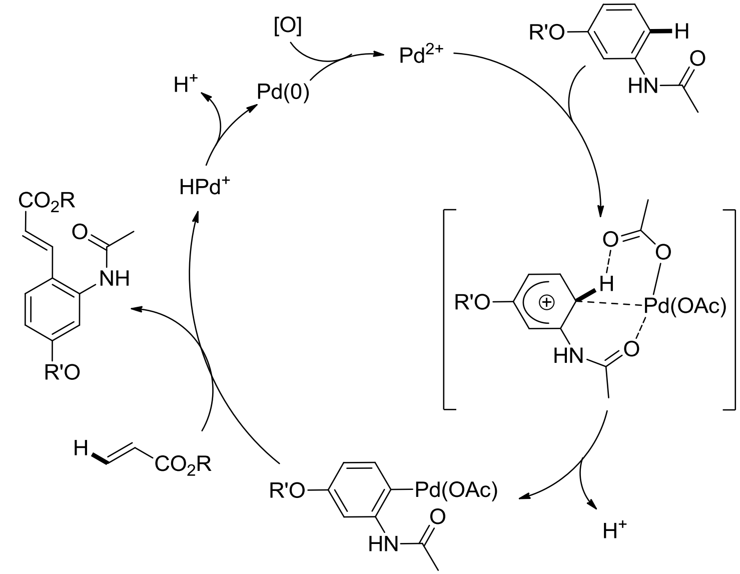


- Using a **highly active cationic [Pd^{II}(MeCN)$_4$](BF$_4$)$_2$ species** the Fujiwara-Moritani reaction[1] was performed in water, at ambient temperature and most notably **without the need of an external acid**.[2]

- Use of oxidising agents (**1,4-benzoquinone and AgNO$_3$**) were critical for the reaction to be successful.

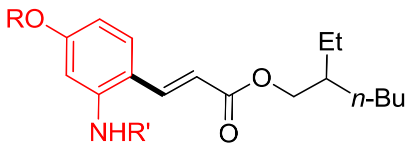
- In the absence of PTS, the so-called "**on-water**" reaction, yields were noticeably lower (66% vs. 85%).
  → Other commercial surfactants (Brij 35, Triton X-100, Solutol) gave significantly lower yields.

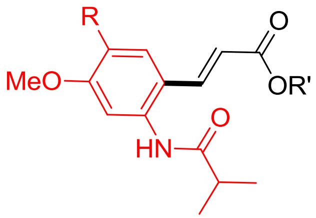
Proposed Catalytic Cycle



Fujiwara Moritani reaction under micellar conditions

R = Me	R' = Ac	76%
n-Pr	Ac	96%
i-Pr	Ac	90%
Me	CONMe$_2$	74%
Me	CO*n*-Pr	80%
Me	CO*i*-Pr	91%





R = H	R' = (CH$_2$)$_2$Cy	77%
H	(CH$_2$)$_{11}$CH$_3$	80%
Me	CH$_2$CH(Et)*n*-Bu	72%
OMe	CH$_2$CH(Et)*n*-Bu	89%

Reaction conditions: Anilide (1 eq.), Acrylate ester (2 eq.), 10 mol% [Pd(MeCN)$_4$](BF$_4$)$_2$, BQ (1 eq.), AgNO$_3$ (2 eq.), 2 wt% PTS/H$_2$O, RT, 20hrs

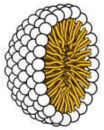
- This protocol affords the **single, regiospecifically *ortho* C-H substituted product**.

- A variety of alkyl substituted acrylates and multisubstituted anilides participated smoothly in the reaction.

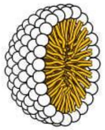
---

[1] a) I. Moritani, Y. Fujiwara, *Tet. Lett.* **1967**, *8*, 1119-1122; b) Y. Fujiwara, I. Moritani, S. Danno, R. Asano, S. Teranishi, *J. Am. Chem. Soc.* **1969**, *91*, 7166-7169

[2] T. Nishikata, B. H. Lipshutz, *Org. Lett.* **2010**, *9*, 1972-1975

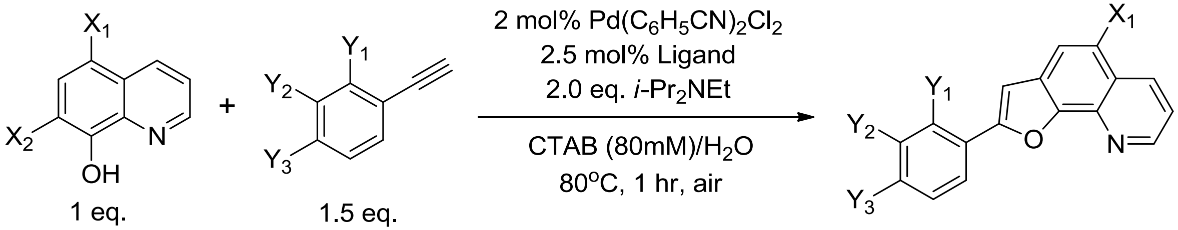


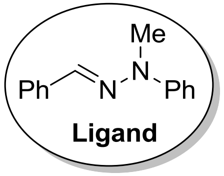
Pd catalysed Domino Reaction in water with the aid of micelles



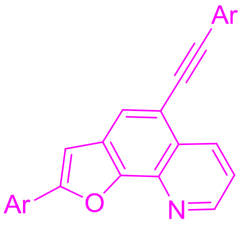
- A. Kumar Sen et al. developed a simple, fast, environmentally benign **synthesis of furoquinolines** in aqueous micellar medium, by a two step: Cu-free Sonogashira-cyclisation **cascade reaction under aerobic conditions**.

- Furoquinolines core is present in many pharmacologically active molecules and natural products.





X_1 = Cl,	X_2 = I	$Y_1 = Y_2$ = H, Y_3 = OMe	Yield = 89%
Cl	I	$Y_1 = Y_2$ = H, Y_3 = *n*-pentyl	90%
Cl	I	Y_1 = F, $Y_2 = Y_3$ = H	91%
Cl	I	Y_1 = Cl, $Y_2 = Y_3$ = H	88%
Cl	I	$Y_1 = Y_2$ = H, Y_3 = NO_2	92%
NO_2	I	$Y_1 = Y_2 = Y_3$= H	87%
Cl	I	*o*-pyr	83%
Cl	I	cyclopropyl	52%
Br	Br	$Y_1 = Y_2 = Y_3$= H	89%
Cl	Cl	$Y_1 = Y_2 = Y_3$= H	83%
Cl	Cl	*o*-pyr	80%



- The analogous "on-water" reactions were ineffective even up to 12 hrs.

- **Cationic surfactant CTAB** (cetyl trimethylammonium bromide) with a concentration of 80 mM was found to be the most effective amphiphile.

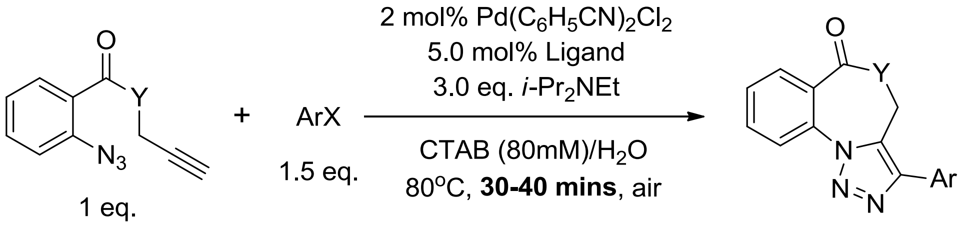
- All reactions yielded **exclusively the 5-*endo* cyclised product**; no formation of homo-coupled byproducts.

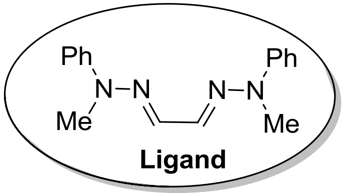
1. S. Sarkar, R. Pal, N. Chatterjee, S. Dutta, S. Naskar, A. K. Sen, *Tet. Lett.* **2013**, *54*, 3805-3809

Pd catalysed Domino Reaction in water with the aid of micelles

- A. Kumar Sen et al. extended their methodology to a '**one-pot two-step**' synthesis of triazolo benzoxazepines and benzodiazepines using $Pd(CH_3CN)_2Cl_2$ as the catalyst

- Cu-free Sonogashira reaction followed by an intramolecular azide-alkyne cyclisation **under aerobic conditions**





Ligand

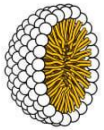
Y	Ar	X	Yield
O	2-OMeC_6H_4	I	81%
O	3-$CF_3C_6H_4$	I	90%
O	pyridyl	I	79%
O	thiophenyl	I	78%
O	Ph	Br	68%
NMe	2-OMeC_6H_4	I	76%
NMe	napthyl	I	80%
NMe	4-FC_6H_4	I	74%
NMe	pyridyl	I	83%

High yielding and short reaction times

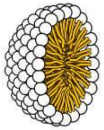
- In the absence of any surfactant (i.e. "on-water" reaction) no significant amount of product was formed even after 24 hrs.

- There was **no formation of homo-coupled byproducts** (Glaser coupling) **nor acyclic Sonogashira products** resulting from no tandem process.

1. R. Pal, S. Sarkar, N. Chatterjee, A. K. Sen, *Tet. Lett.* **2014**, *55*, 1452-1455

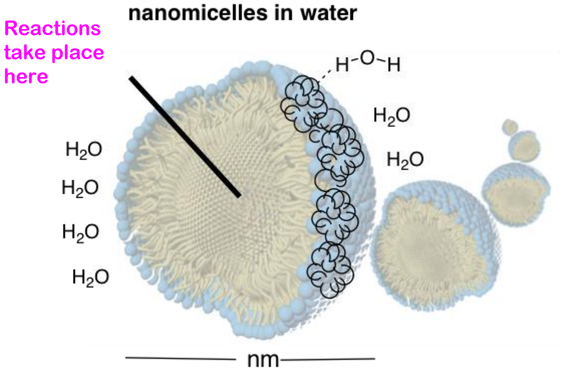


Summary and Outlook



- Greater consideration is being given to the idea of “**greening-up**” organic chemistry in the present era.

- **B. H. Lipshutz et al.** have contributed significantly to the field of **Pd catalysed reactions conducted in water with the aid of micelles**, as well the design and development of novel surfactants, all of which are commercially available.



- Several well-known “**named reactions**” were performed in a water/ surfactant reaction medium but what is especially noteworthy is these reactions were largely undertaken at **room temperature**.

- The possibility of **recycling** the surfactant and/or aqueous medium has been demonstrated.

- Comparisons with “on-water” reactions always show the **superior performance** (reaction times and yields) **of micellar catalysis**.

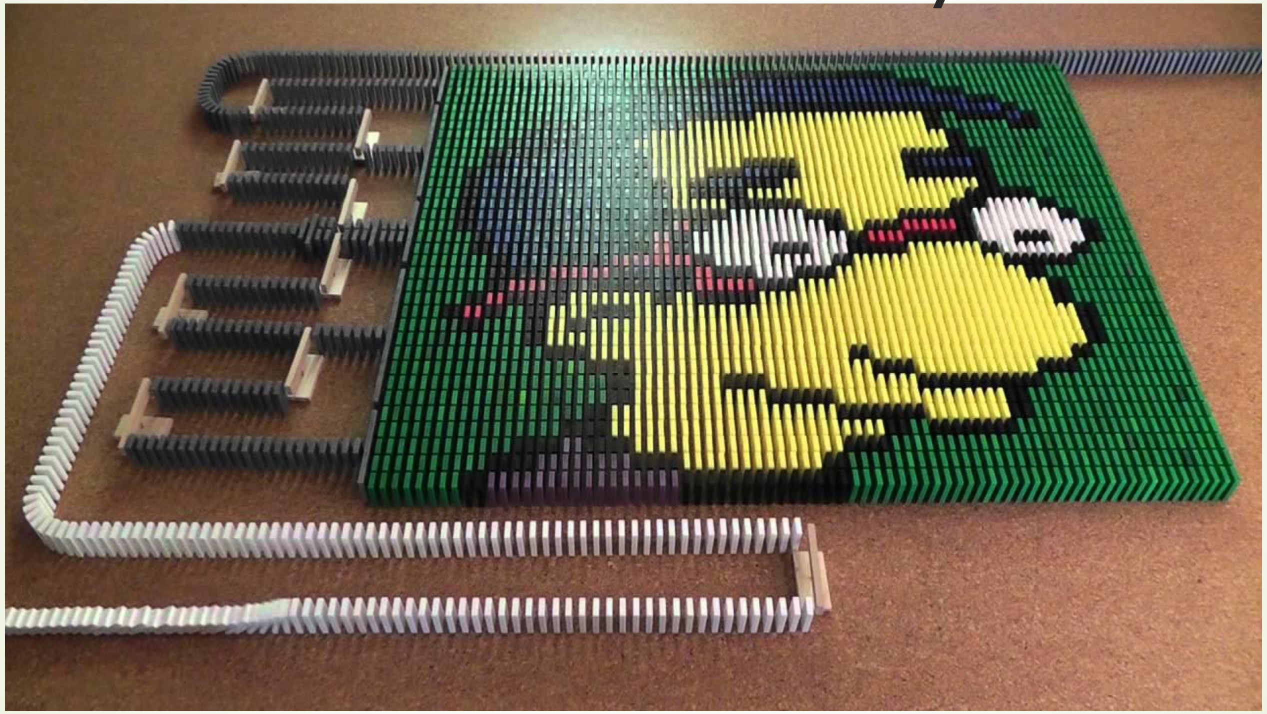
- In several cases where traditional, organic literature procedures fail or give low yields, or long reaction times or high temperatures, **combinatorial Pd and micellar triumph**.

Improvements

- Much of the work presented deals with aryl or heteroaryl substrates with not much work focusing on **alkenyl substrates** (except Stille and Negishi example).

- Concern over the **treatment of the water** in which these reactions have been performed.

Selected examples of Domino Reactions in Total Synthesis



Dagoneau Dylan

Zhu Group

Frontiers in Chemical Synthesis

May 22th, 2014

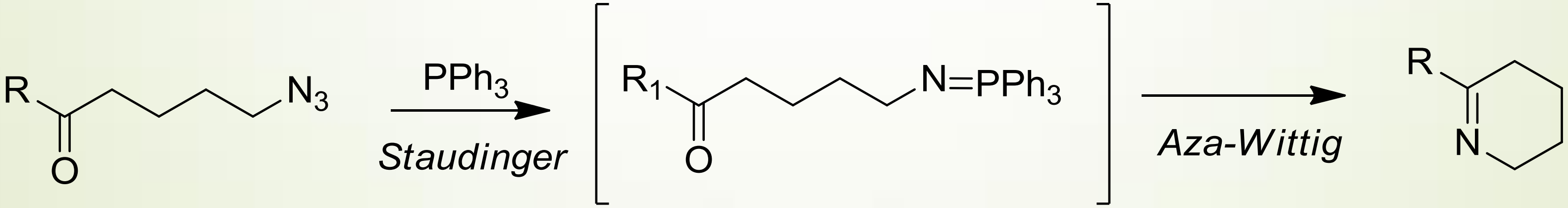
Table of Contents

Introduction and Definitions

- Domino, Cascade and Tandem reactions : 3 different terms for the same idea

- Definition: *A domino reaction is a process involving two or more bond-forming transformations (usually C-C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step.* **L. F. Tietze**

- The « Tandem » term : connotation of **2**



Tietze, L. F. *Chem. Rev.* **1996,** 96, 115–136

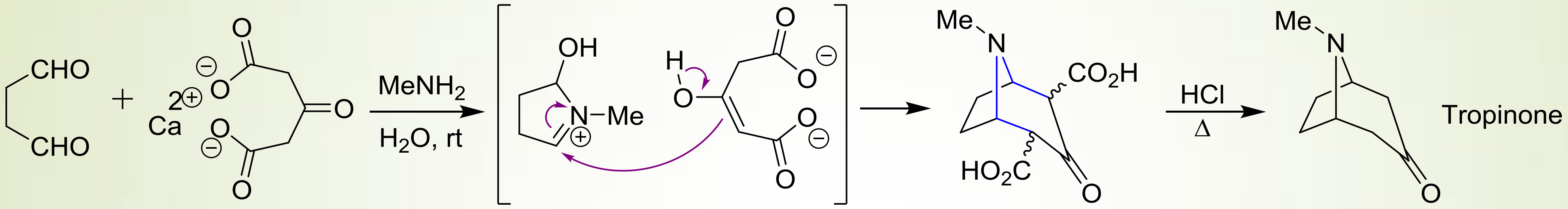
Introduction and Definitions

Why use Domino Reaction?

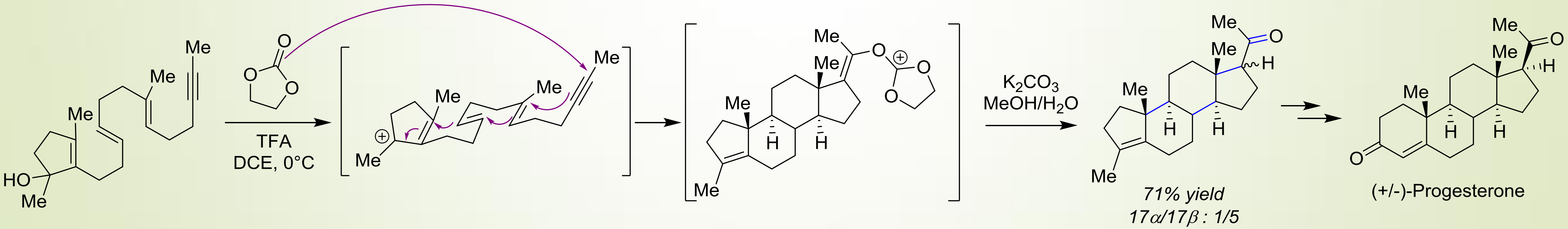
- One advantage: Economy
- But a lot of different economy : atom, step, time, labor, resource management and waste generation --> « Green chemistry » ?
- Synthesize fused/caged ring and formation of multiple quaternary center in a single reaction.

Introduction and Definitions

- First reported « domino » reaction : Robinson’s total synthesis of Tropinone (1917)



- Johnson’s total synthesis of (+/-)-Progesterone by cationic polyolefin cyclization (1971)



Robinson, R. *J. Chem. Soc. Trans.* **1917**, 762-768
Johnson, W. S. et al, *J. Am. Chem. Soc.* **1971**, 93, 4332-4334

Questions

- What are the major common points with all the domino reactions?
- In your opinion, what is the best (or the worst) strategy?

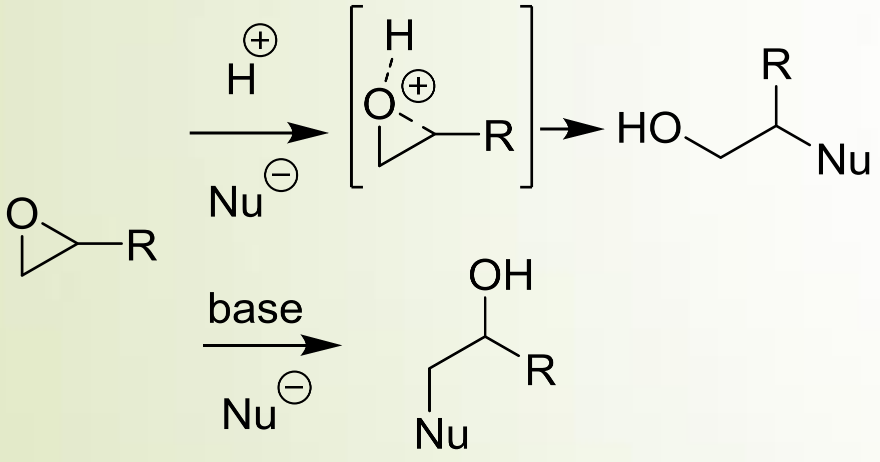
Table of Contents

- Introduction and Definitions
- **I/ Electrophilic Domino Reactions**
- II/ Nucleophilic Domino Reactions
- III/ Radical Domino Reactions
- IV/ Pericyclic Domino Reactions
- V/ Transition Metal Catalyzed Domino Reactions
- Conclusion

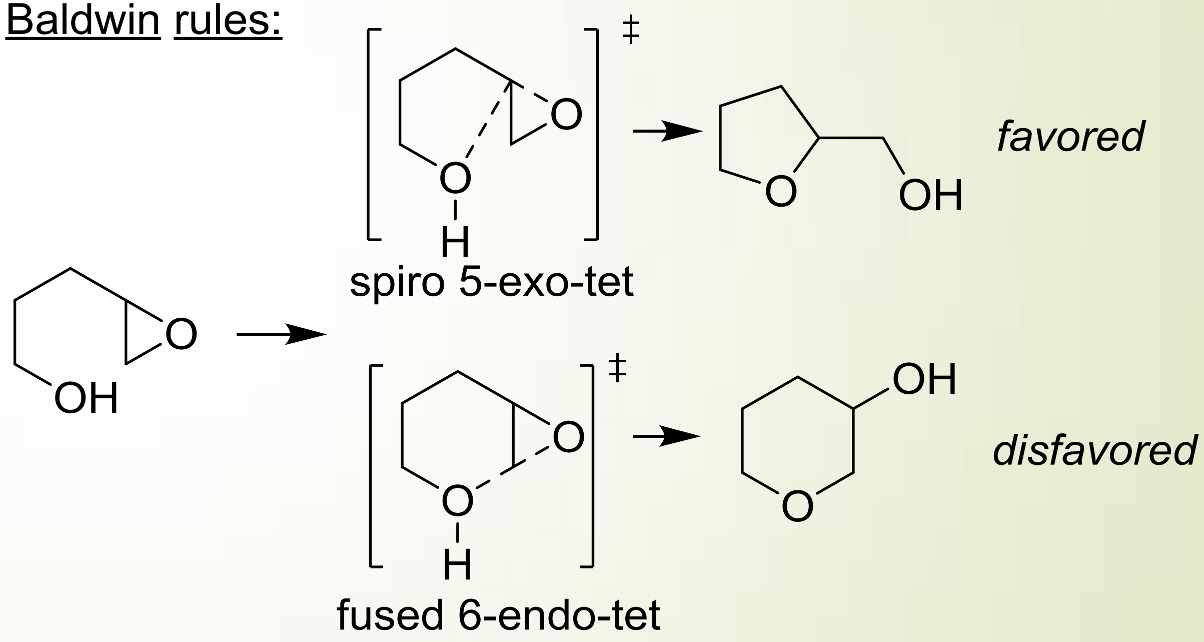
I/ Electrophilic Domino Reactions

I-1/ Epoxide opening

- Predictible opening selectivity



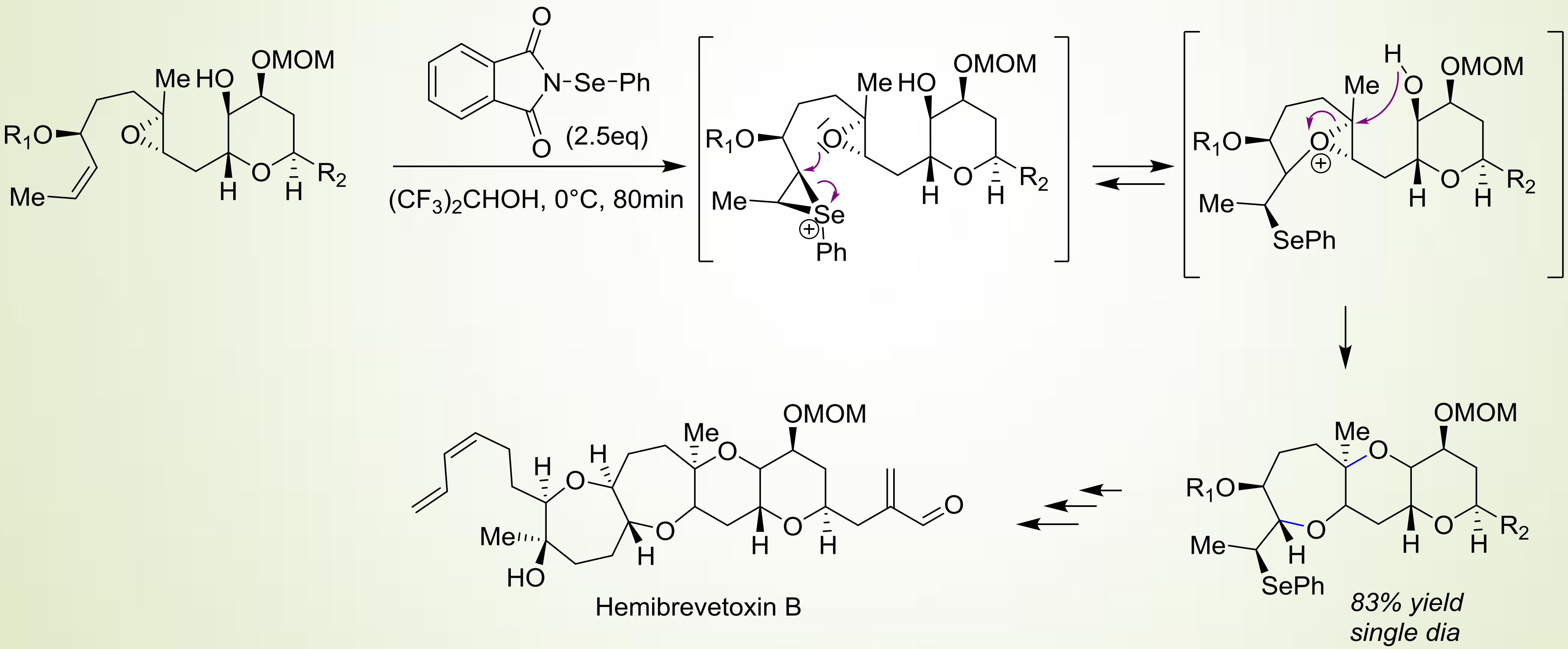
Baldwin rules:



I/ Electrophilic Domino Reactions

I-1/ Epoxide opening

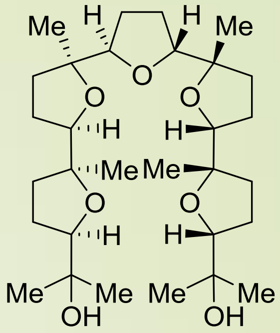
- Holton's total synthesis of Hemibrevetoxin B by epoxy-olefin cyclization (2003)



Zakarian, A. Batch, R. A. Holton, *J. Am. Chem. Soc.* **2003**, *125*, 7822–7824.
See also with bromonium: J. Tanuwidjaja, S.-S. Ng, T. F. Jamison, *J. Am. Chem. Soc.* **2010**, *131*, 12084–12085

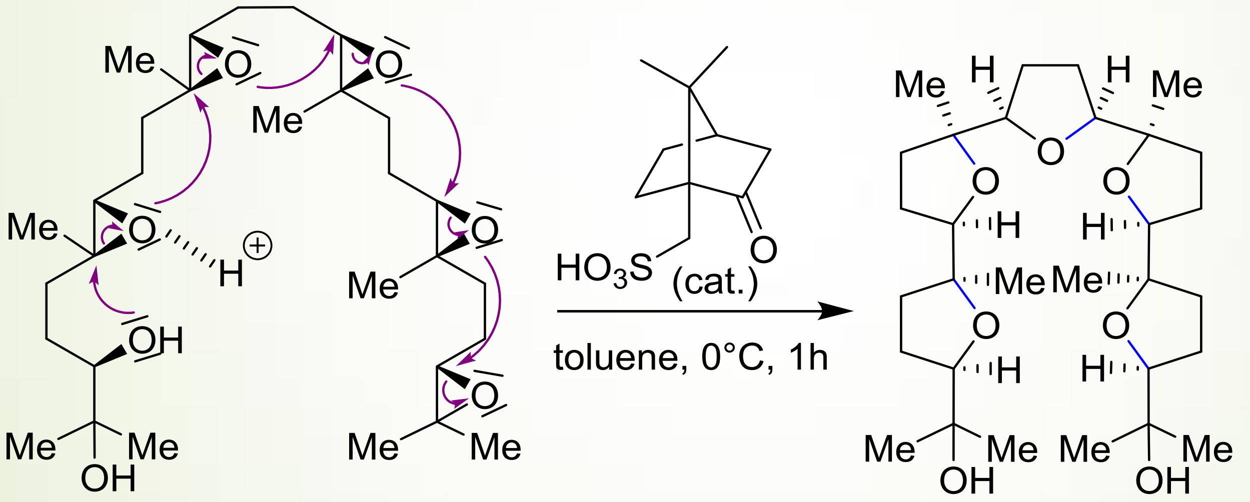
I/ Electrophilic Domino Reactions

I-1/ Epoxide opening



Real structure of Glabrescol

- Corey’s total synthesis of the proposed structure of Glabrescol (2000)



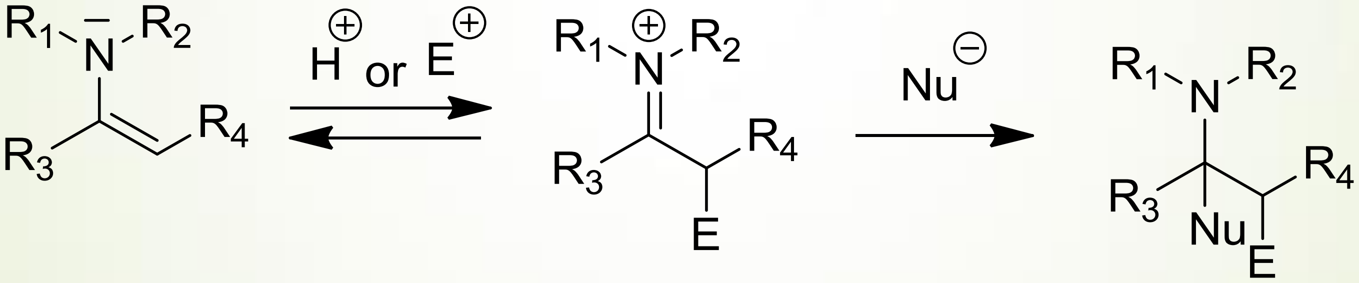
31% yield
Proposed Glabrescol

Z. Xiong, E. J. Corey, *J. Am. Chem. Soc.* **2000**, *122*, 4831–4832.

I/ Electrophilic Domino Reactions

I-2/ Enamine-Iminium

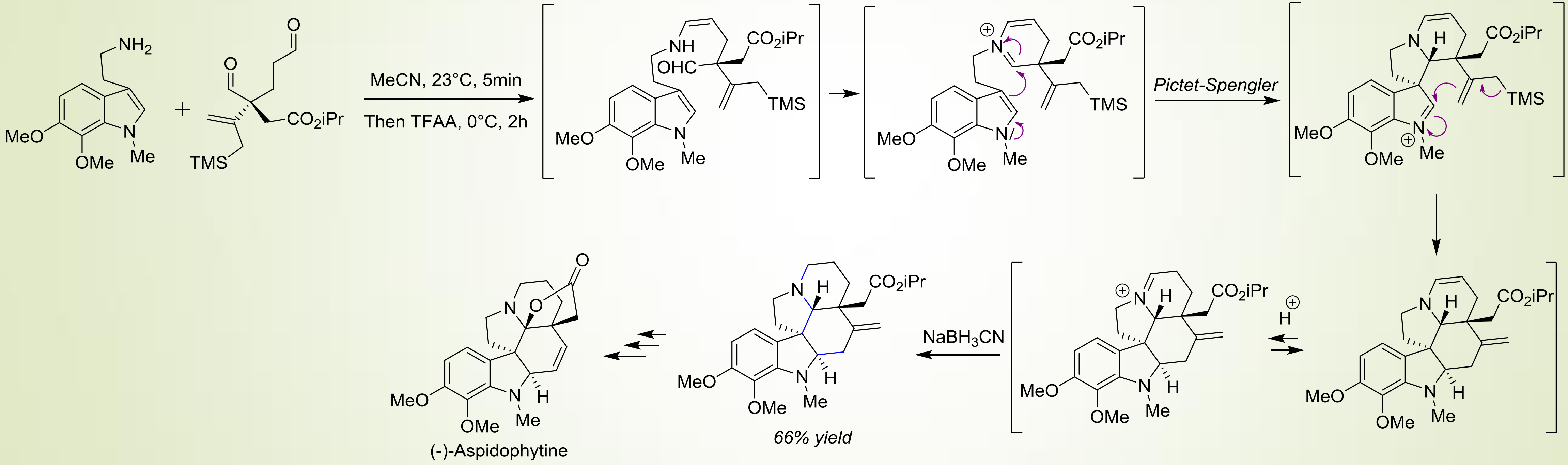
- Enamine : good nucleophile
- Iminium : good electrophile



I/ Electrophilic Domino Reactions

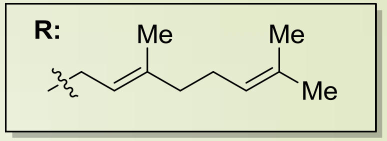
I-2/ Enamine-Iminium

- Corey's total synthesis of (-)-Aspidophytine (1999)



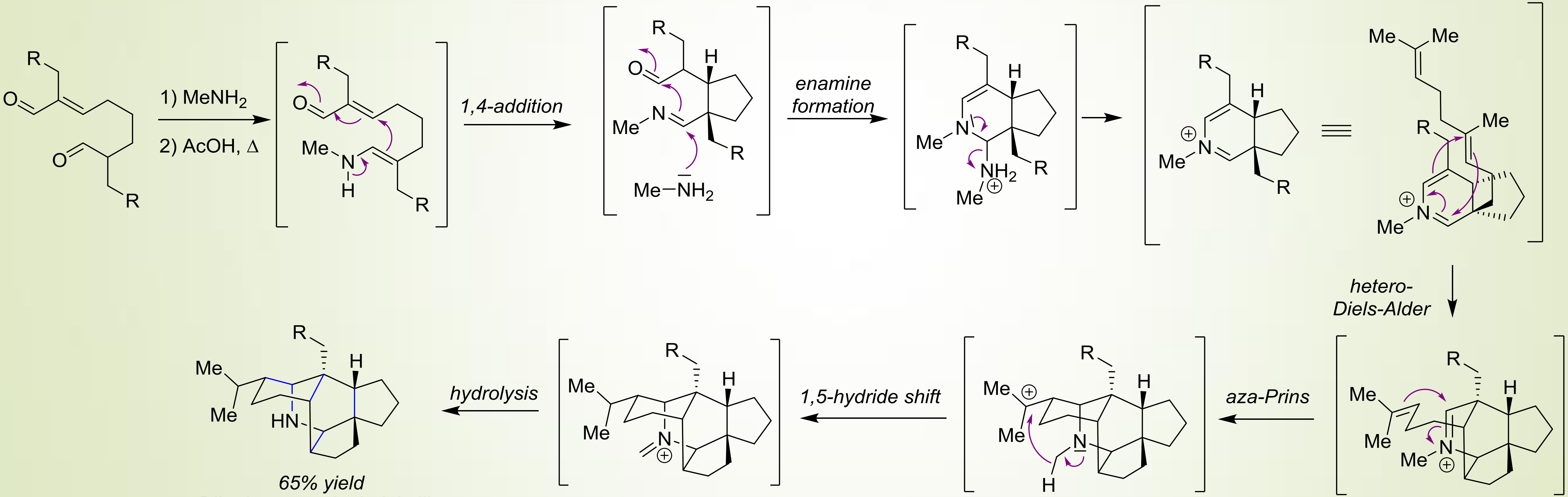
F. He, Y. Bo, J. D. Altom, E. J. Corey, *J. Am. Chem. Soc.* **1999**, *121*, 6771–6772.

I/ Electrophilic Domino Reactions



I-2/ Enamine-Iminium

- Heathcock's total synthesis of dihydro-proto-daphniphylline (1992)



65% yield
Dihydro-*proto*-daphniphylline

C. H. Heathcock, M. M. Hansen, R. B. Ruggeri, J. C. Kath, *J. Org. Chem.* **1992**, *57*, 2544–2553
C. H. Heathcock, S. Piettre, R. B. Ruggeri, J. A. Ragan, J. C. Kath, *J. Org. Chem.* **1992**, *57*, 2554–2566.

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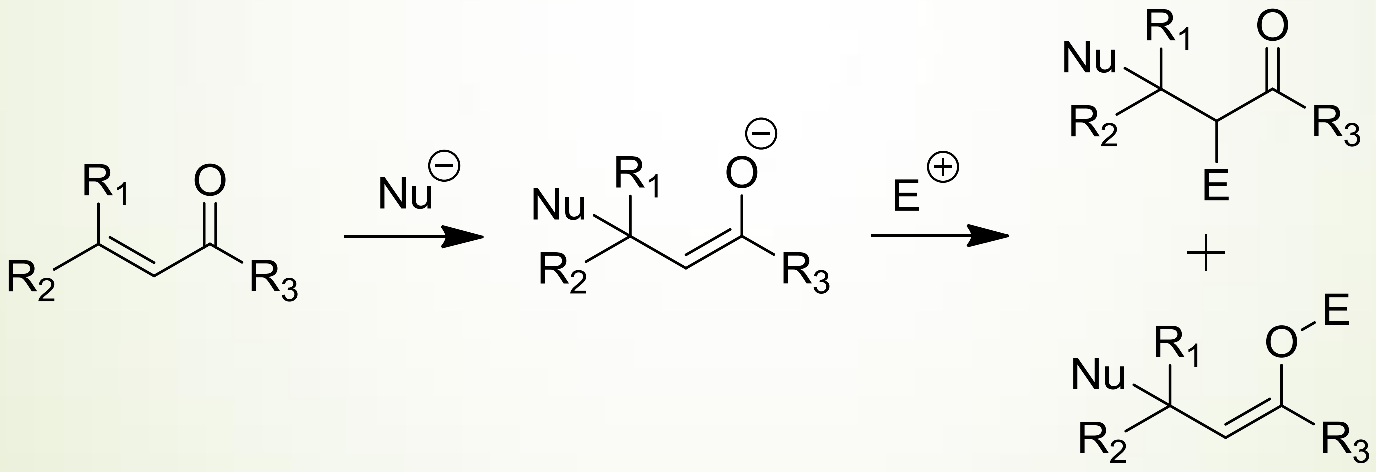
II/ Nucleophilic Domino Reactions

Michael acceptor

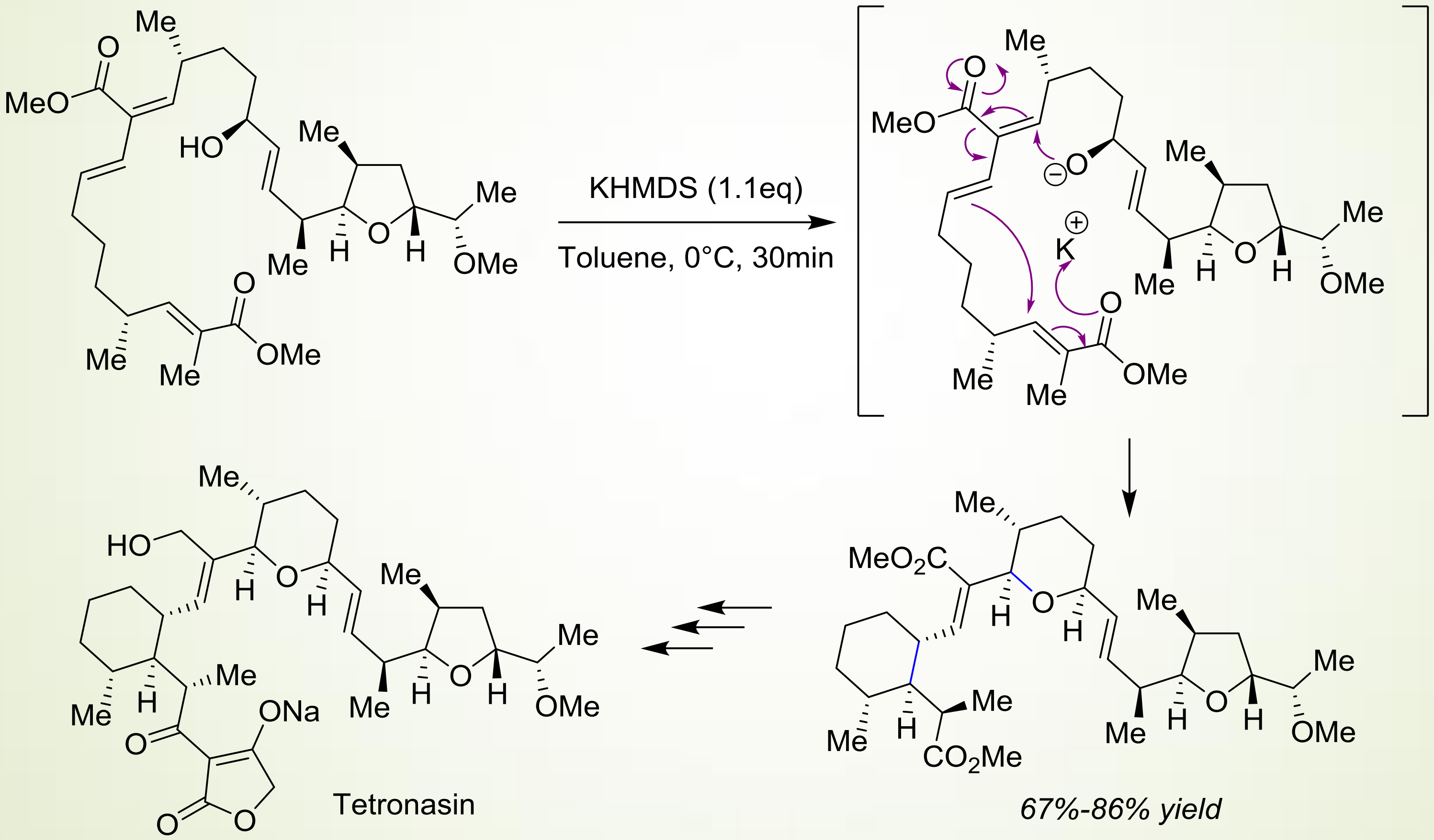
- Enone : good electrophile
- Enol : good nucleophile with competition between C- and O- attack



II/ Nucleophilic Domino Reactions

II-1/ Michael acceptor

- Ley’s total synthesis of Tetronasin (1998)



Tetronasin

67%-86% yield

G.-J. Boons, D. S. Brown, J. A. Clase, I. C. Lennon, S. V. Ley, *Tetrahedron Lett.* **1994**, *35*, 319 – 322.

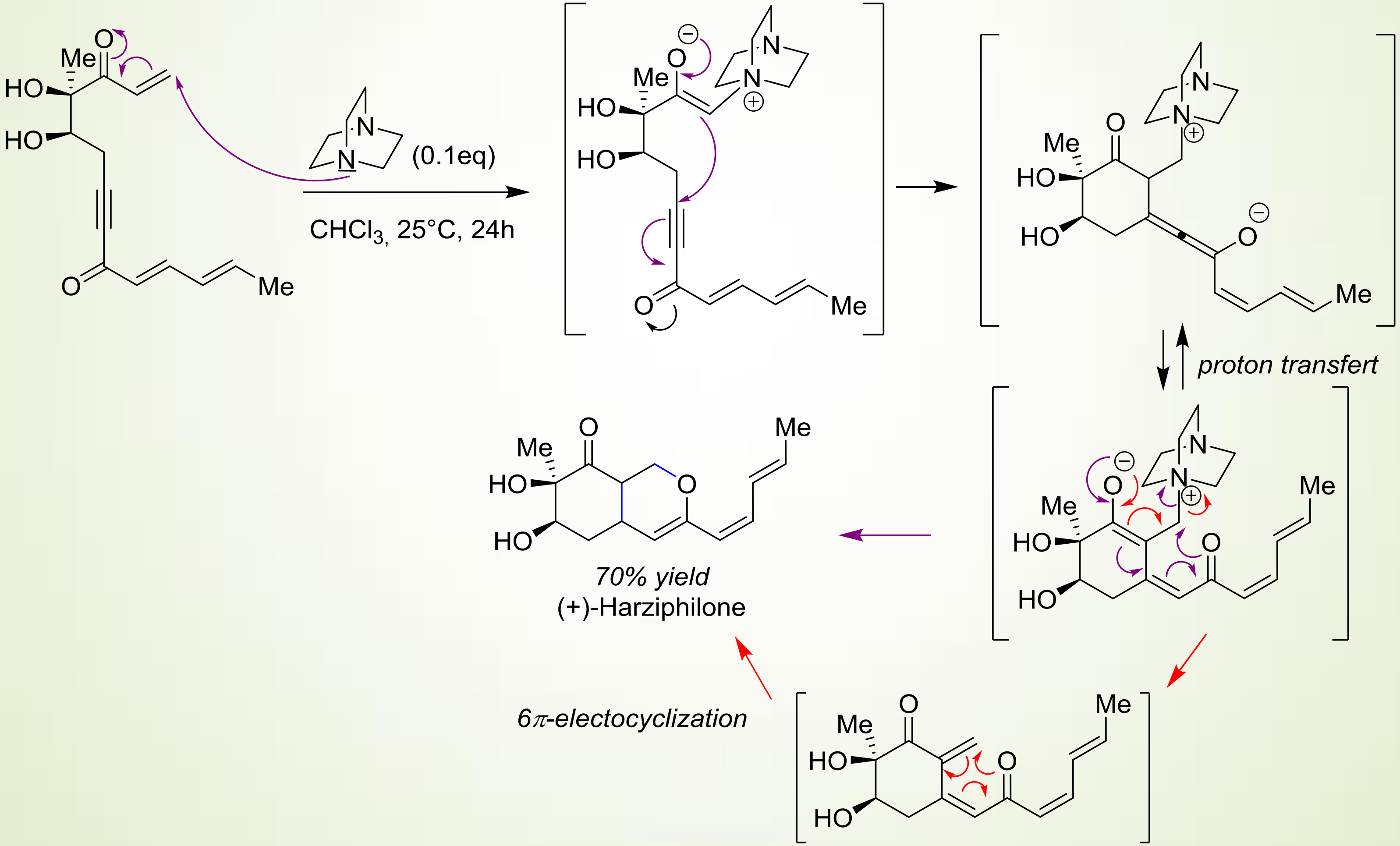
G.-J. Boons, I. C. Lennon, S. V. Ley, E. S. E. Owen, J. Staunton, D. J.Wadsworth, *Tetrahedron Lett.* **1994**, *35*, 323 – 326.

S. V. Ley, D. S. Brown, J. A. Clase, A. J. Fairbanks, I. C. Lennon, H. M. I. Osborn, E. S. E. Stokes (née Owen), D. J. Wadsworth, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2259 – 2276.

II/ Nucleophilic Domino Reactions

II-1/ Michael acceptor

- Sorensen’s total synthesis of (+)-Harziphilone (2004)



(0.1eq)

$CHCl_{3,}$ 25°C, 24h

proton transfert

70% yield

(+)-Harziphilone

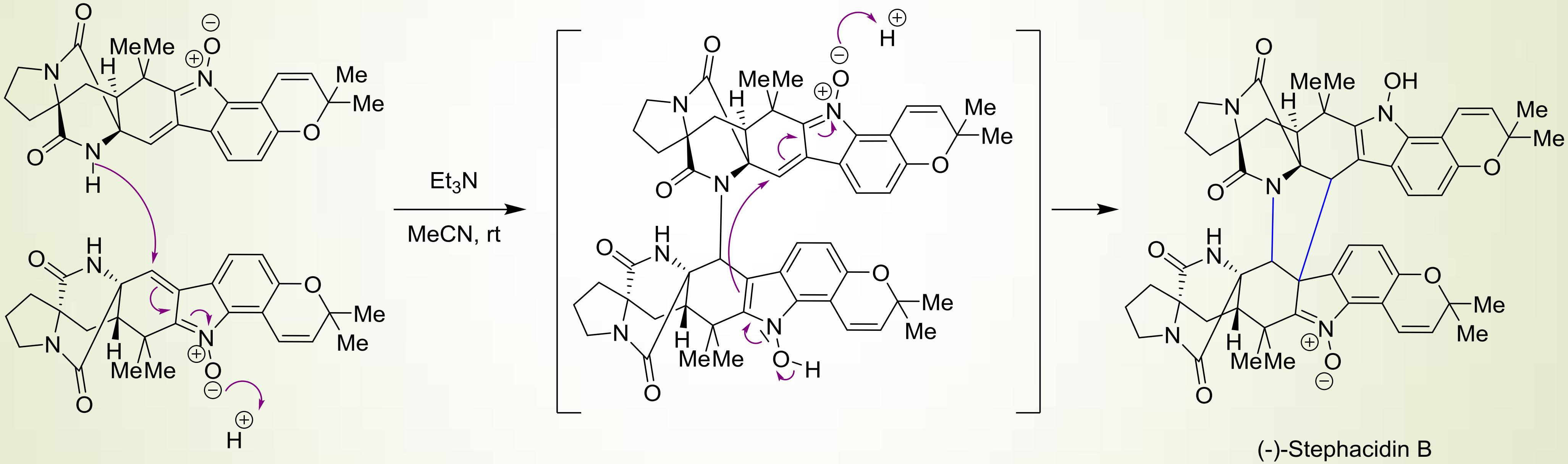
6π-electocyclization

L. M. Stark, K. Pekari, E. J. Sorensen, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12064–12066.

II/ Nucleophilic Domino Reactions

II-2/ Michael acceptor containing nitrogen

- Dimerization of (+)-Avrainvillamide in (-)-Stephacidin (Myers and Baran, 2005)



(+)-Avrainvillamide

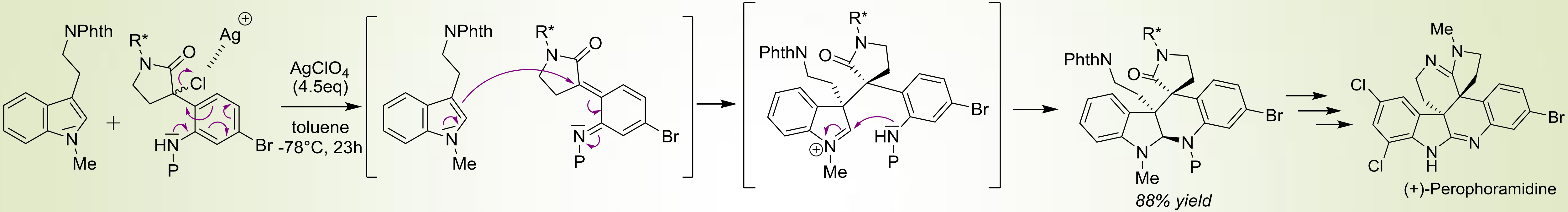
(-)-Stephacidin B

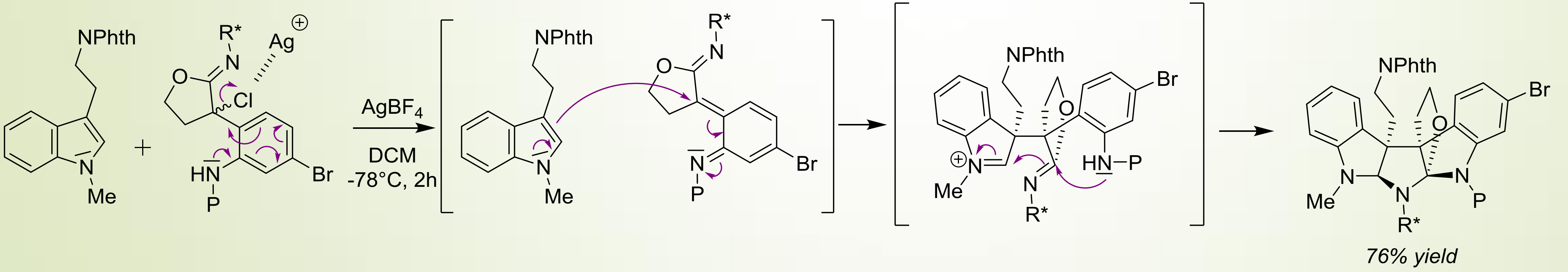
S. B. Herzon, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 5342–5344.
P. S. Baran, C. A. Guerrero, B. D. Hafensteiner, N. B. Ambhaikar, *Angew. Chem.* **2005**, 117, 3960–3963; *Angew. Chem. Int. Ed*. **2005**, *44*, 3892–3895.
P. S. Baran, B. D.Hafensteiner, N. B. Ambhaikar, C. A. Guerrero, J. D. Gallagher, *J. Am. Chem. Soc*. **2006**, *128*, 8678–8693.

II/ Nucleophilic Domino Reactions

II-2/ Michael acceptor containing nitrogen

- Qin's total synthesis of (+)-Perophoramidine (2010)





H. Wu, F. Xue, X. Xiao, Y. Qin, *J. Am. Chem. Soc.* **2010**, *132*, 14052–14054
H. Wu, F. Xue, X. Xiao, Y. Qin, *Synlett* **2011**, *11*, 907

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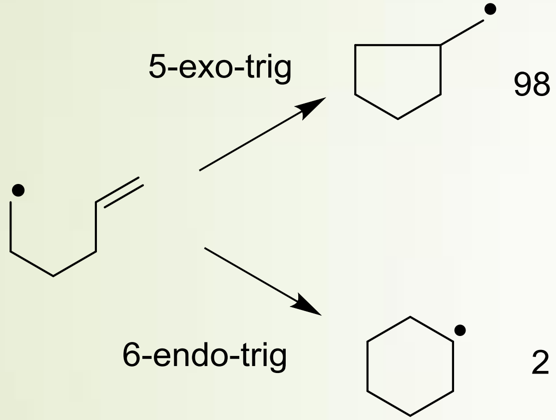
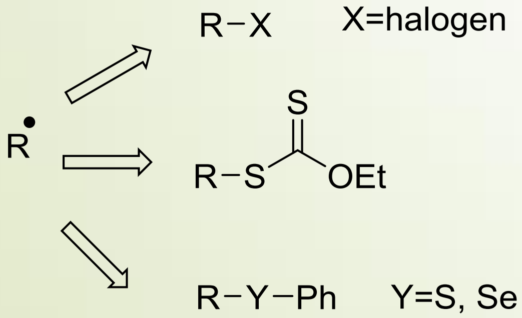
III/ Radical Domino Reactions

Radical cyclization

- Reactivity – Baldwin rules



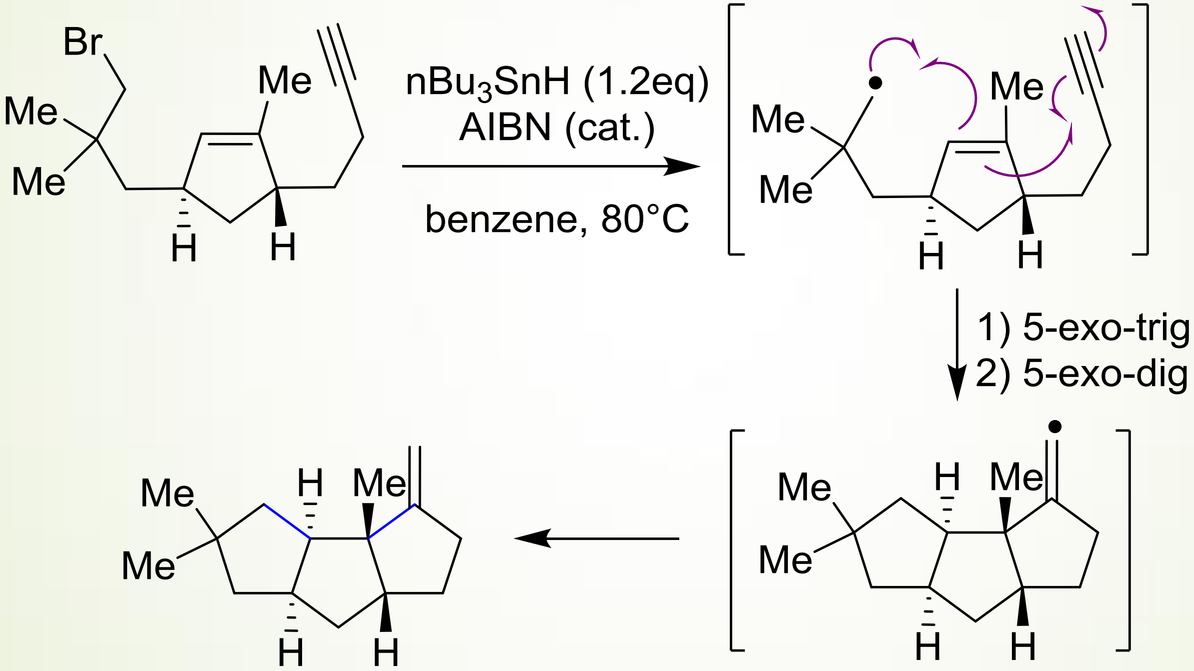
- Radical precursor



III/ Radical Domino Reactions

III-1/ Alkyl radical cyclization

- Curran’s total synthesis of (+/-)-Hirsutene (1985)



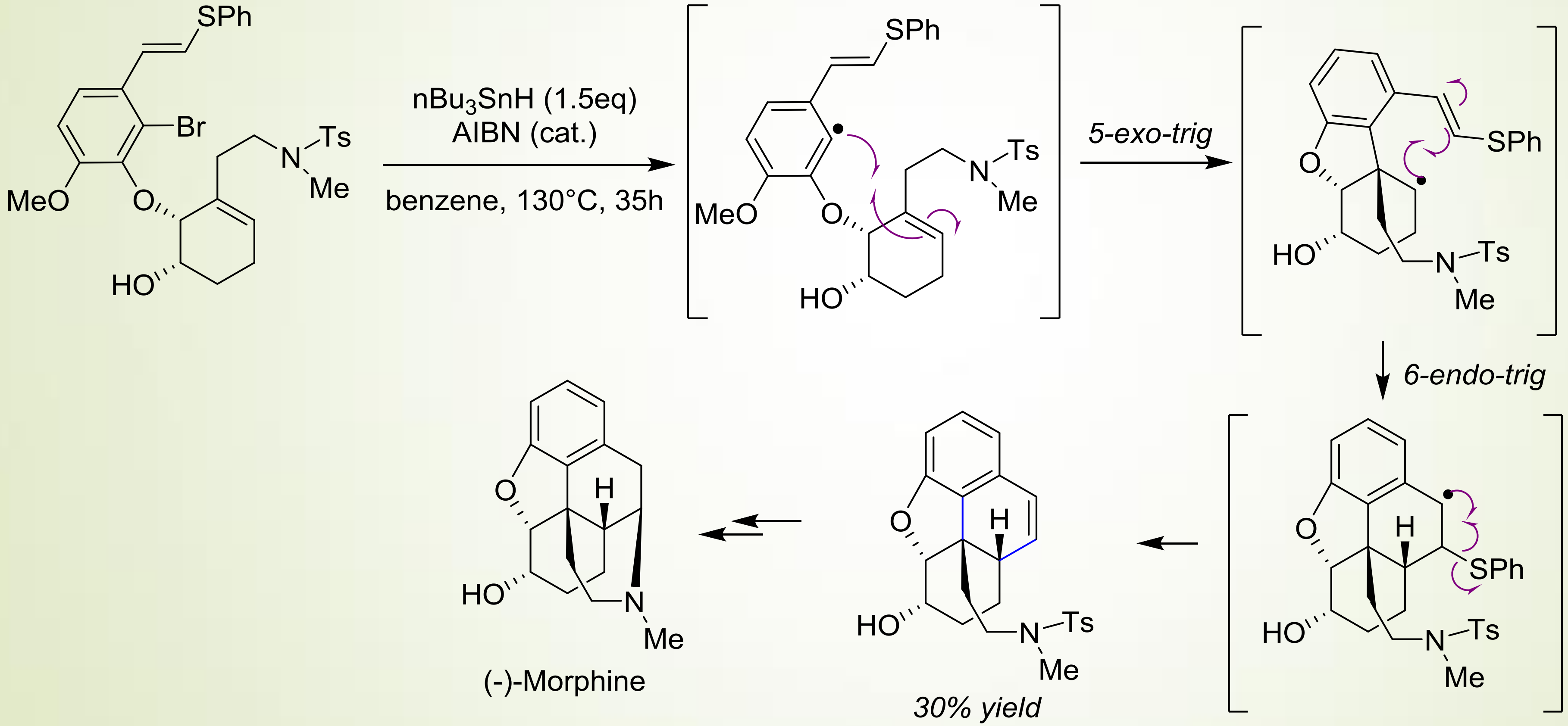
61% yield
(+/-)-Hirsutene

D. P. Curran, M.-H. Chen, *Tetrahedron Lett.* **1985**, 26, 4991-4994.

III/ Radical Domino Reactions

III-2/ Aryl radical cyclization

- Fokas and Parker's total synthesis of (-)-Morphine (2006)

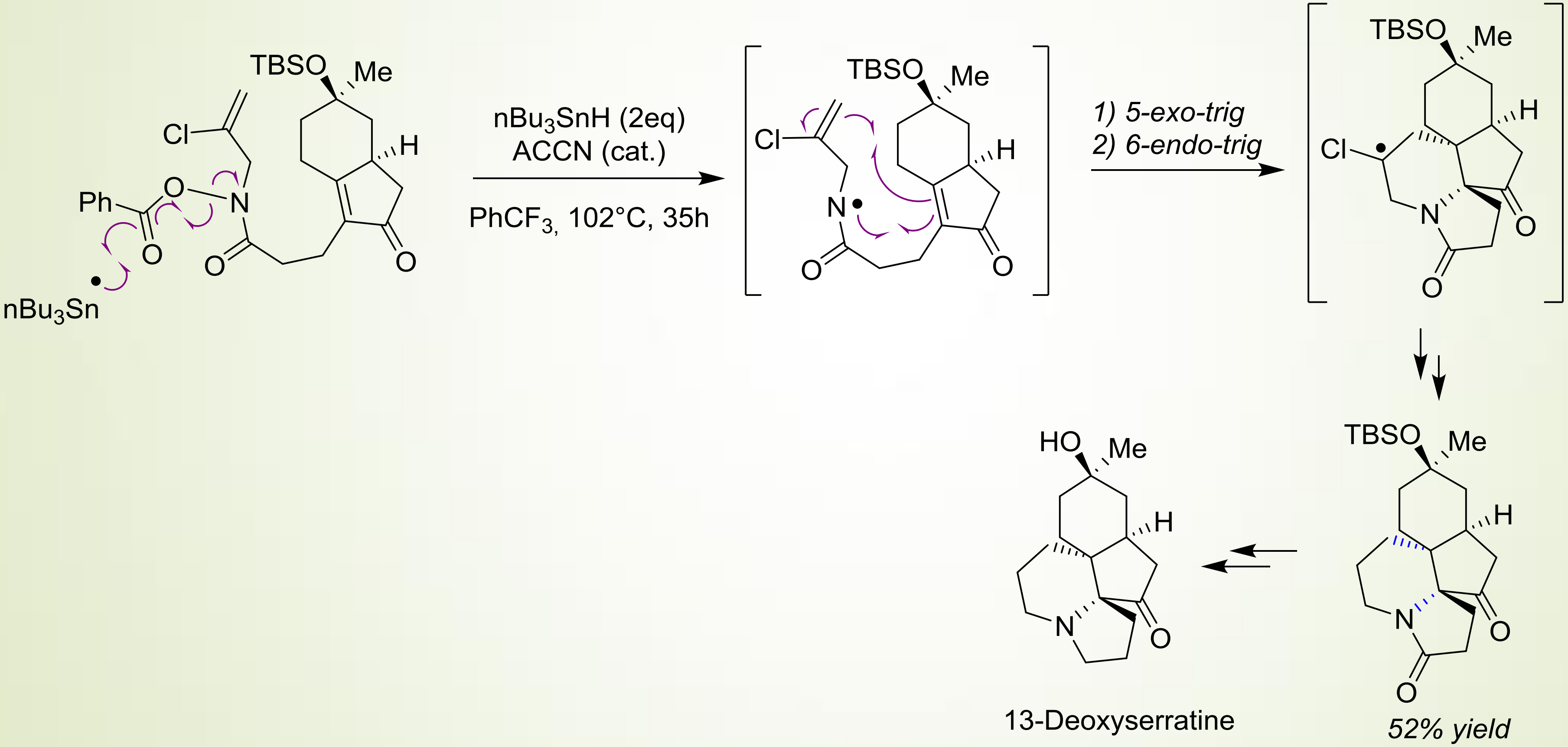


K. A. Parker, D. Fokas, *J. Am. Chem. Soc.* **1992**, *114*, 9688–9689.
K. A. Parker, D. Fokas, *J. Org. Chem.* **2006**, *71*, 449–455.

III/ Radical Domino Reactions

III-3/ Nitrogen-centered radical cyclization

- Zard’s total synthesis of 13-Deoxyserratine (2002)



13-Deoxyserratine

52% yield

J. Cassayre, F. Gagosz, S. Z. Zard, *Angew. Chem.* **2002**, *114*, 1861–1863; *Angew. Chem. Int. Ed.* **2002**, *41*, 1783–1785.

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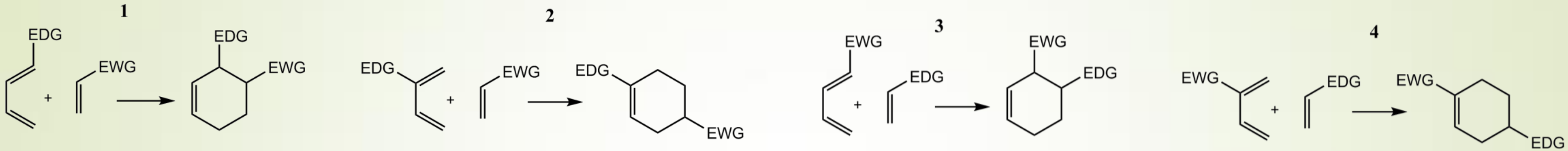
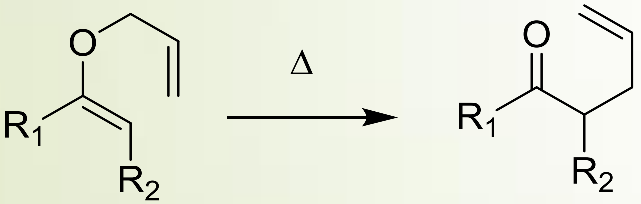
IV/ Pericyclic Domino Reactions

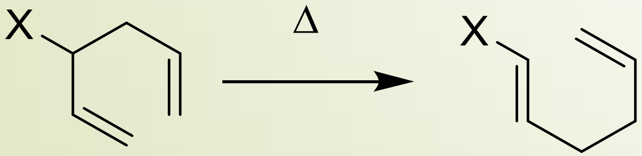
- Diels-Alder reaction



- Claisen rearrangement



- Cope rearrangement

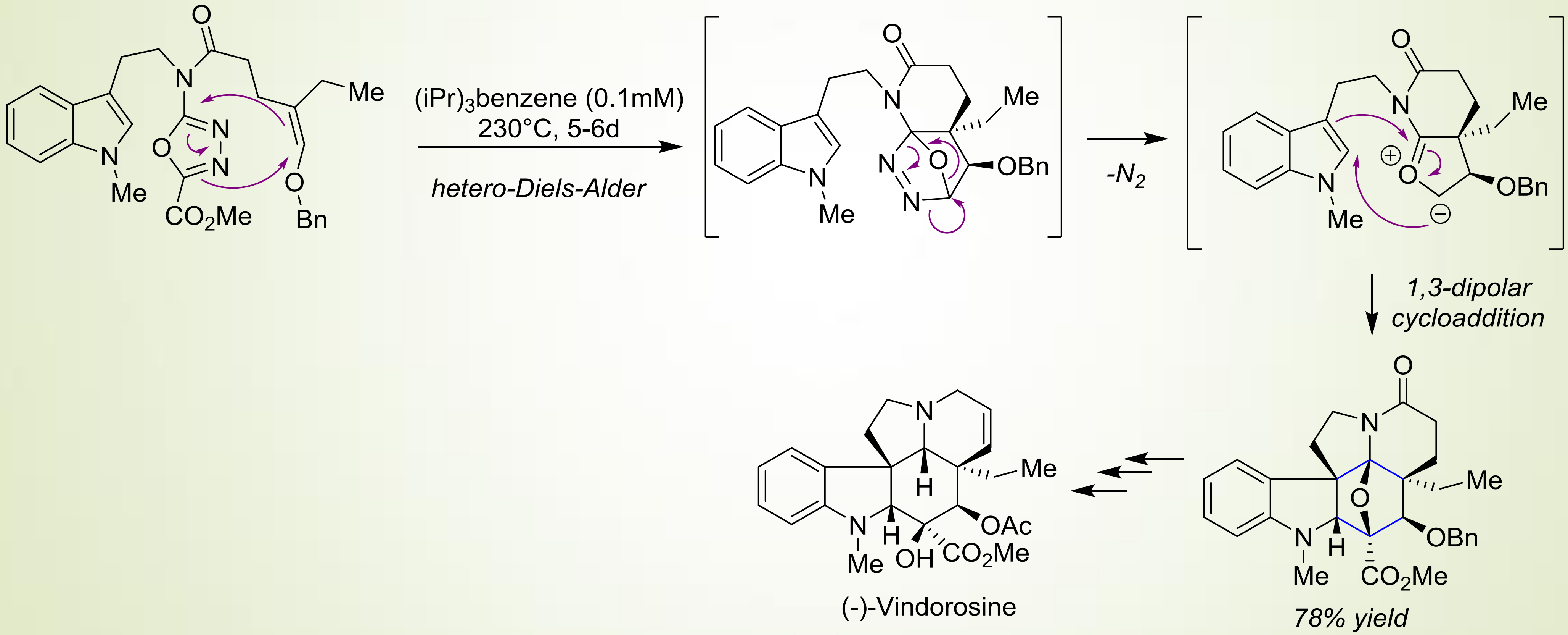


X: CH_3, OH

IV/ Pericyclic Domino Reactions

IV-1/ [4+2] / [3+2] domino process

- Boger's total synthesis of (-)-Vindorosine (2006)

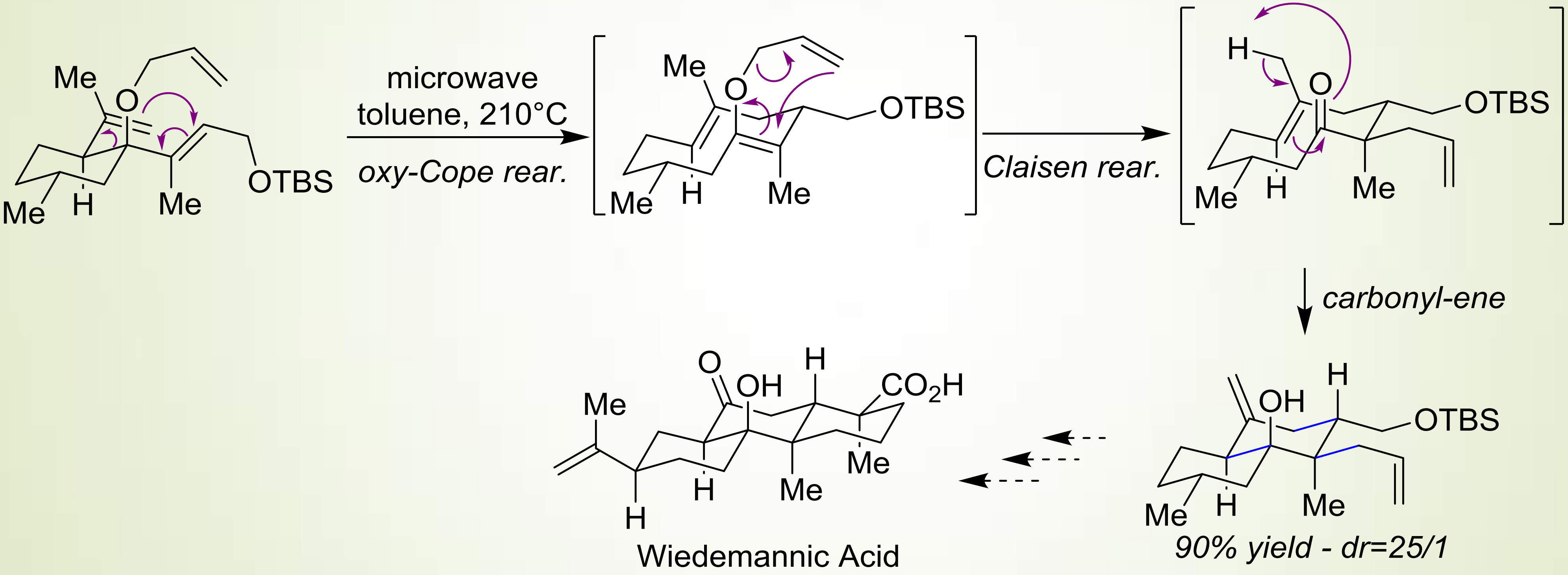


G. I. Elliot, J. Velcicky, H. Ishikawa, Y. Li, D. L. Boger, *Angew. Chem.* **2006**, *118*, 636–638; *Angew. Chem. Int. Ed.* **2006**, *45*, 620–622.

IV/ Pericyclic Domino Reactions

IV-2/ [3,3] / [3,3] / ene domino process

- Barriault's synthesis of Wiedemannic Acid skeleton (2004)



E. L. O. Sauer, L. Barriault, *Org. Lett.* **2004**, 6, 3329-3322

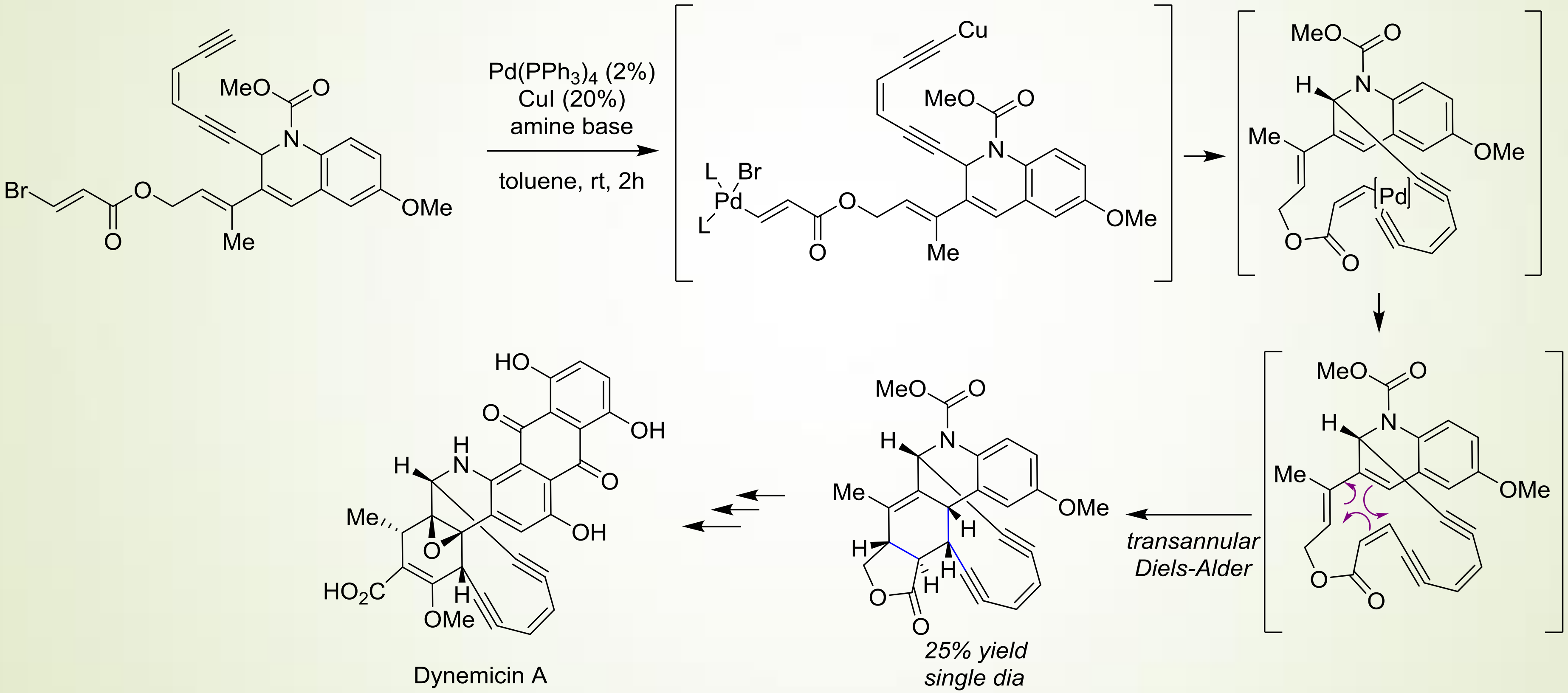
Table of Contents

- Introduction and Definitions
- I/ Electrophilic Domino Reactions
- II/ Nucleophilic Domino Reactions
- III/ Radical Domino Reactions
- IV/ Pericyclic Domino Reactions
- **V/ Transition Metal Catalyzed Domino Reactions**
- Conclusion

V/Transition Metal Catalyzed Domino Reactions

V-1/ Palladium-Copper catalyst

- Schreiber’s total synthesis of Dynemicin A (1993)

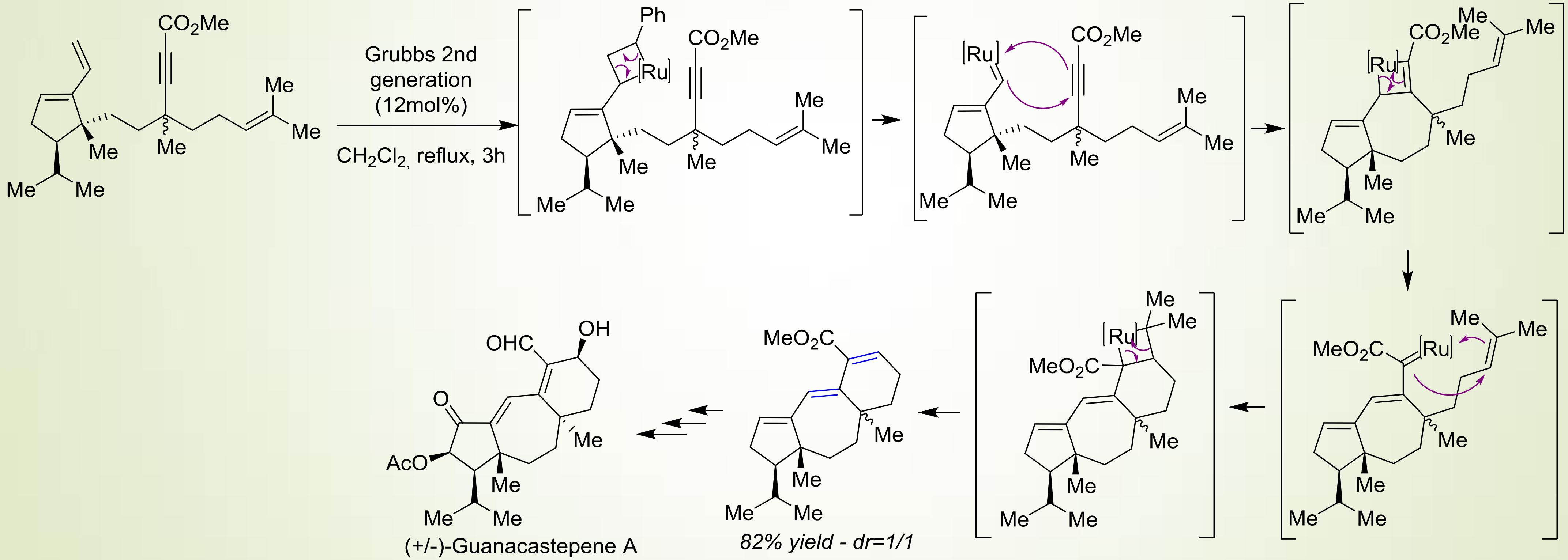


J. Taunton, J. L. Wood and S. L. Schreiber, *J. Am. Chem. Soc.* **1993**, *115*, 10378–10379.
J. A. Porco Jr., F. J. Schoenen, T. J. Stout, J. Clardy and S. L. Schreiber, *J. Am. Chem. Soc.* **1990**, *112*, 7410–7411.

V/Transition Metal Catalyzed Domino Reactions

V-2/ Ruthenium catalyst

- Hanna's formal synthesis of (+/-)-Guanacastepene A (2004)



Boyer, F. D.; Hanna, I.; Ricard, L. *Org. Lett.* **2004**, 6, 1817-1820.

Conclusion

- Advantages:
- Economy
- Increase of molecular complexity

- Drawbacks:
- Often take time to find suitable precursors and conditions to obtain the desired domino reaction (reduce the economy advantage…)
- Often only the thermodynamical product is obtain during a domino process

- Outlook:
- Very few example of catalytic enantioselective domino reaction --> Future of domino?

Thanks for your attention!

Questions

- What the major common points with all the domino reactions?
- In your opinion, what is the best (or the worst) strategy?

(LSPN)
LABORATOIRE DE SYNTHESE
ET PRODUITS NATURELS

Cinchona Alkaloids : Efficient Bifunctional Organocatalyts in Asymmetric Synthesis

Antonin Clemenceau

Frontiers in Chemical Synthesis

PhD in J. Zhu Group

23.05.14

Questions :

- What is a pseudo-enantiomer ?
- What could be the future or the other possibilities of this organocatalyst?

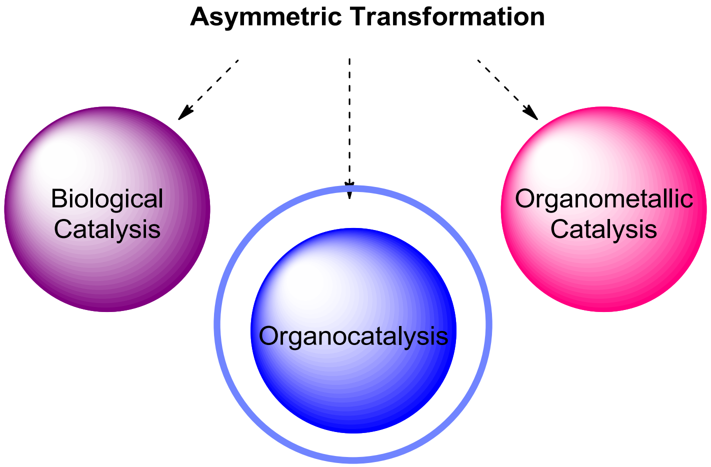
Plan :

- Introduction
    - Organocatalysis: Concepts and Principle
    - Organocatalysts
- Cinchona Alkaloids
    - Presentation
    - History
    - Other Potential Examples

Introduction

Organocatalysis

- Concept borns in the late 1990s
- Before only enzymes and metal-catalyst were used for asymmetric catalysis
- Another powerful tool for the Modern Organic Chemistry
- Explosion of this field during this century



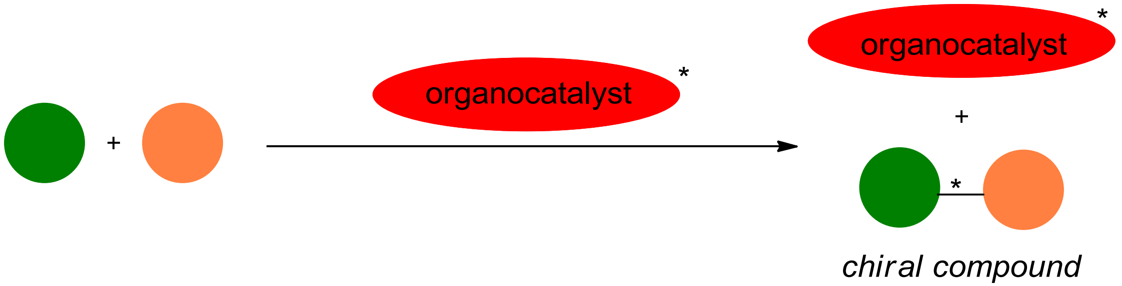
Organocatalysis: Concepts and principle

- Definition : The use of small organic molecules to catalyse asymmetric transformation
- First example of asymmetric organic synthesis was reported with proline catalyst in 1971 by two industrial research groups

Advantage:

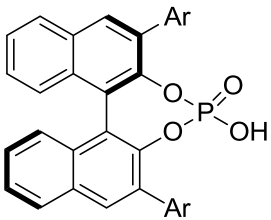
- Non-toxic, environmentally friendly
- Low cost
- Robust
- Metal-free reaction

Principle

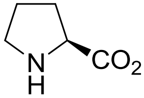


Creation of a new C-C or C-heteroatom bond controlled by the organocatalyst
===> Induction of chirality

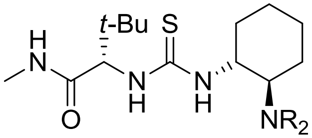
Organocalysts



Phosphoric acid

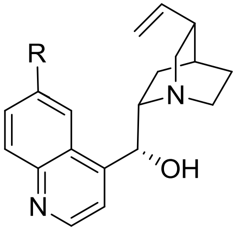


L-Proline

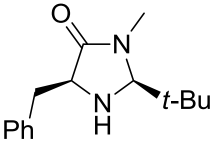


Thioruea

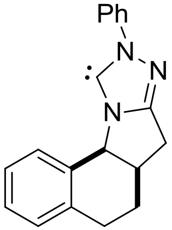
Famous organocatalysts with different reactivities and activation modes used all around the world



Cinchona Alkaloid



Imidazolidinone



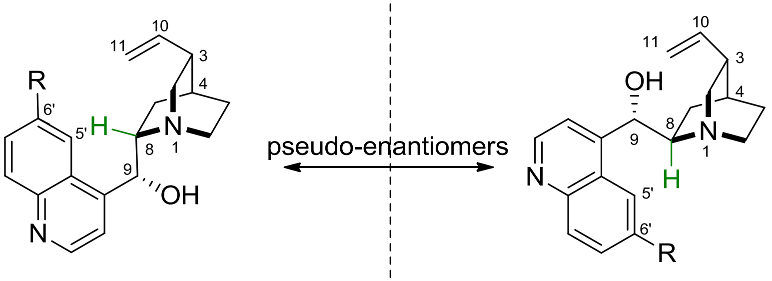
N-Carbene

Cinchona Alkaloids

- Quinine isolated by Pelletier in 1820
- First used for a resolution of a racemate in 1853 by Pasteur
- Quinine and derivatives were recognized as antimalarial agent
- First Total Synthesis in 1944 by Woodward and Doering
- Used as potential ligand for Lewis acidic metal at the beginning

Quinquina Tree

Nomenclature



Quinine (QN)	R = OMe	Quinidine (QD)	R = OMe
Cinchonidine (CD)	R = H	Cinchonine (CN)	R = H
Cupreine (CPN)	R = OH	Cupreidine (CPD)	R = OH

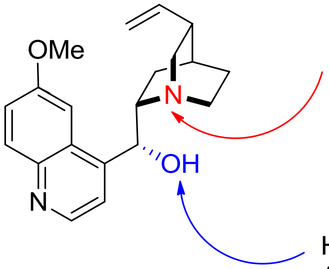
Considered as pseudo-enantiomers because

- The stereogenic centers (C8, C9) have the opposite absolute configuration
- The centers in the quinuclidine fragment (C3, C4) are identical

Ref: T. Marcelli, J. H. van Maarseveen, H. Hiemstra *Angew. Chem. Int. Ed.* **2006**, *45*, 7496 – 7504

Cinchona Alkaloids

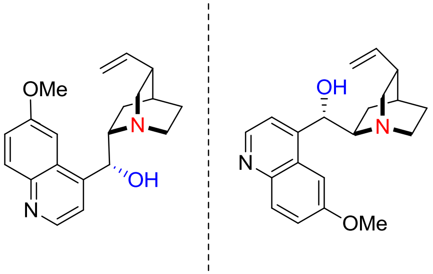
Bifunctional Catalyst



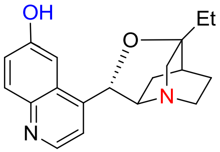
Lewis / Brønsted base
Activate Nucleophile

Hydrogen bond donating group
Activate Electrophile

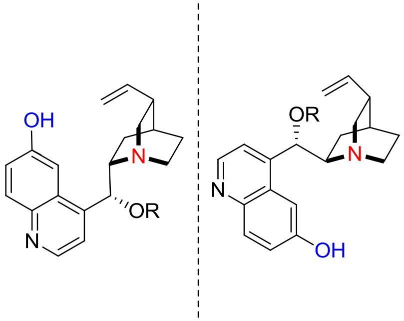
Easily tunable moiety



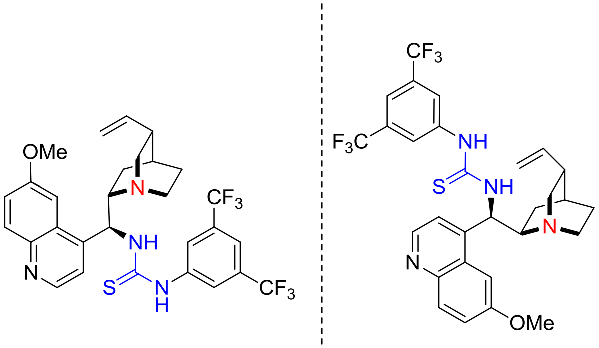
Wynberg, 1981
Conjugate Addition



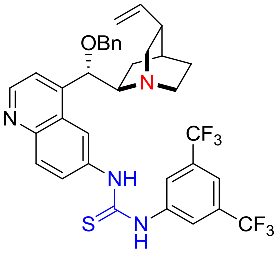
Hatakeyama, 1999
Baylis-Hilman Reaction



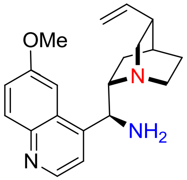
Deng, 2004
Conjugate Addition



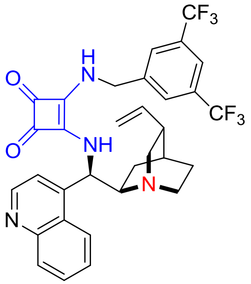
Connon, Dixon, Soós 2005
Conjugate Addition



Hiemstra, 2006
Henry Reaction



Chen 2007
Michael Addition

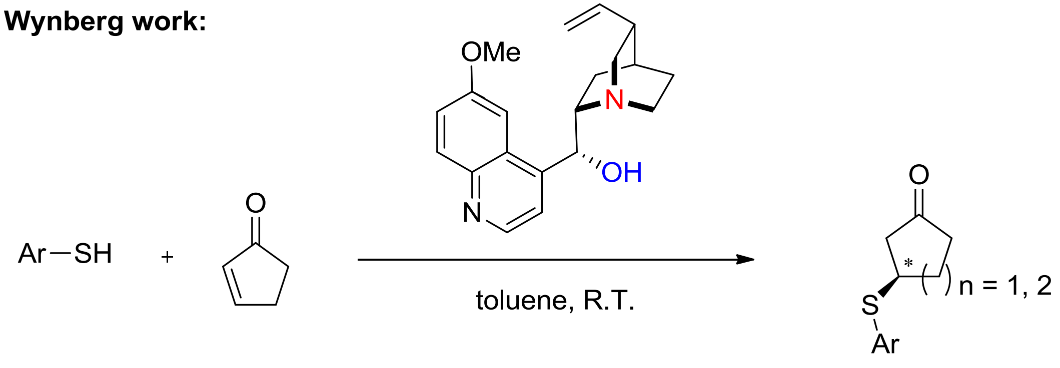


Rawal, 2008
Conjugate Addition

Ref: A. G. Doyle, E. N. Jacobsen *Chem. Rev.* **2007**, *107*, 5713 – 5743
J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen *Chem. Eur. J.* **2011**, *17*, 6890 – 6899
J. -W. Xie, W. Chem, R. Li, M. Zeng, W. Du, L. Yue, Y. -C. Chen, Y. Wu, J. Zhu, J. -G. Deng *Angew. Chem. Int. Ed.* **2007**, *46*, 389 –392

1981: **Quinine**

Enantioselective conjugate addition of aromatic thiols to conjugated cycloalkenones

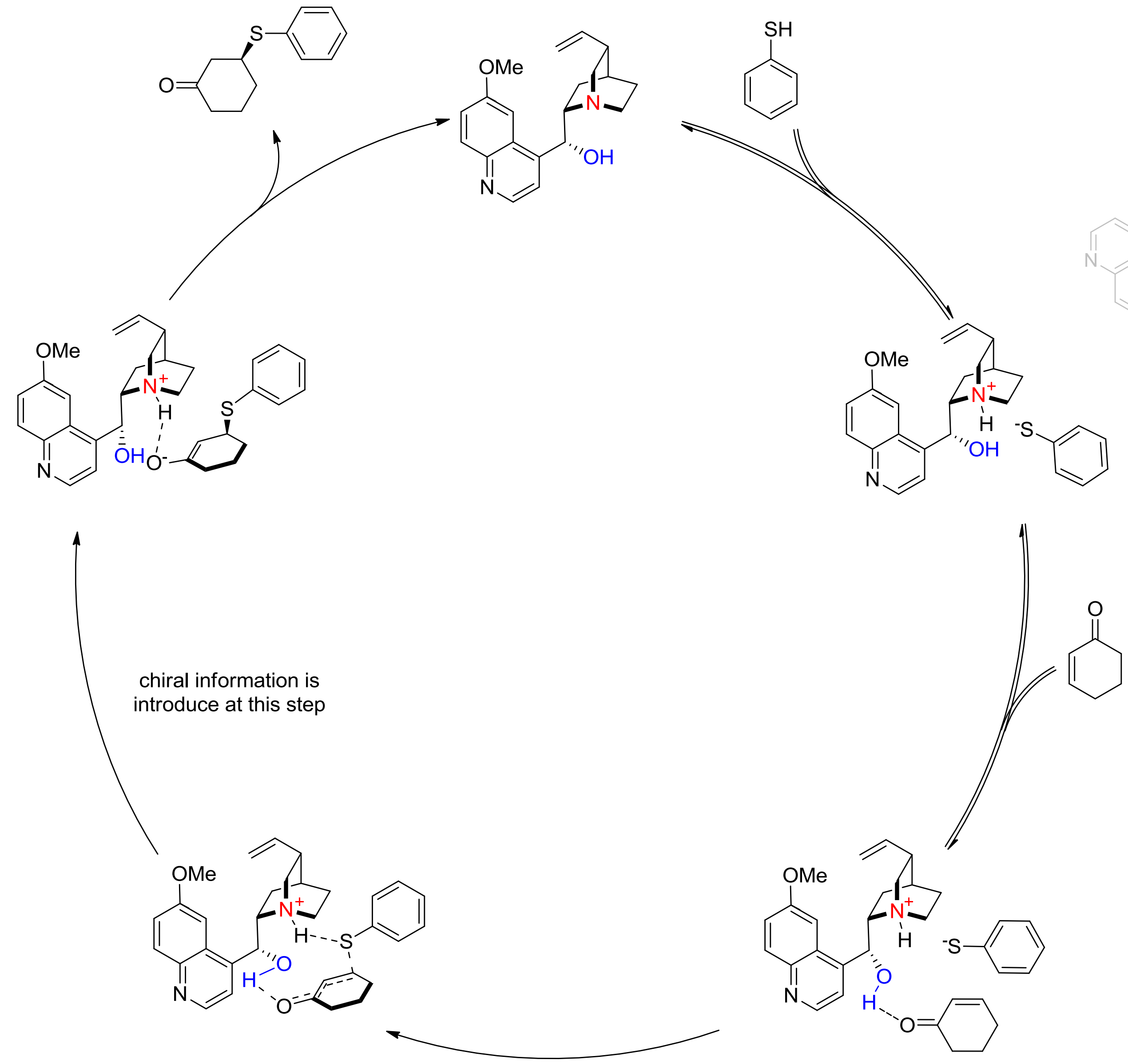


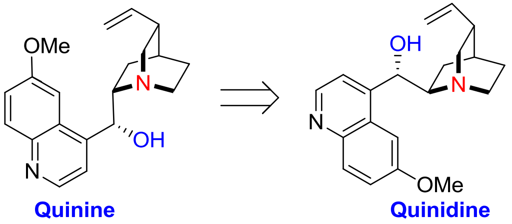
15 examples
up to 75 % ee

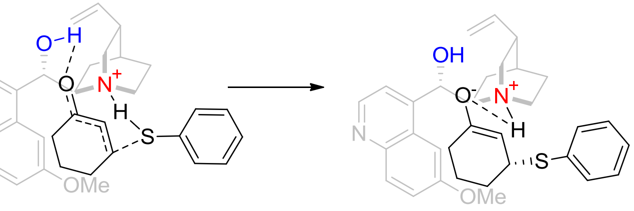
First example of Cinchona Alkaloid as Organocatalyst

Ref: H. Hiemstra, H. Wynberg *J. Am. Chem. Soc.* **1981**, *103*, 417.

1981: **Suggested Mechanism**







If the other pseudo-enantiomer catalyst is used, the other enantiomer can be formed

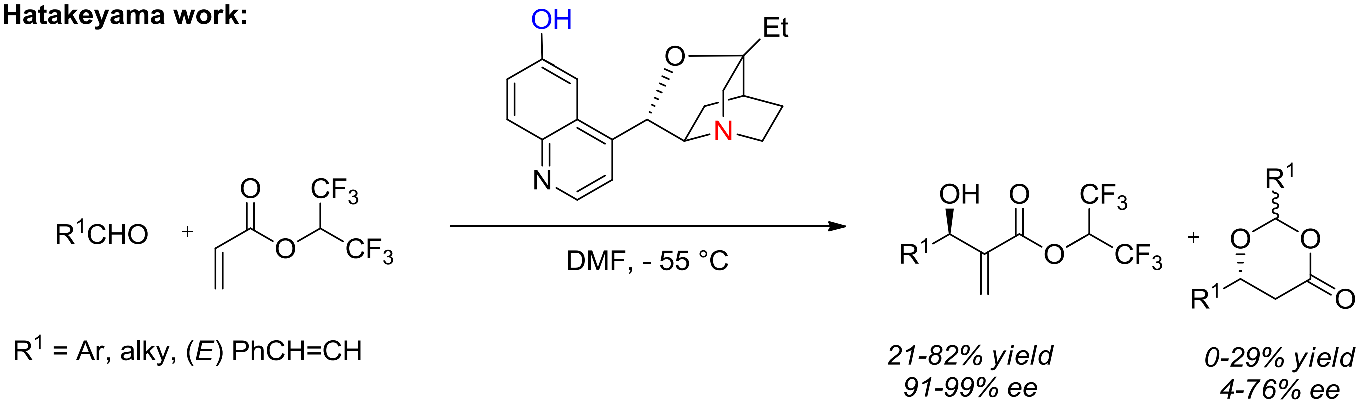
Ref: H. Hiemstra, H. Wynberg *J. Am. Chem. Soc.* **1981**, *103*, 417.

1999 : β-Isocupreine

Asymmetric Baylis–Hillman Reaction

Reaction between 1,1,1,3,3,3-hexafluoroisopropyl (HFIP) acrylate and aldehydes

Hatakeyama work:

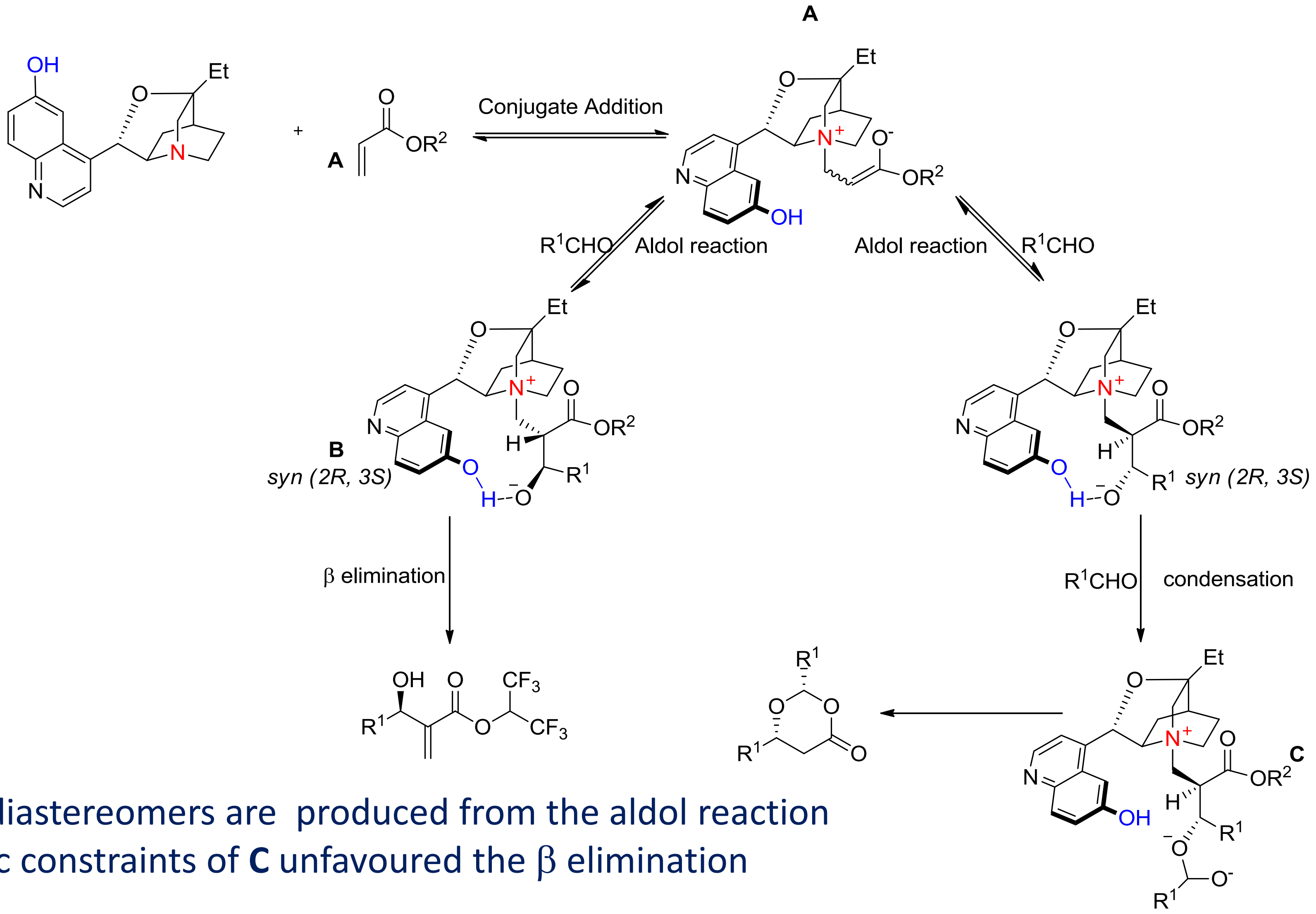


β-Isocupreine

- Cagelike structure
- Conformationally rigid
- No pseudoenantiomer of the β-isocupreine easily accessible

Ref: Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama *J. Am. Chem. Soc.* **1999**, *121*, 10219-10220

1999 : **Proposed Reaction Mechanism**



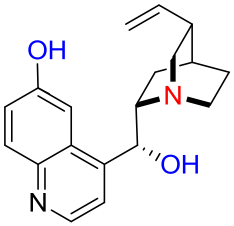
- *Syn* diastereomers are produced from the aldol reaction
- Steric constraints of **C** unfavoured the β elimination

Ref: Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama *J. Am. Chem. Soc.* **1999**, *121*, 10219-10220
See also: G. Masson, J. Zhu, C. Housseman *Angew. Chem. Int. Ed.* **2007,** *46*, 4614 – 4628

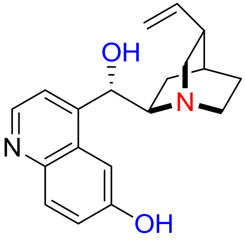
2004 : **Cupreine and Isocupreine**

Enantioselective Conjugate Addition of Malonate and β-Ketoester to Nitroalkane

in this example
2 H-bond donors

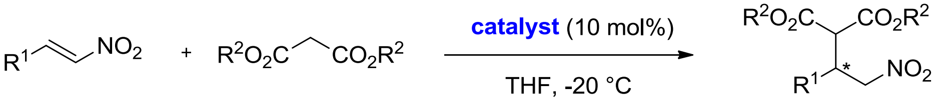


Cupreine (**CP**)



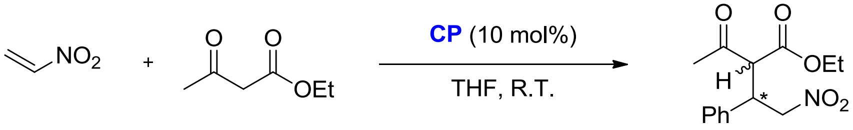
Cupreidine (**CPD**)

Deng work:



R^1 = Ar, alkyl
R^2 = Me, Et

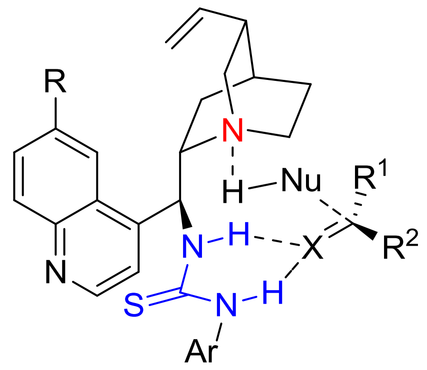
CP: 71-99% yield; 91-98% ee
CPD: 73-99% yield; 91-96% ee



93% yield
91% ee

Ref: H. Li, Y. Wang, L. Tang, L. Deng *J. Am. Chem. Soc.* **2004**, *126*, 9906-9907

2005 : **Thiourea Cinchona Alkaloids**

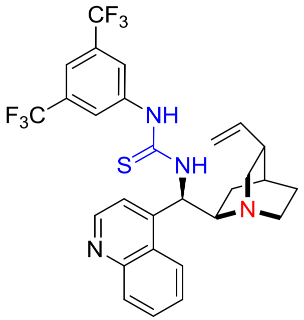


- *Simultaneous donation of two hydrogens*
- *Electrophile activation as enzymes system*
- *Strong and directional H-bonds favour asymmetric transformation*

Ref: J. Ye, D. J. Dixon, P. S. Hynes *Chem. Commun.* **2005**,4481
S. H. McCooey, S. J. Connon *Angew. Chem. Int. Ed.* **2005**, *44*, 6367
B. Vakulya, S. Varga, A. Csámpai, T. Soós *Org. Lett.*, **2005**, *7*, 1967-1969
M. S. Taylor, E. N. Jacobsen *Angew. Chem. Int. Ed.* **2006**, *45*, 1520 – 1543

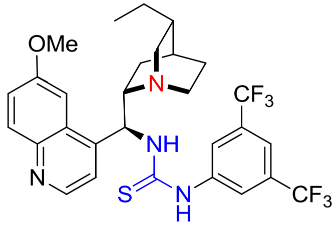
2005 : **Thiourea Cinchona Alkaloids**

Enantioselective Conjugate Addition

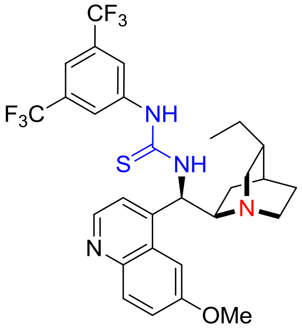


9-epi-CT

Dixon catalyst



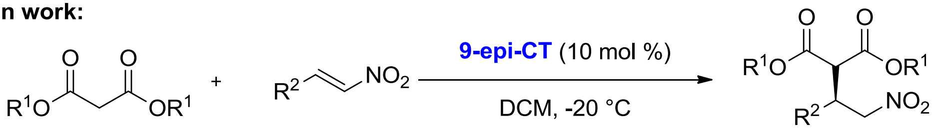
9-epi-DHQT



9-epi-DHQDT

Connon, Soós catalysts

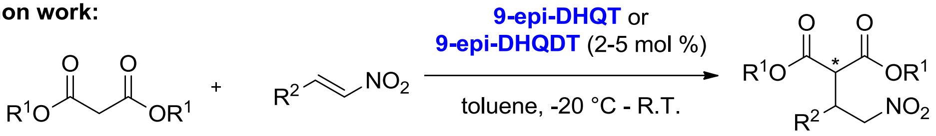
Dixon work:



16 examples

81-99% yield
82-97% ee

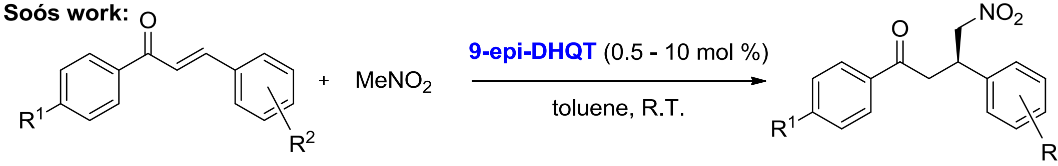
Conon work:



13 examples

63-95% yield
75-99% ee

Soós work:



5 examples

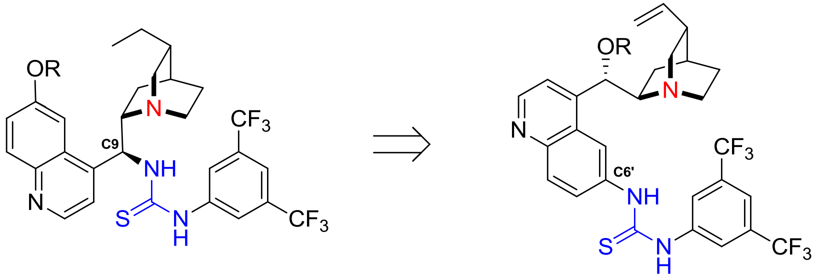
80-97% yield
89-98% ee

Ref: J. Ye, D. J. Dixon, P. S. Hynes *Chem. Commun.* **2005**,4481
S. H. McCooey, S. J. Connon *Angew. Chem. Int. Ed.* **2005**, *44*, 6367
B. Vakulya, S. Varga, A. Csámpai, T. Soós *Org. Lett.*, **2005**, *7*, 1967-1969

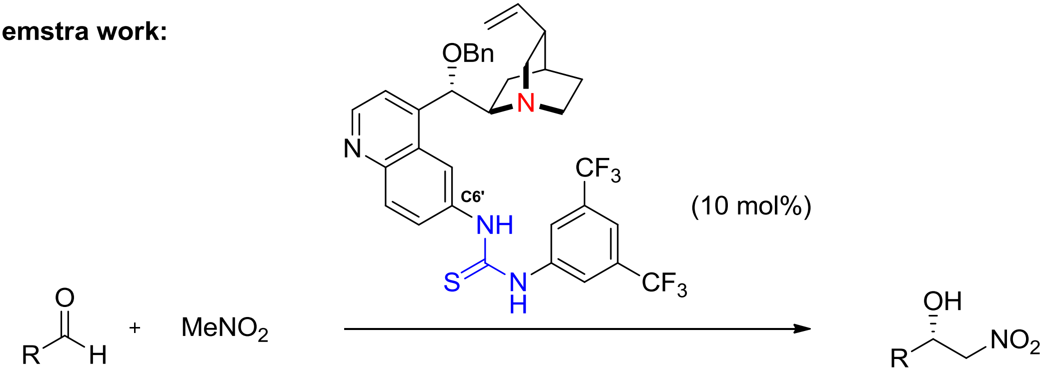
2006 : **C6’-Thiourea Cinchona Alkaloids**

Asymmetric Henry reaction between aldehydes and nitromethane

Switch of the H-bond donor **C9** to **C6’**



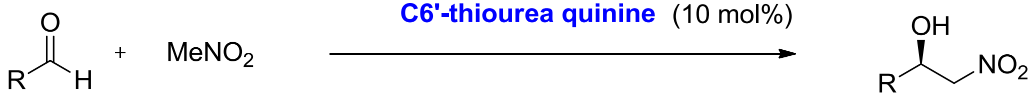
Hiemstra work:



(10 mol%)

THF, -20 °C

8 examples
90-99% yield
85-92% ee



C6'-thiourea quinine (10 mol%)

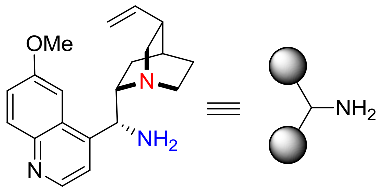
THF, -20 °C

3 examples
87-97% yield
87-93% ee

Ref: T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen, H. Hiemstra *Angew. Chem. Int. Ed.* **2006**, *45*, 929 –931

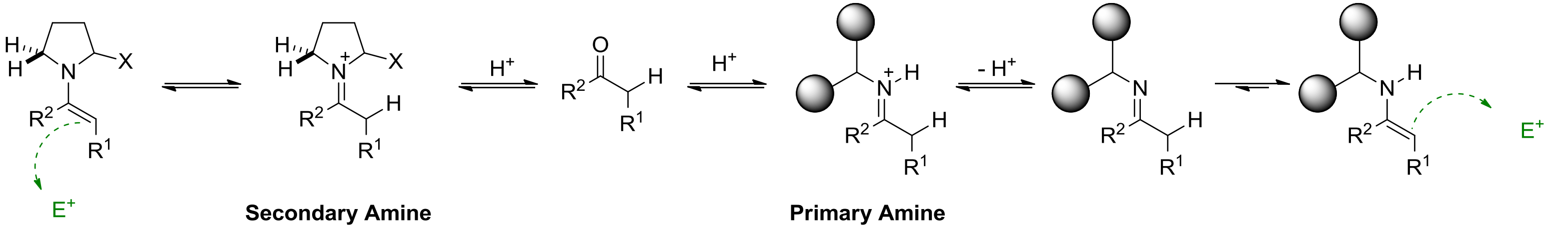
2007 : **Amino Cinchona Alkaloids**

Activation mode: Secondary amine vs Primary amine



<u>Enamine activation mode</u> (*α-functionalisation)*

Example 1: non-hindered carbonyl compound

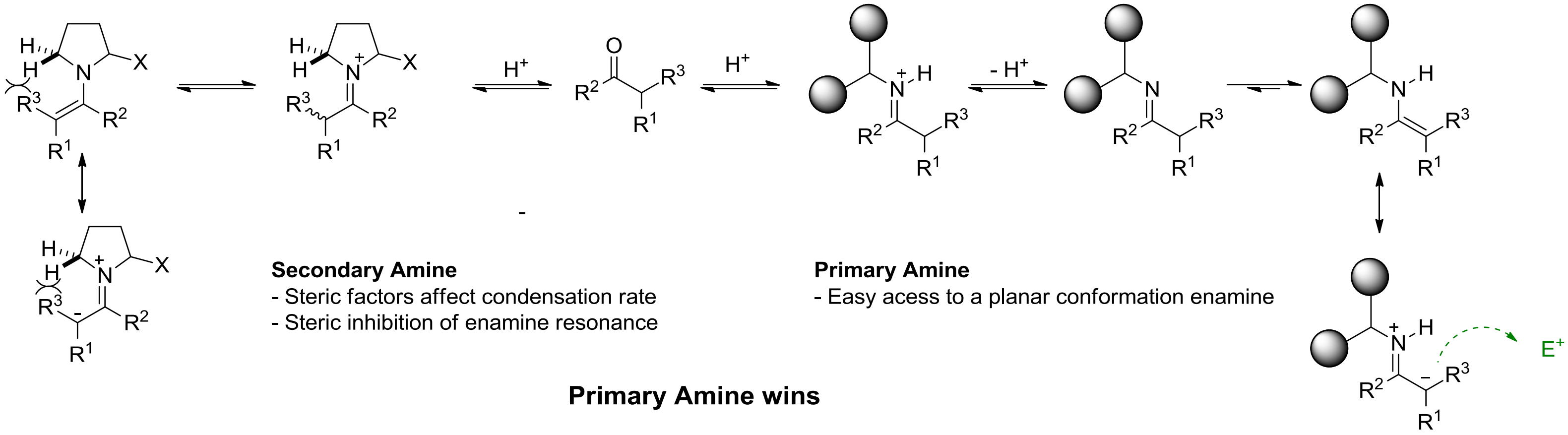


Secondary Amine
- More nucleophilic
- Better stabilization of the iminium ion by hyperconjugation

Primary Amine
- Unfavorable imine-enamine equilibrium

Example 2: hindered carbonyl compound

Secondary Amine wins



Secondary Amine
- Steric factors affect condensation rate
- Steric inhibition of enamine resonance

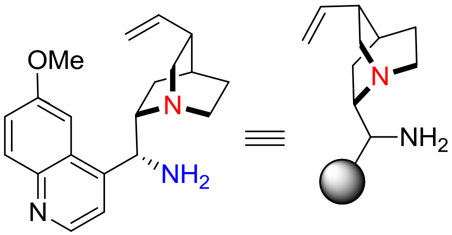
Primary Amine
- Easy acess to a planar conformation enamine

Primary Amine wins

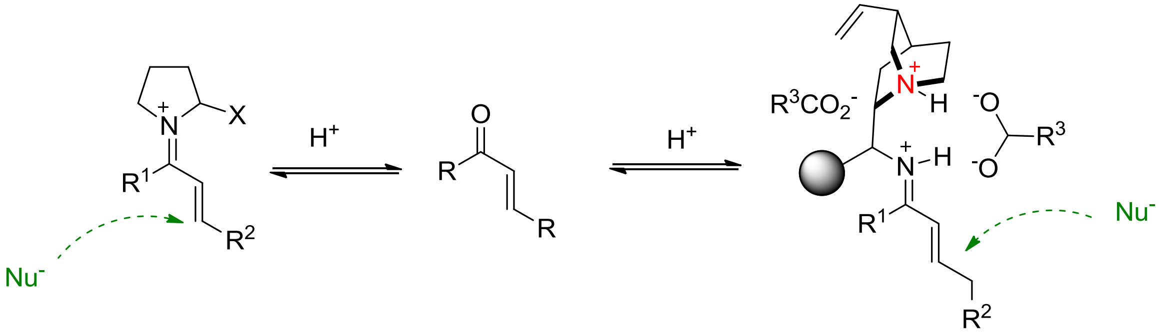
<u>Ref:</u> P. Melchiorre *Angew. Chem. Int. Ed.* **2012**, *51*, 9748 – 9770
L. Jiang, Y. -C. Chen *Catal. Sci. Technol.* **2011**,*1*, 354-365
S. Bertelsen, K. A. Jørgensen *Chem. Soc. Rev.*, **2009**, *38*, 2178–2189

2007 : **Amino Cinchona Alkaloids**

Activation mode



Iminium activation mode: *(β-functionalisation)*



Secondary Amine is sensitive to hinderance

Primary Amine need acid as a cocatalyst

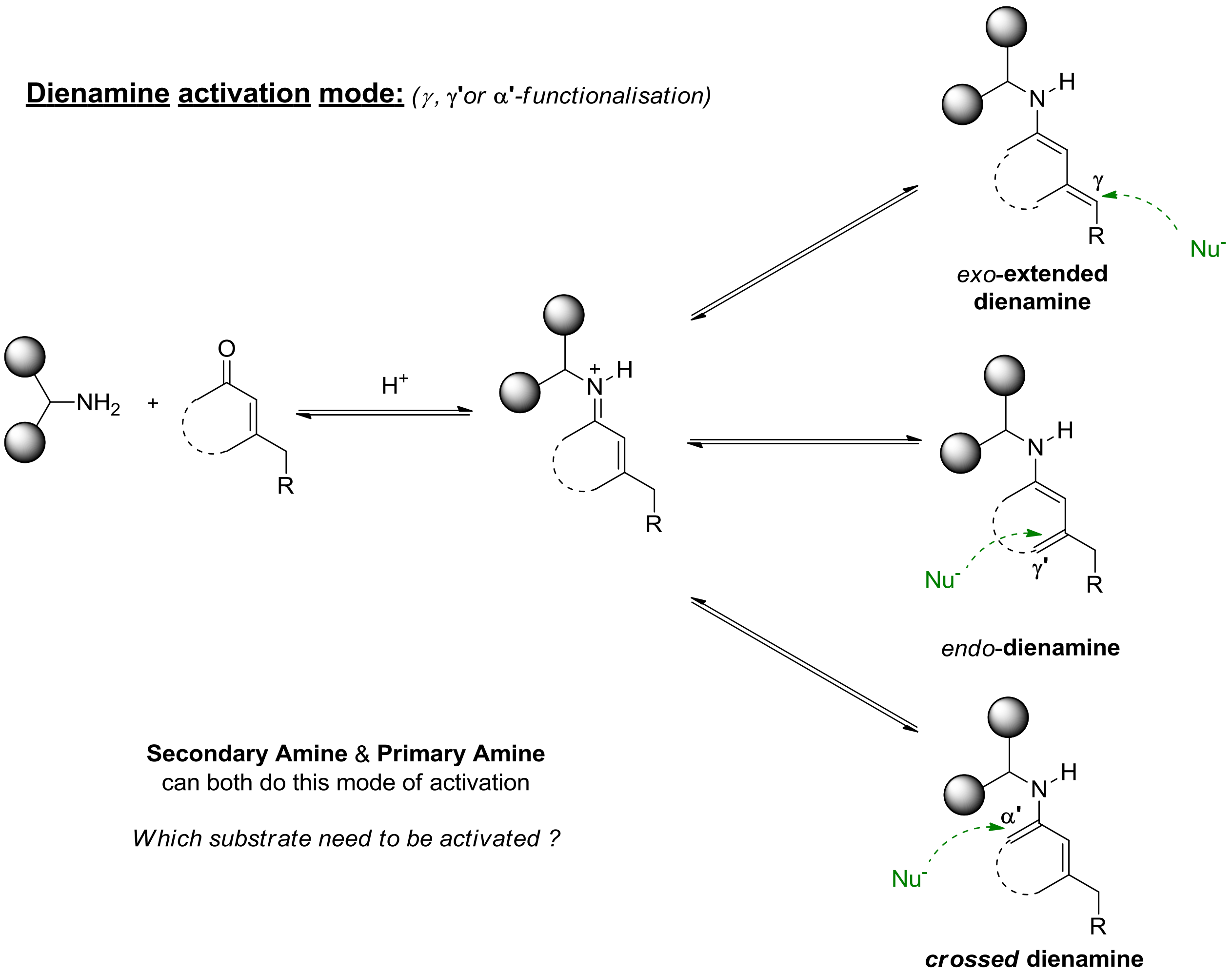
Choose the good catalyst in function of the substrate to activate

Ref: P. Melchiorre *Angew. Chem. Int. Ed.* **2012**, *51*, 9748 – 9770
L. Jiang, Y. -C. Chen *Catal. Sci. Technol.* **2011**,*1*, 354-365
S. Bertelsen, K. A. Jørgensen *Chem. Soc. Rev.*, **2009**, *38*, 2178–2189

2007 : **Amino Cinchona Alkaloids**

Activation mode

Dienamine activation mode: *(γ, γ'or α'-functionalisation)*



Secondary Amine & **Primary Amine**
can both do this mode of activation

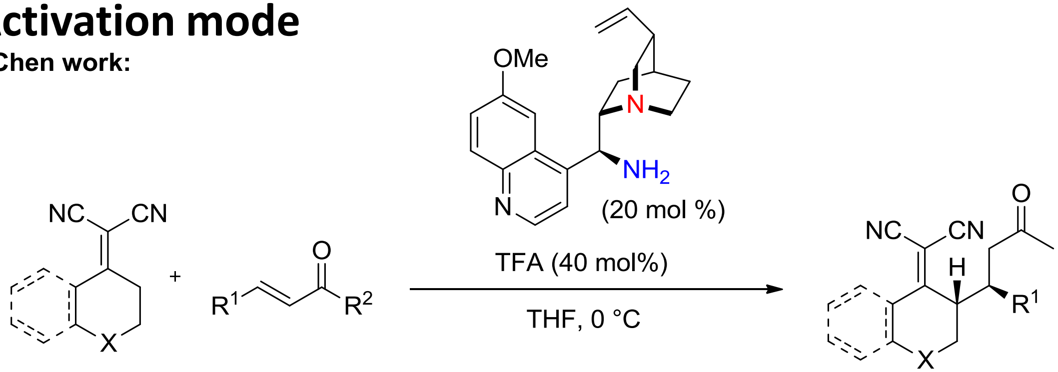
Which substrate need to be activated ?

Ref: P. Melchiorre *Angew. Chem. Int. Ed.* **2012**, *51*, 9748 – 9770
L. Jiang, Y. -C. Chen *Catal. Sci. Technol.* **2011**,*1*, 354-365
S. Bertelsen, K. A. Jørgensen *Chem. Soc. Rev.*, **2009**, *38*, 2178–2189

2007 : **Amino Cinchona Alkaloids**

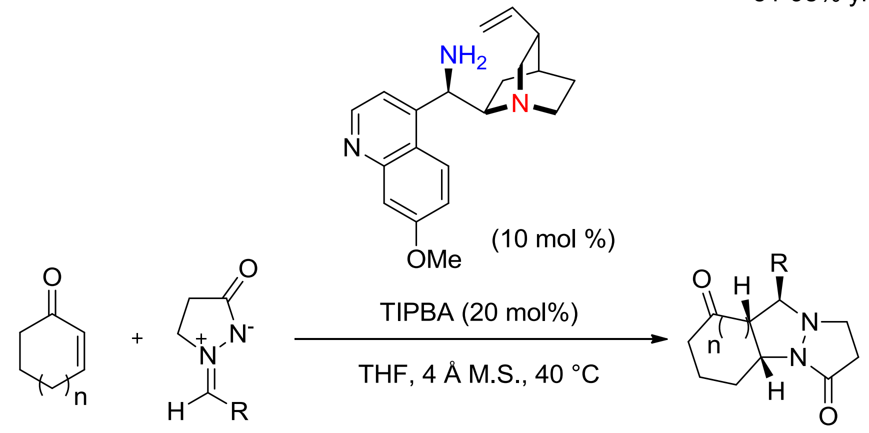
Iminium Activation mode

Chen work:



13 examples

87-99% ee
51-98% yield



n = 0, 1, 2 R = Aryl

22 examples

86-95% ee
67-99% yield

Ref: J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y. –C. Chen, Y. Wu, J. Zhu, J. –G. Deng *Angew. Chem. Int. Ed.* **2007**, *46*, 389 –392
W. Chen, W. Du, Y. –Z. Duan, Y. Wu, S.-Y. Yang, Y.- C. Chen *Angew. Chem. Int. Ed.* **2007**, *46*, 7667 –7670

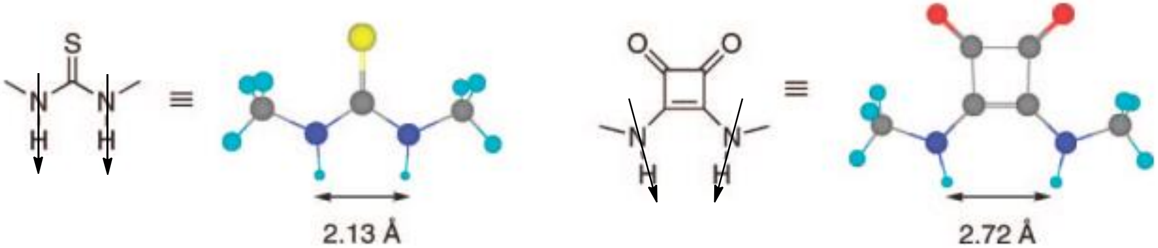
The same year, 2 other groups published organocatalytic reaction with Amino Cinchona Alkaloids:

S. H. McCooey, S. J. Connon *Org. Lett.* **2007**, *9*, 599 – 602.

G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre *Org. Lett.* **2007**, *9*, 1403 – 1405.

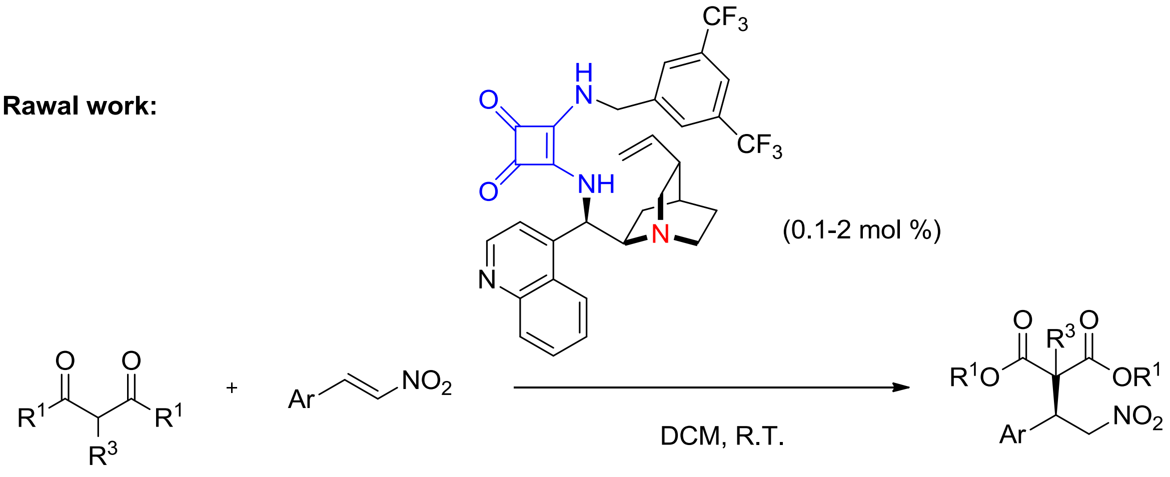
2008 : **SquaramideCinchona Alkaloids**

Difference with thiourea:



Asymmetric conjugate addition of dicarbonyle to nitroalkene

Rawal work:



21 examples

65-98% yield
77-99% ee
1:1-50:1 dr

Ref: J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416.
J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen *Chem. Eur. J.* **2011**, *17*, 6890 – 6899

Other Potential Application

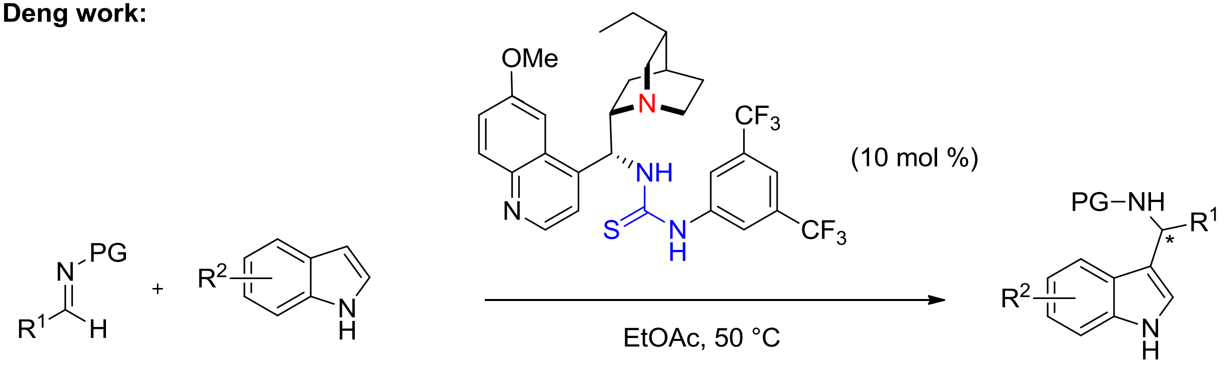
Over the years **Conjugate Addition** is the most common transformation performs with **Cinchona Alkaloids**

Other potential transformation possible?

Other Potential Application

Asymmetric Friedel-Crafts Reaction of Indoles with Imines

Deng work:



(10 mol %)

EtOAc, 50 °C

R^1 = alkyl, aryl

20 examples

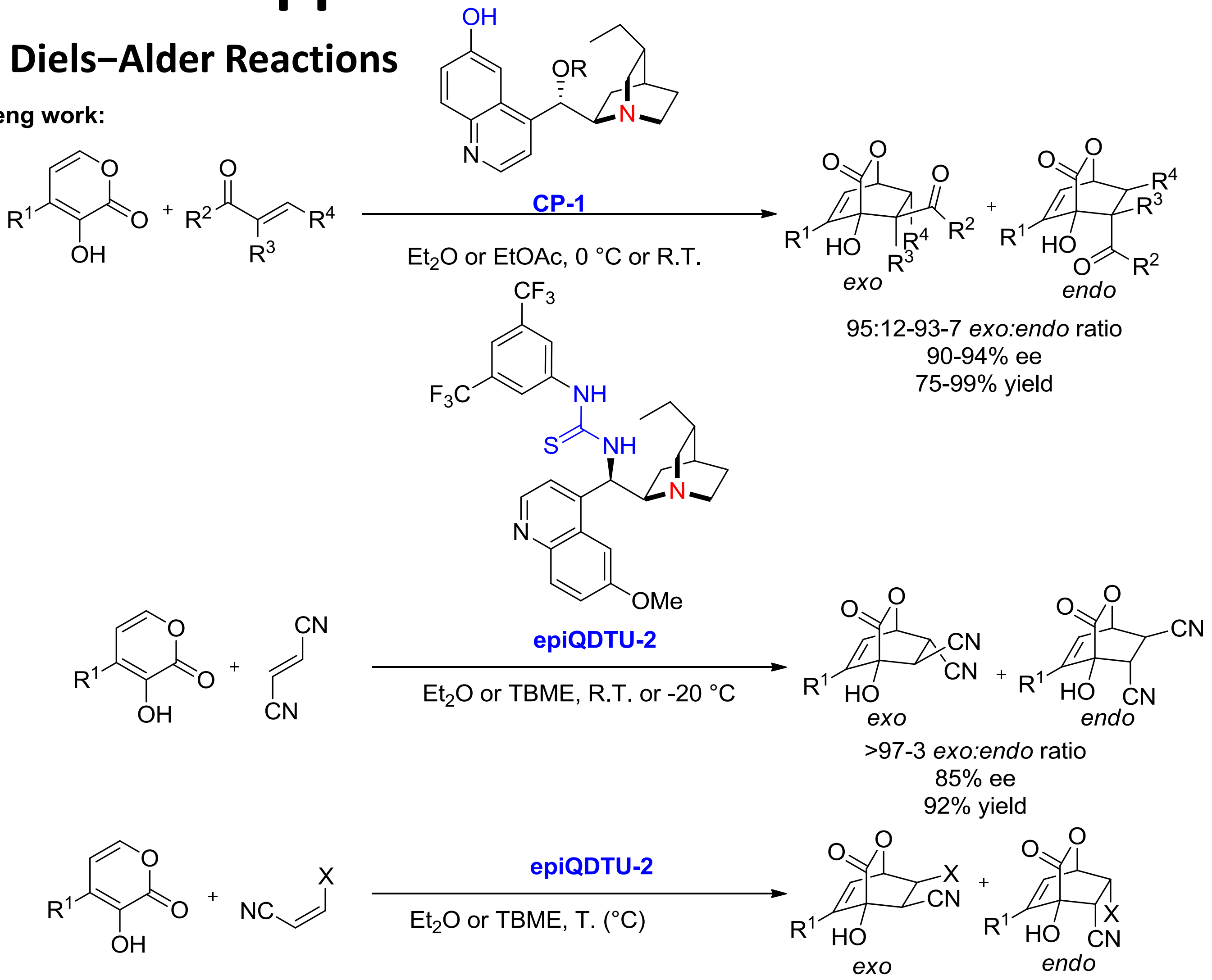
up to 97% ee
up to 98 % yield

Ref.: Y. -Q. Wang, J. Song, R. Hong, H. Li, L. Deng *J. Am. Chem. Soc.* **2006**, *128*, 8156

Other Potential Application

Asymmetric Diels–Alder Reactions

Deng work:



CP-1

Et_2O or EtOAc, 0 °C or R.T.

95:12-93-7 *exo:endo* ratio
90-94% ee
75-99% yield

epiQDTU-2

Et_2O or TBME, R.T. or -20 °C

>97-3 *exo:endo* ratio
85% ee
92% yield

epiQDTU-2

Et_2O or TBME, T. (°C)

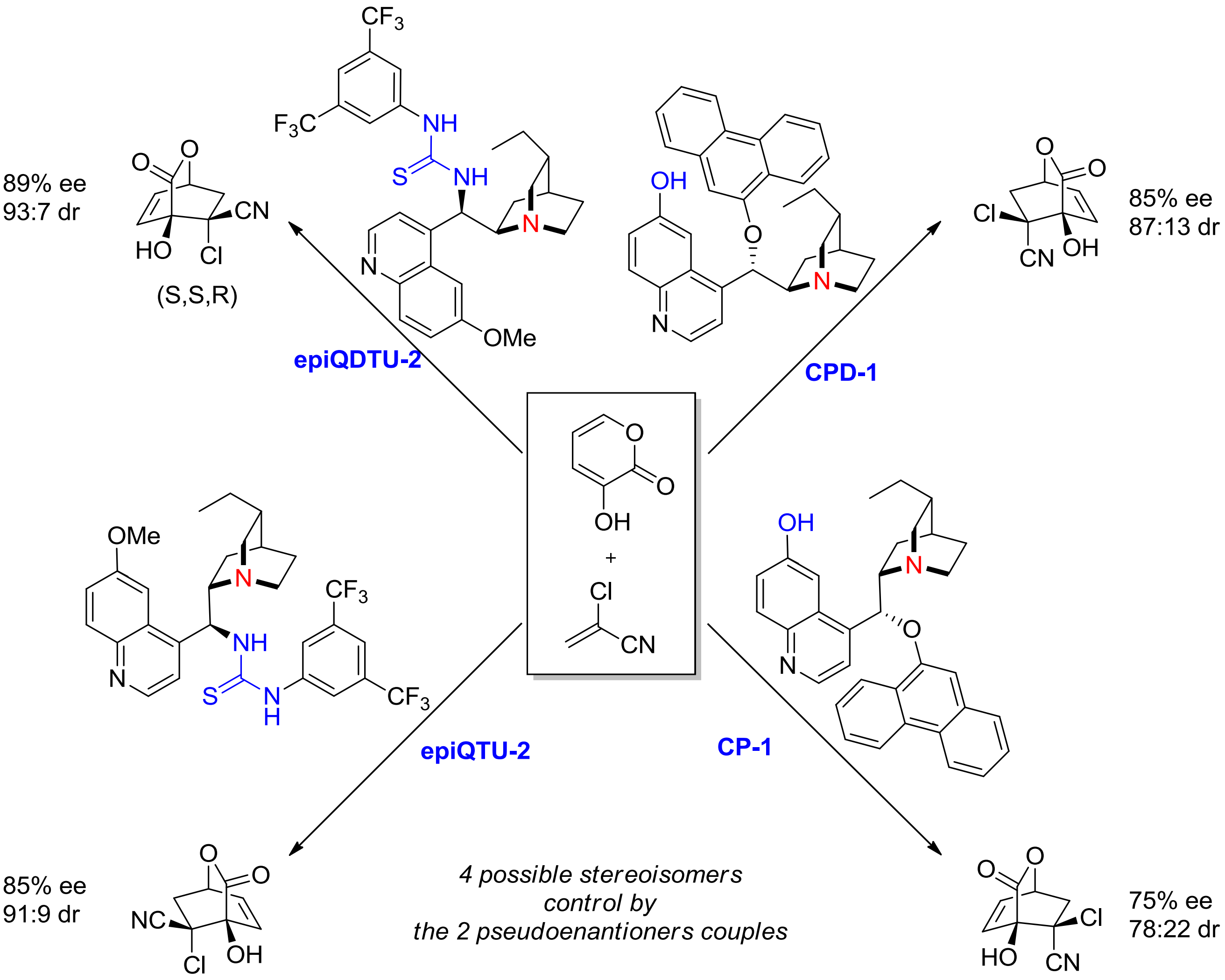
X = H (R.T.)
96-4 *exo:endo* ratio
91% ee
94% yield

X = CN (-20 °C)
93-7 *exo:endo* ratio
81% ee
97% yield

Ref.: Y. Wang, H. Li, Y. -Q. Wang, Y. Lui, B. M. Foxman, L. Deng *J. Am. Chem. Soc.* **2007**, *129*, 6364-6365

Other Potential Application

Asymmetric Diels–Alder Reactions



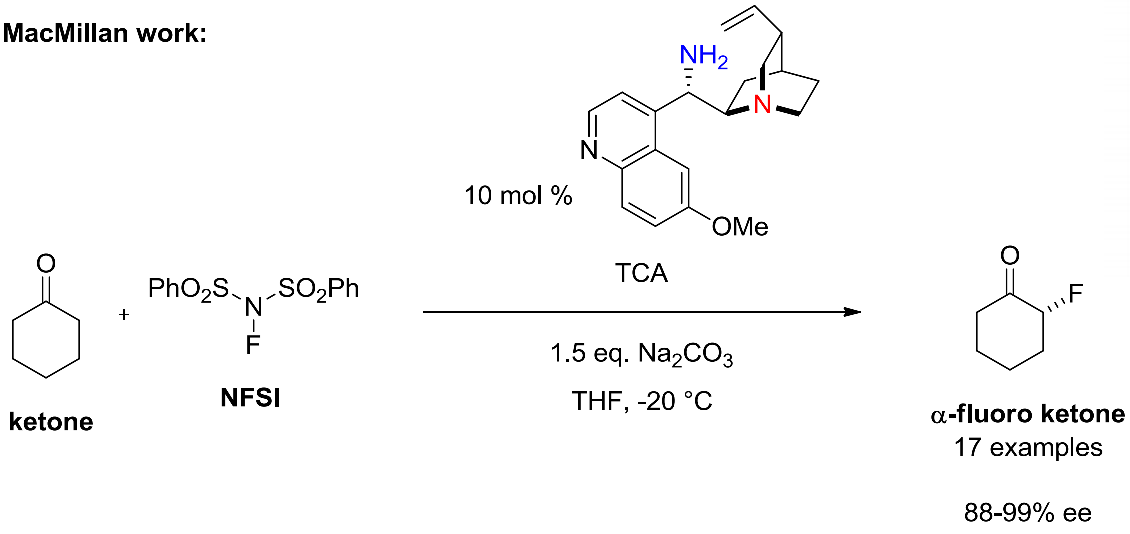
4 possible stereoisomers control by the 2 pseudoenantioners couples

<u>Ref.:</u> Y. Wang, H. Li, Y. -Q. Wang, Y. Lui, B. M. Foxman, L. Deng *J. Am. Chem. Soc.* **2007**, *129*, 6364-6365

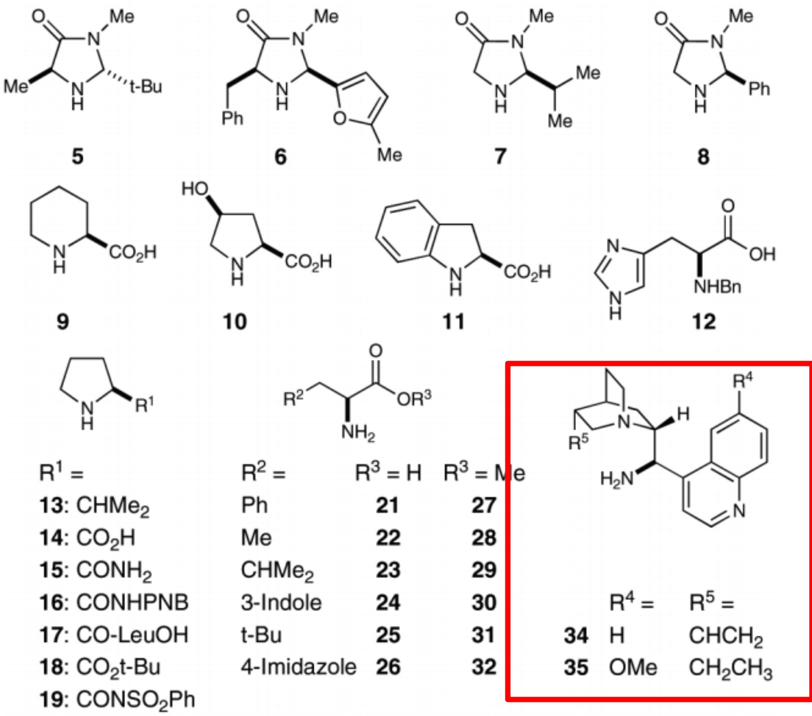
Other Potential Application

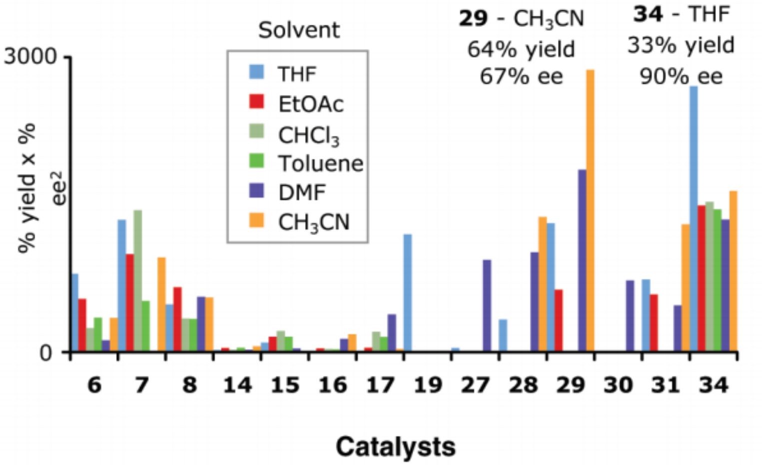
Enantioselective α-Fluorination of Cyclic Ketones

MacMillan work:



- First highly enantioselective fluoration using Organocatalysis
- Cinchona Alkaloids give the best result
- Enamine activation mode





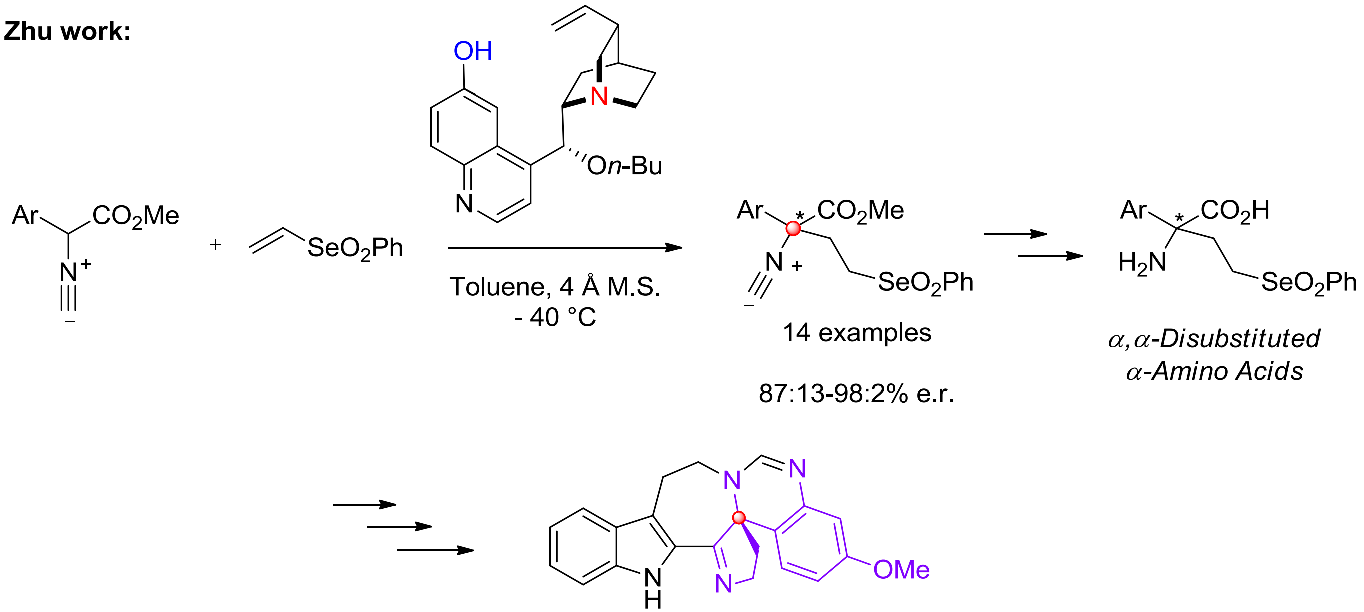
And **35 :** 88 % 99 % ee with THF and TCA (as co-solvant)

Ref: P. Kwiatkowski, T. D. Beeson, J. C. Conrad, D. W. C. MacMillan *J. Am. Chem. Soc.* **2011**, *133*, 1738–1741

Other Potential Application …Toward Total Synthesis

Enantioselective Michael Addition of α-Aryl-α-Isocyanoacetates to Vinyl Selenone

Zhu work:



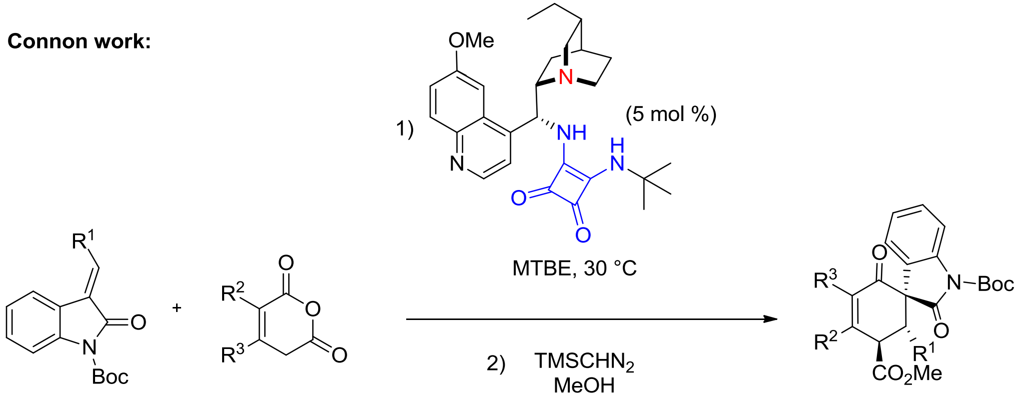
Total Synthesis of the
(+)-Trigonoliimine A (overall yield 7.5%)
and (-)-Trigonoliimine A (9 steps, overall yield 6.8%).

Ref: T. Buyck, Q. Wang, J. Zhu *Angew. Chem. Int. Ed.* **2013**, *52*, 12714 – 12718

Other Potential Application

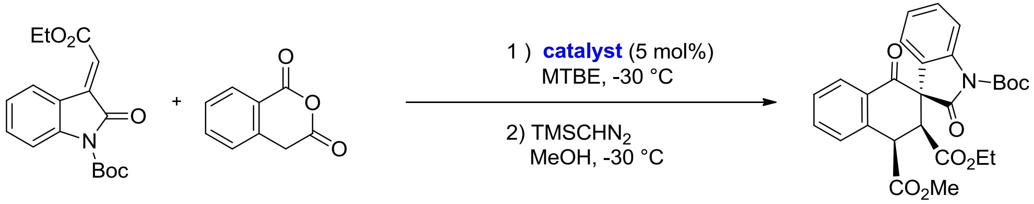
Asymmetric Tamura cycloadditions

Connon work:



10 examples

65-98% yield
89-99% ee



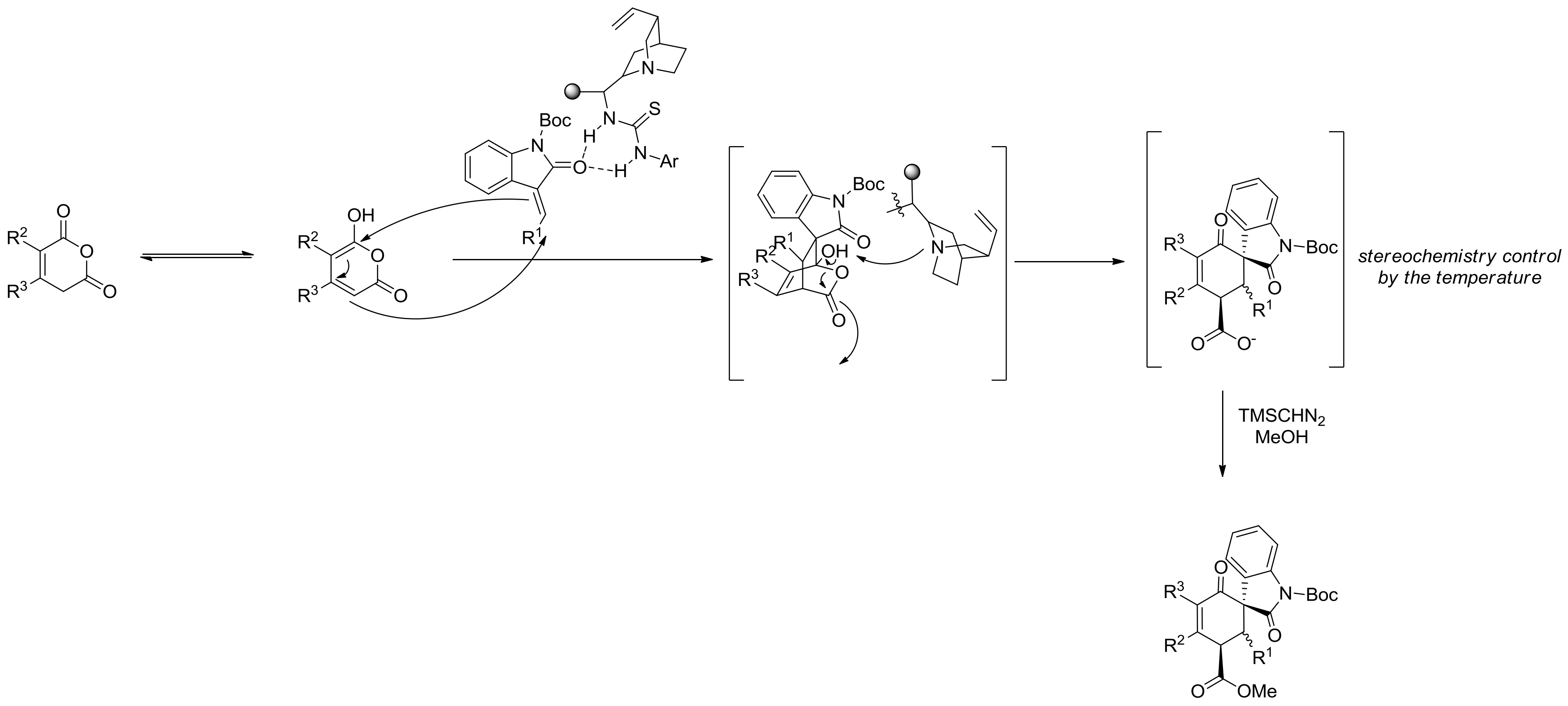
74% yield
98% ee

Syn diastereomer obtained at low temperature

Ref: F. Manoni, S. J. Connon *Angew. Chem. Int. Ed.* **2014**, *53*, 2628 –2632

Suggested Mechanism

Asymmetric Tamura cycloadditions



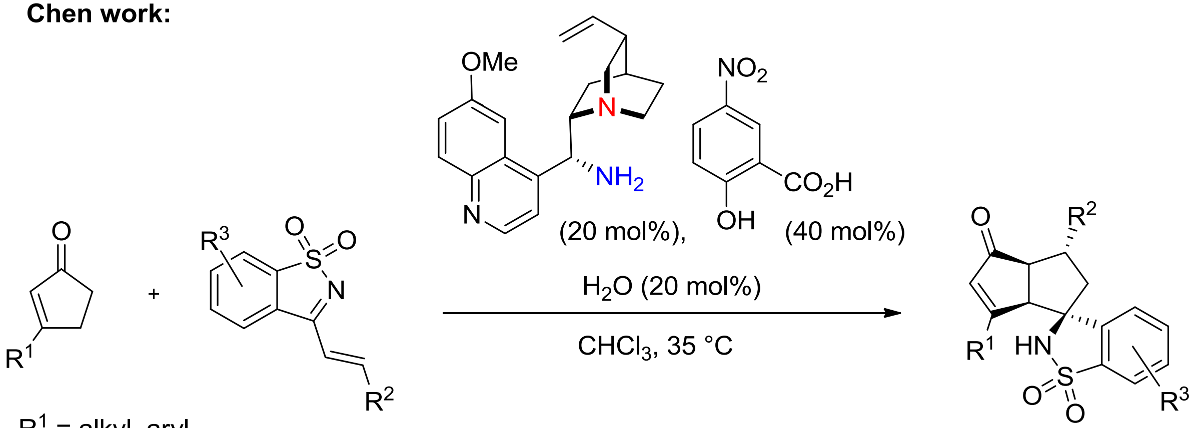
stereochemistry control by the temperature

Ref: X. Yin, Y. Zheng, X. Feng, K. Jiang, X. -Z. Wei, N. Gao, Y. –C. Chen *Angew. Chem. Int. Ed.* **2014**, *53*, asap

Other Potential Application

Asymmetric [5+3] formal cycloadditions of cyclic enones with 3-vinyl-1,2-benzoisothiazole-1,1-dioxides

Chen work:

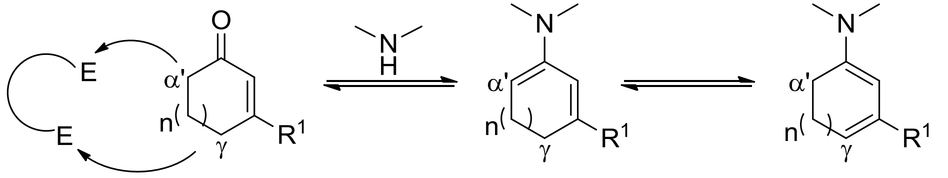


R^1 = alkyl, aryl
R^2 = aryl

24 examples

97-99% ee
63-99% yield

Cascade Dienamine-Dienamine activation mode



m carbons *5 carbons*

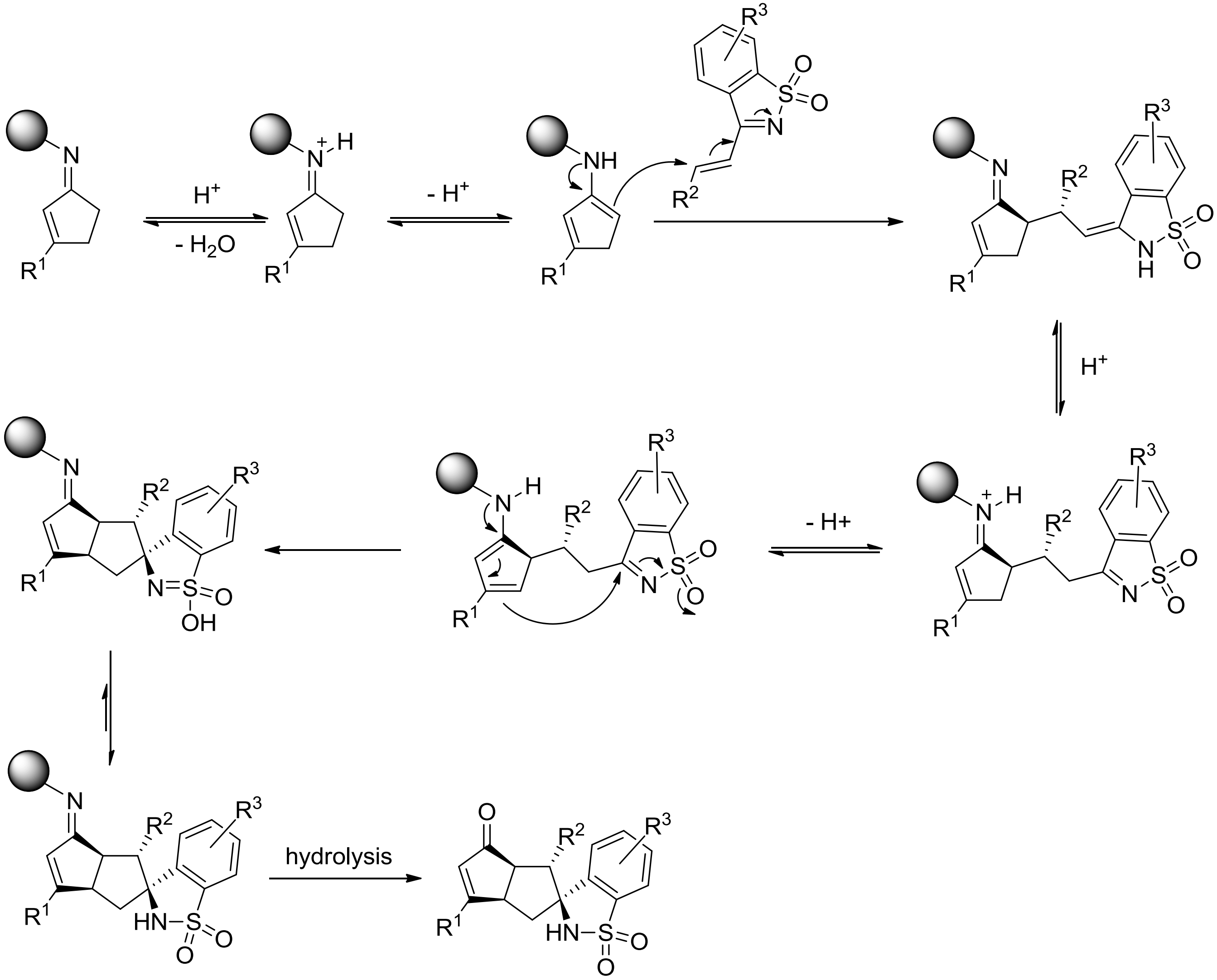
formal [5+m] cycloaddition

dienamine

endo-dienamine

Ref: X. Yin, Y. Zheng, X. Feng, K. Jiang, X. -Z. Wei, N. Gao, Y. –C. Chen *Angew. Chem. Int. Ed.* **2014**, *53*, asap

Suggested Mechanism

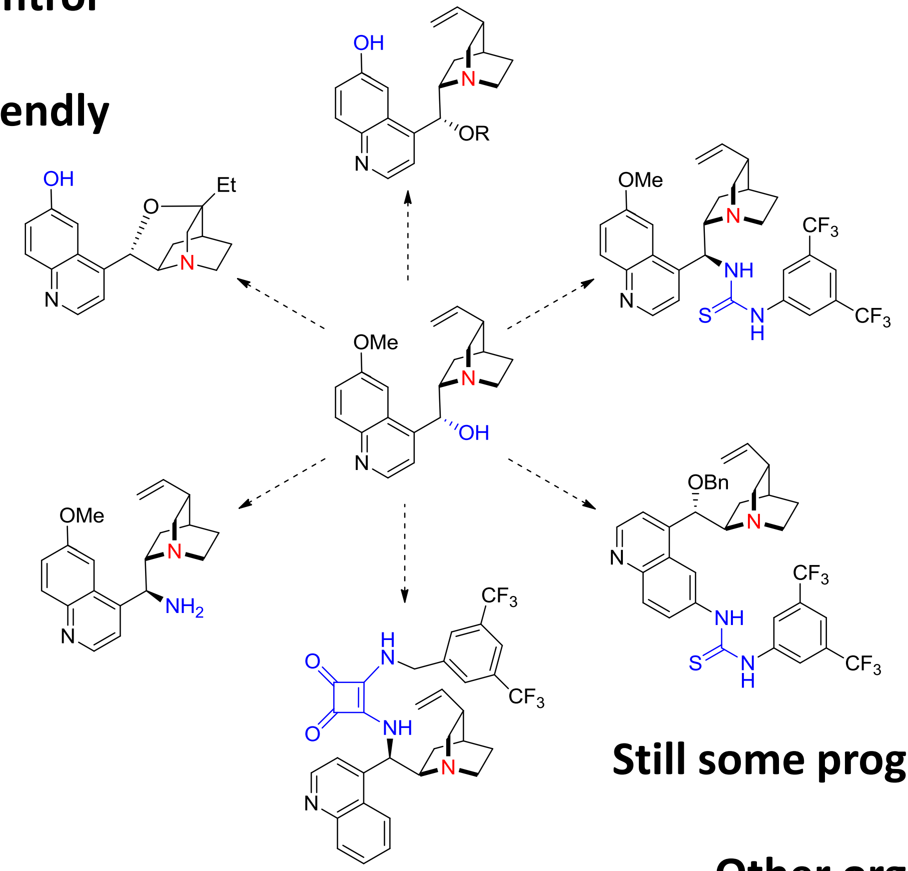


**The stereochemistry of this example is not explain in the paper*

Ref: X. Yin, Y. Zheng, X. Feng, K. Jiang, X. -Z. Wei, N. Gao, Y. –C. Chen *Angew. Chem. Int. Ed.* **2014**, *53*, asap

Conclusion

- Easily avalaible & tunable
- Various way of substrate activation
- Enantioselective control
- Catalytic process
- Environmentally friendly



Still some progress can be possible

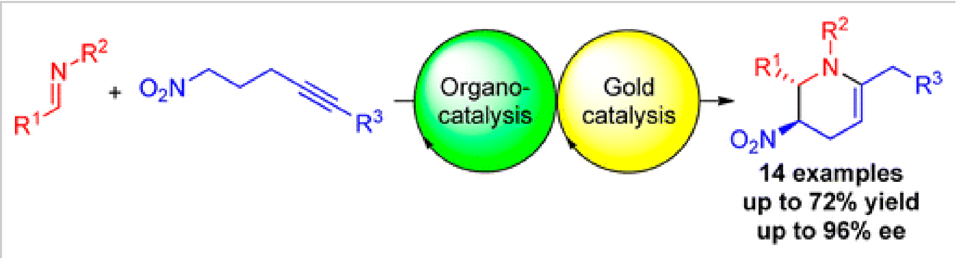
Other organocatalyts or
Metal-catalyst are competitive

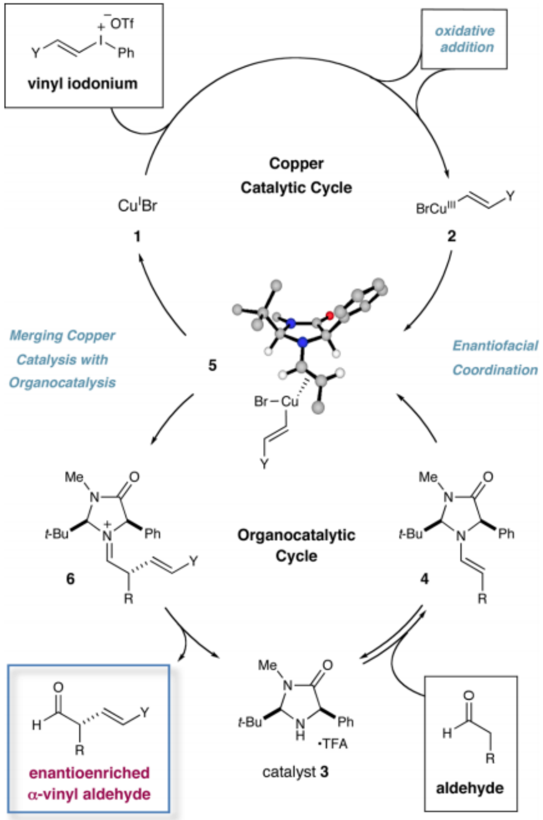
Thanks for your attention

Questions :

- What is a pseudo-enantiomer ?
- What could be the future or the other possibilities of this organocatalyst?

Combined Metal-Catalyzed and Organocatalysis





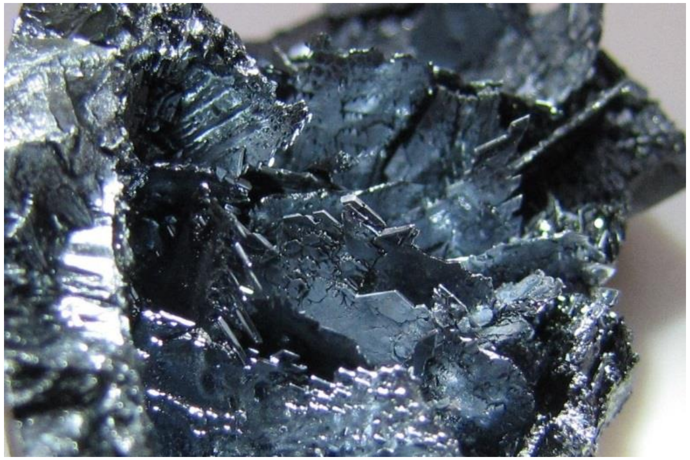
ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Iodonium ylides in organic synthesis

Frontiers in Chemical Synthesis Course, May, 2014

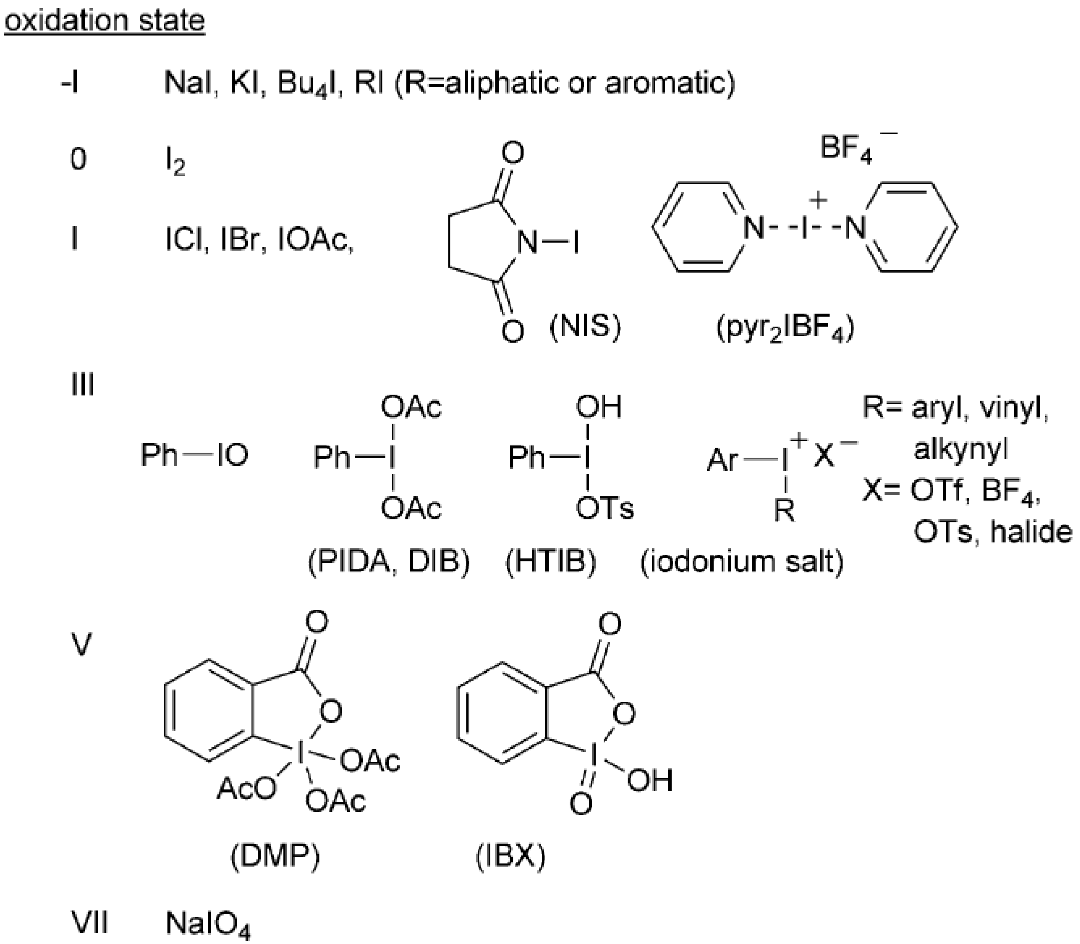
Fedor Zhurkin, LSCI

Introduction



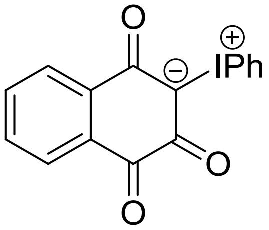
Applications of iodine and its compounds in organic synthesis:

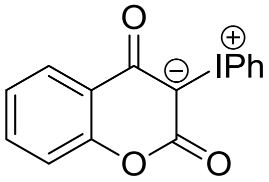
1. Iodinations
2. Oxidations
3. C-C bond formation

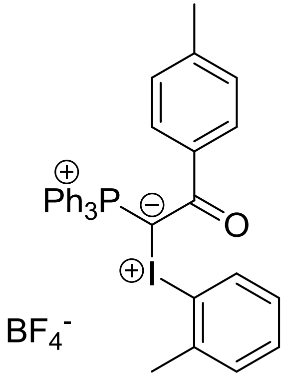


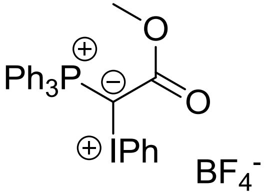
oxidation state	
-I	NaI, KI, Bu_4I, RI (R=aliphatic or aromatic)
0	I_2
I	ICl, IBr, IOAc, (NIS) (pyr_2IBF_4)
III	Ph—IO (PIDA, DIB) (HTIB) (iodonium salt) R= aryl, vinyl, alkynyl X= OTf, BF_4, OTs, halide
V	(DMP) (IBX)
VII	$NaIO_4$

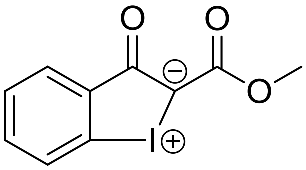
Iodonium ylides

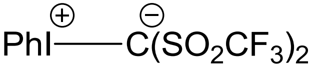




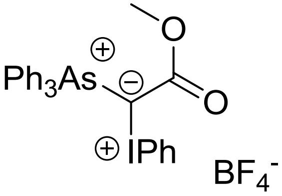








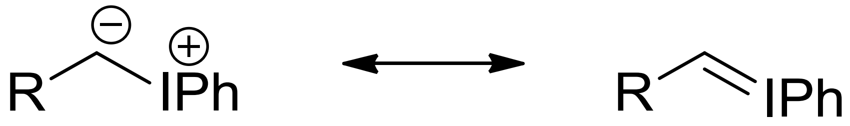
$\overset{+}{PhI}-\overset{-}{C}(SO_2CF_3)_2$



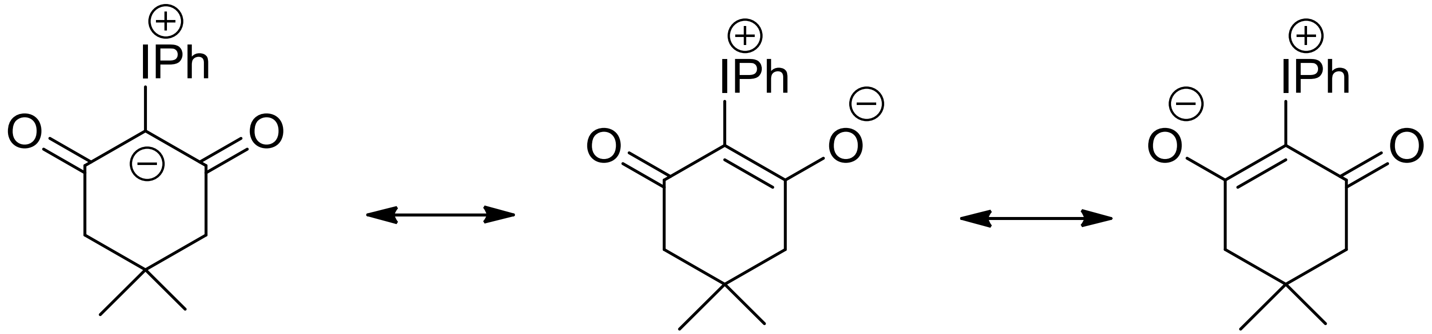
Ylides -
Compounds in which an anionic site Y^- …
is attached directly to a heteroatom X^+ …
carrying a formal positive charge.

IUPAC. Compendium of Chemical Terminology, 2nd ed. (the "Gold Book").

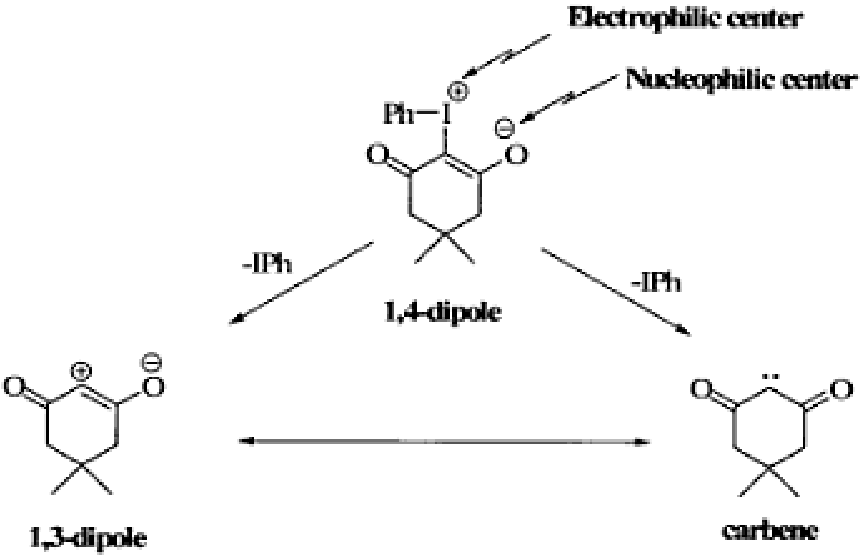
Iodonium ylides structure



Ylide-ylene resonance



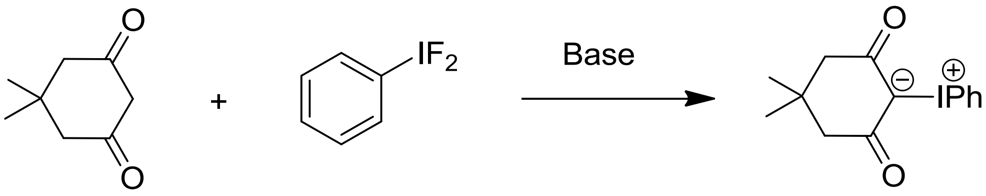
Iodonium ylides reactivity



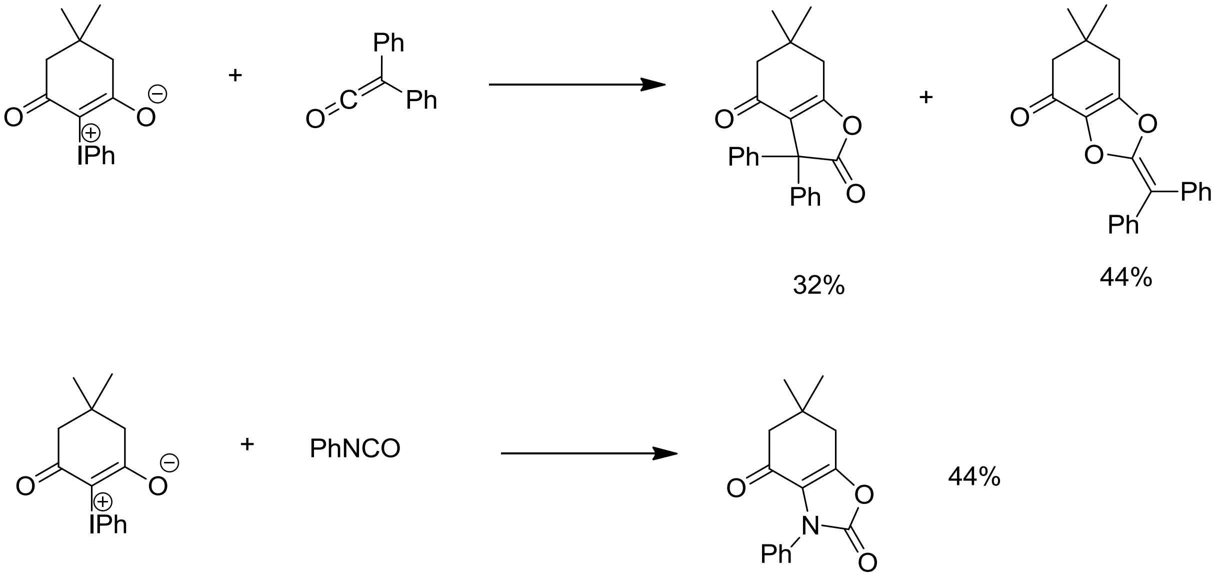
1. Cycloaddition
2. Carbene insertion
3. Cyclopropanation

Pioneering works

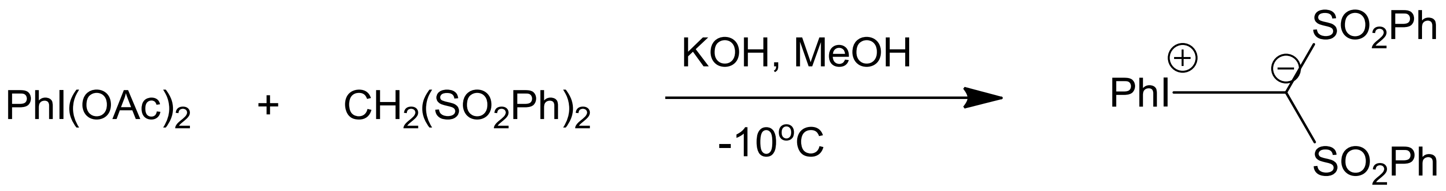
Neiland et al., 1957:

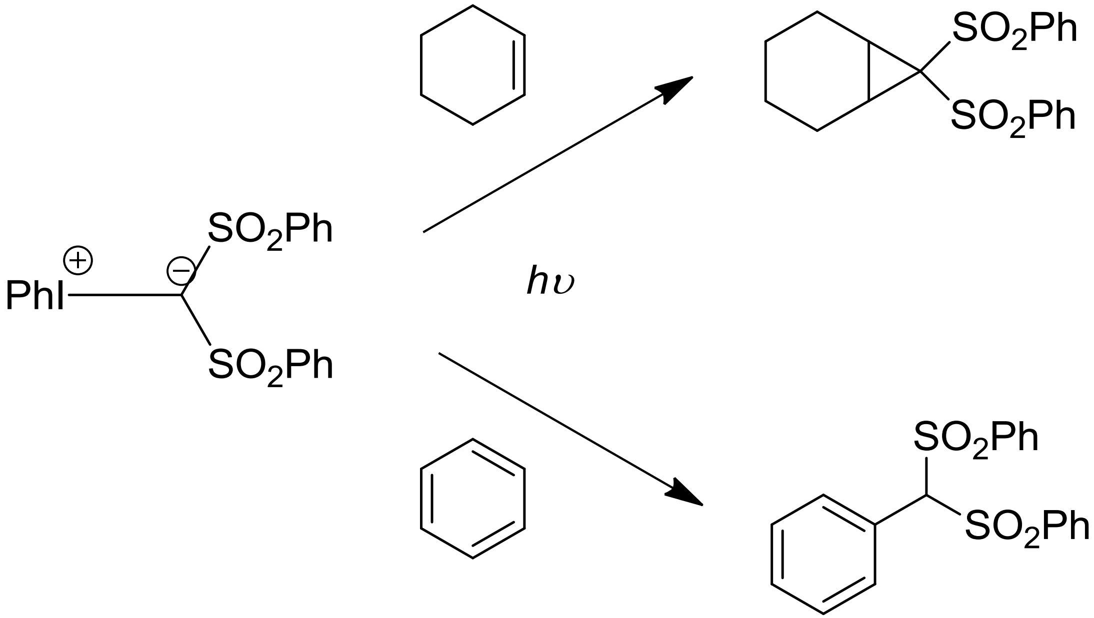


Koser, Yu, 1975:



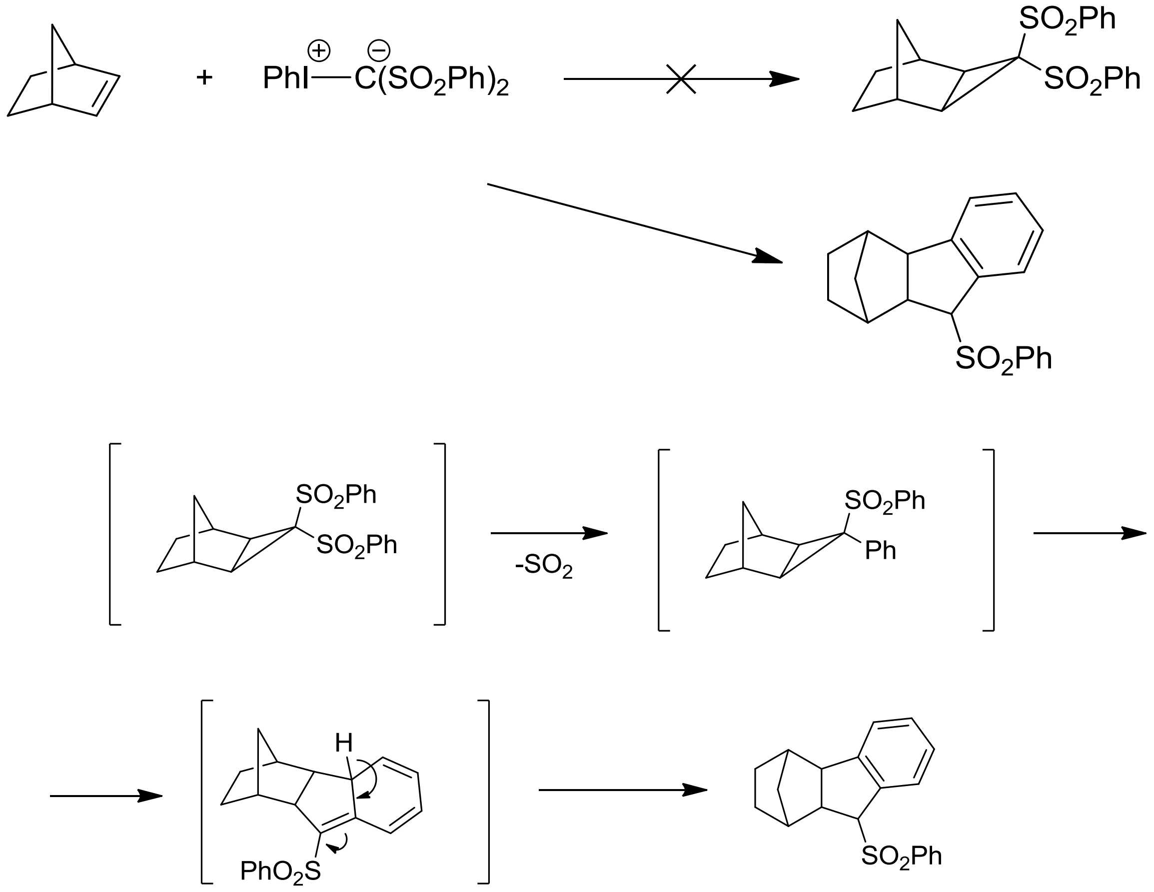
Bis(phenylsulfonyl)methane ylides





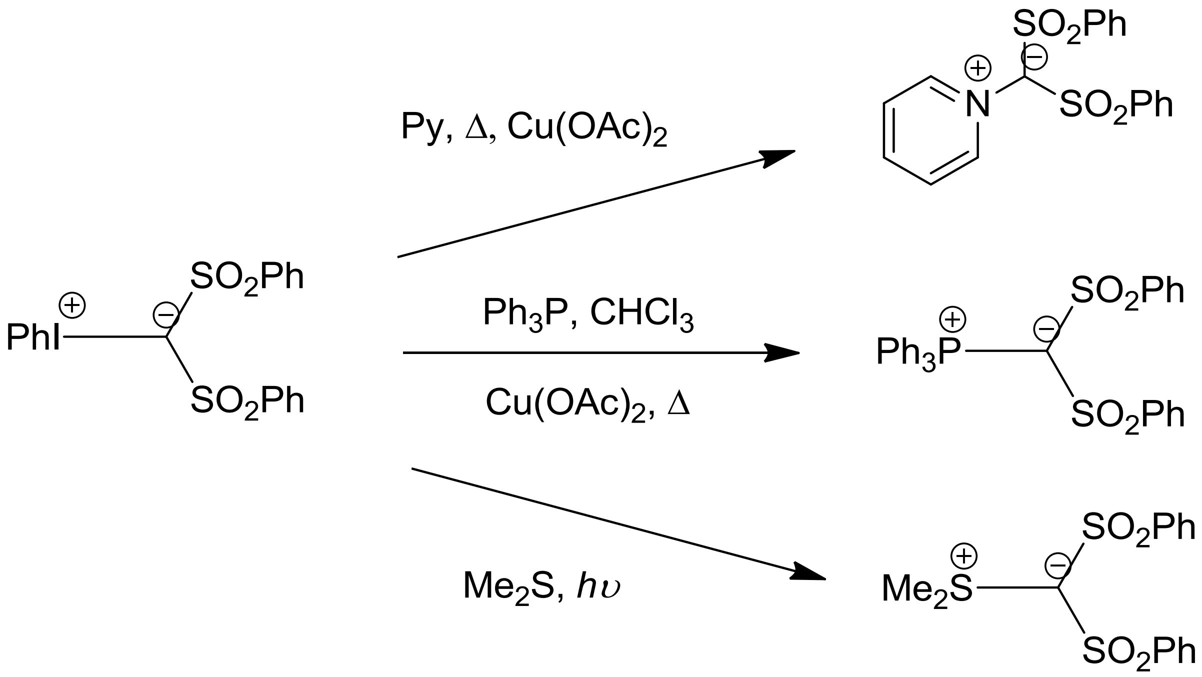
Hadjiarapoglou L., et al. *JACS*, **1985**, 7178

Bis(diphenylsulfonyl)cyclopropanes



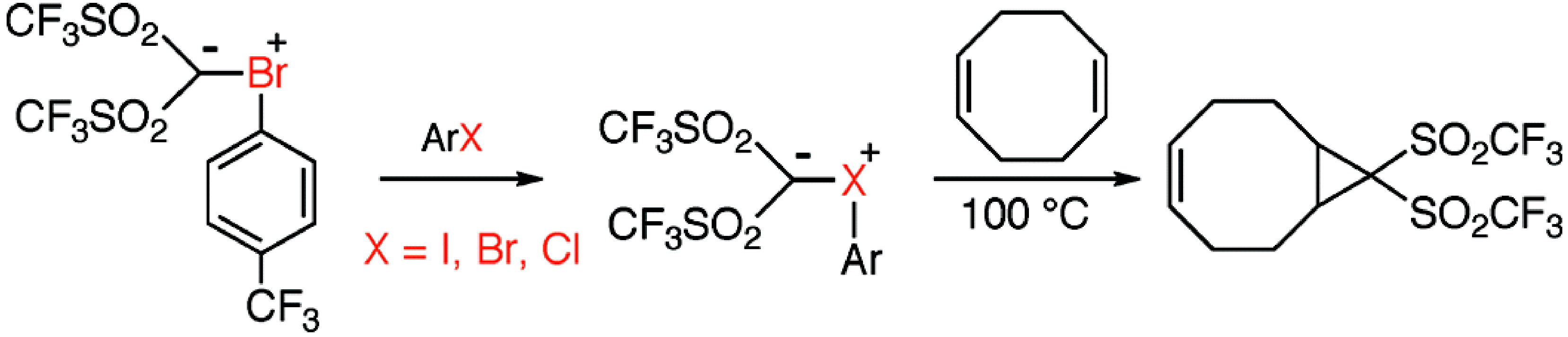
Hadjiarapoglou L., et al. *J. Chem. Soc. Perkin Trans. 1*, **1988**, 2839

Transylidation with S-, N-, and P-nucleophiles



Hadjiarapoglou L., et al. *JACS*, **1985**, 7178

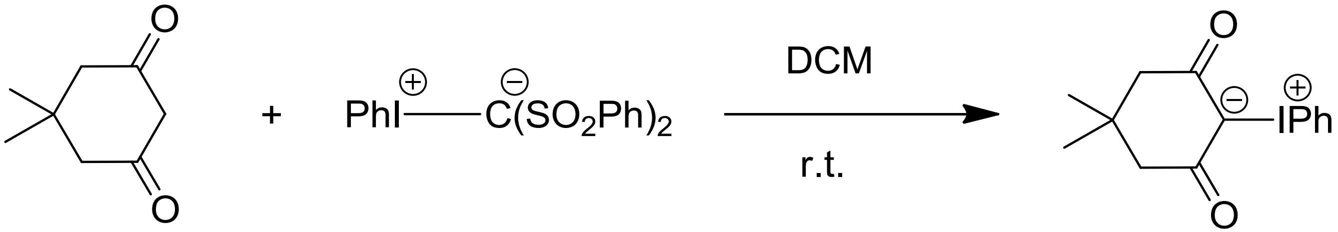
Transylidation of other halonium ylides



For iodobenzene:
160^{o}C, 1h without catalyst
40^{o}C, 5h with $Rh_2(OAc)_4$

Ochiai M., et al. *JACS*, **2008**, 2118

Transylidation between iodonium ylides

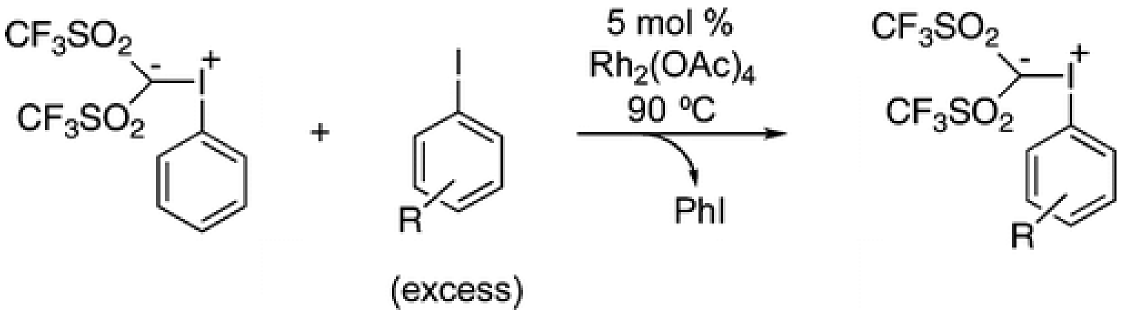


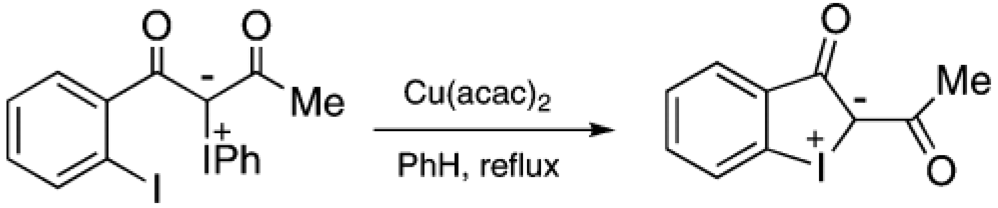
pKa = 5

pKa around 4

Hadjiarapoglou L., et al. *JACS*, **1985**, 7178

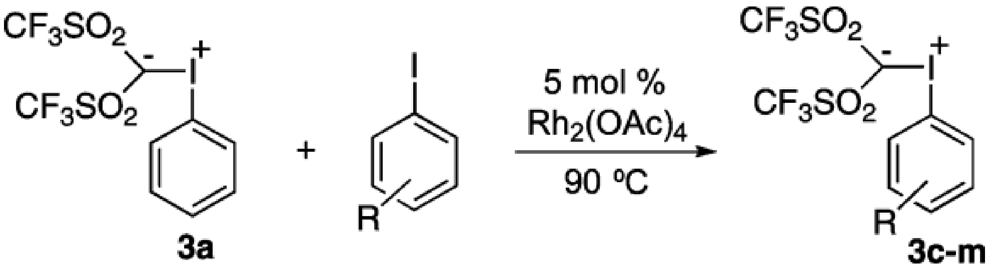
Transylidation between iodonium ylides





Ochiai M., et al. *Org. Lett.*, **2008**, 1425

Evaluating iodonium ylides relative stability



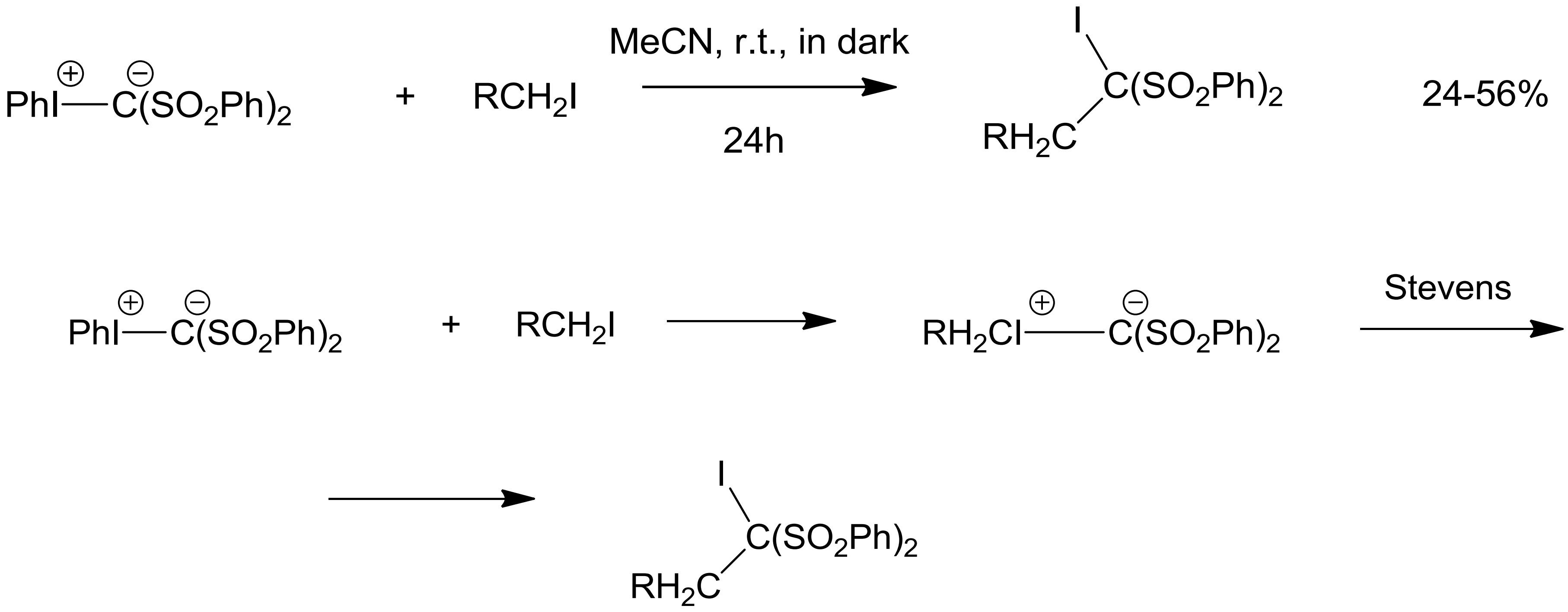
3a

3c-m

entry	iodoarene	t (h)	**3** yield (%)[b]
1	p-$MeOC_6H_4I$	5	**3c** 84
2	o-MeC_6H_4I	5	**3d** 92
3	m-MeC_6H_4I	5	**3e** 92
4	3,5-$Me_2C_6H_3I$	5	**3f** 82
5	p-FC_6H_4I	5	**3g** 89
6	p-ClC_6H_4I	7	**3h** 78
7	p-BrC_6H_4I	10	**3i** 77
8	p-$CF_3C_6H_4I$	24	**3j** 77
9	p-$NO_2C_6H_4I$[c]	24	**3k** 38[d]
10	C_6F_5I	24	**3l** –[d]
11	$CF_3(CF_2)_2CH_2I$	24	**3m** –

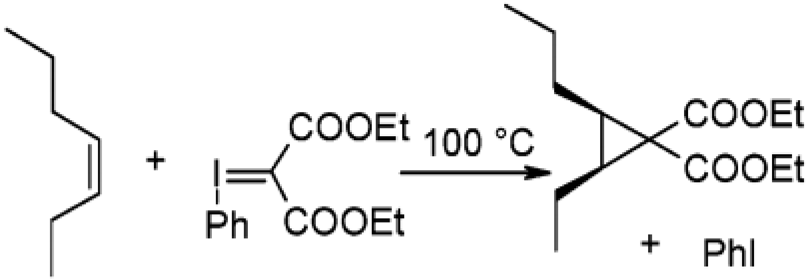
Ochiai M., et al. *Org. Lett.*, **2008**, 1425

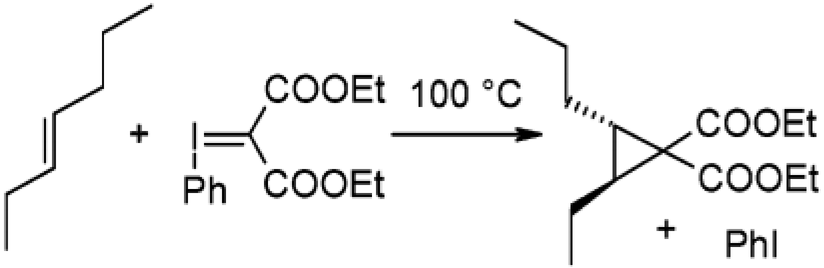
Reactions with alkyl iodides



Gogonas E.P., et al. *Synlett*, **2004**, 2563

Carbene (-oid) formation

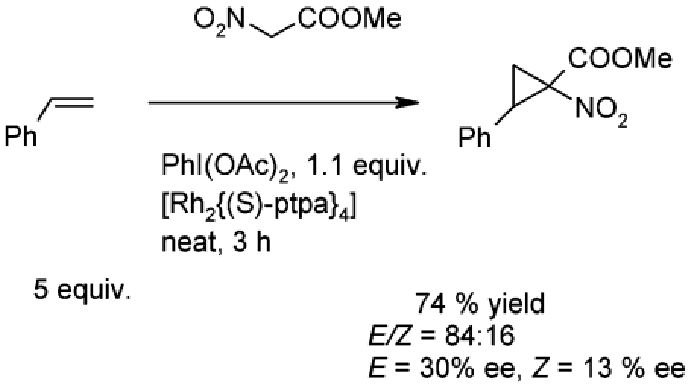


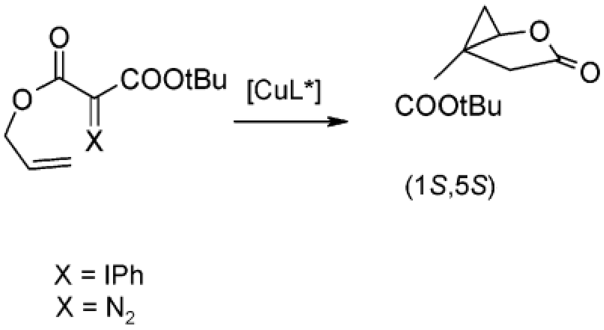


Muller P. *Acc. Chem. Res.*, **2004**, 243

Carbene (-oid) formation

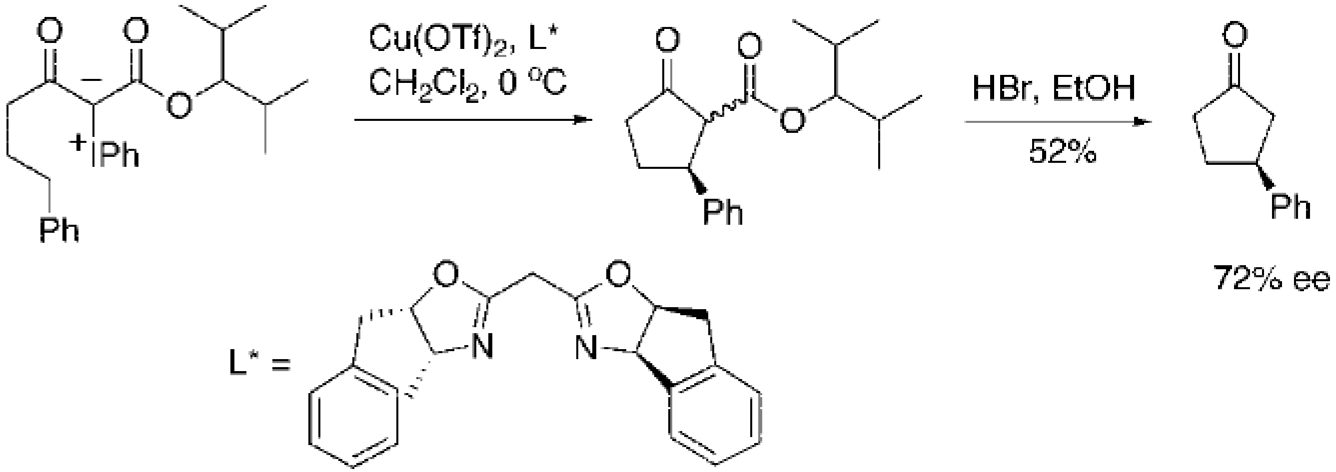
Can be Cu or Rh-catalysed:





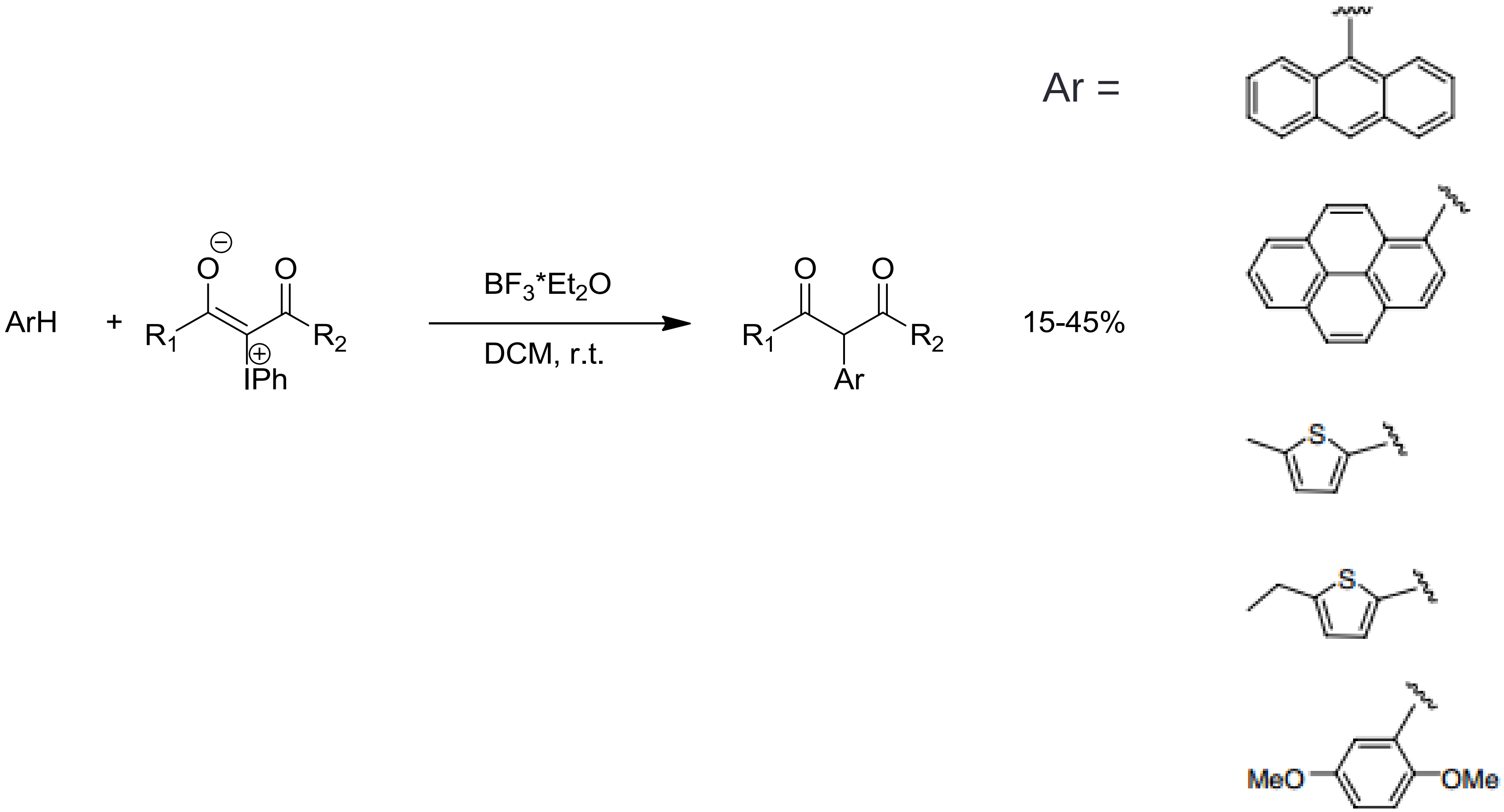
Muller P. *Acc. Chem. Res.*, **2004**, 243

Stereoselective C-H insertion



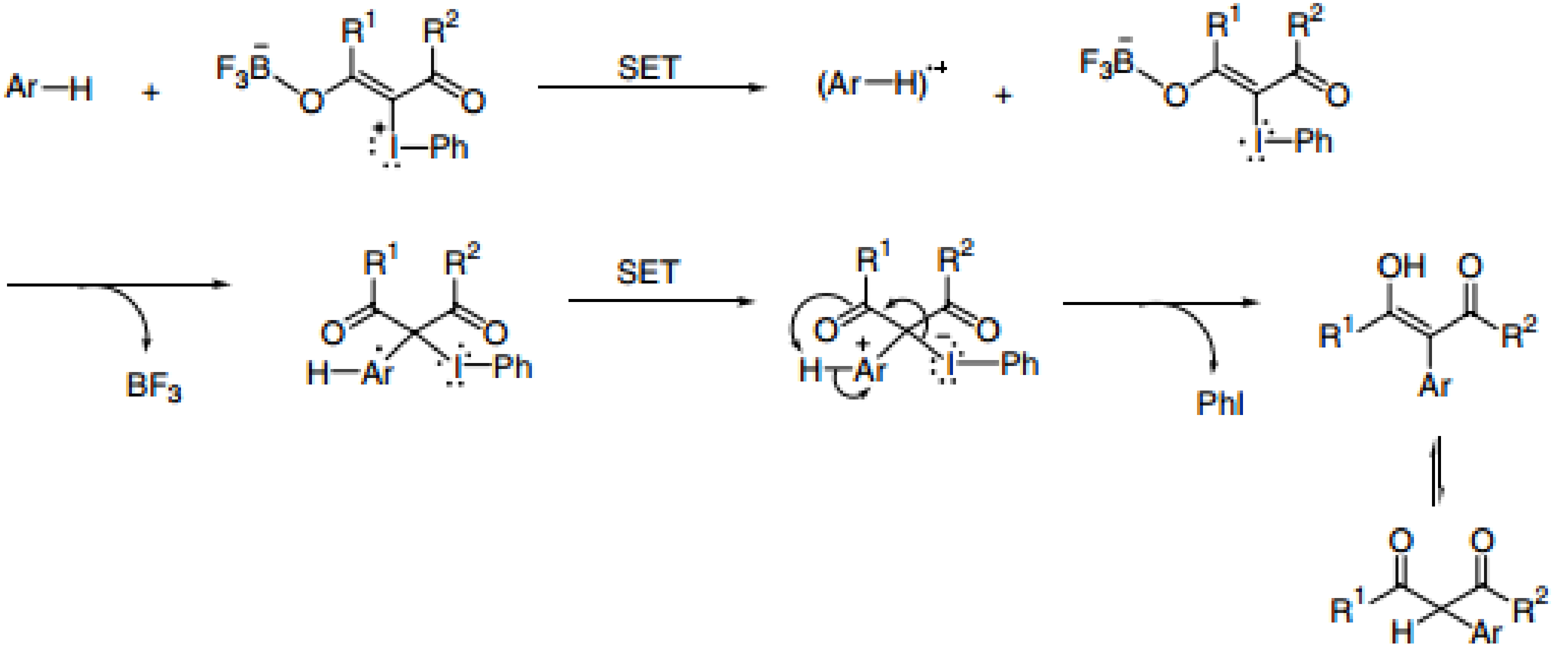
Muller P. et al. *Helv. Chim. Acta*, **2002**, 483

C-H bond insertion



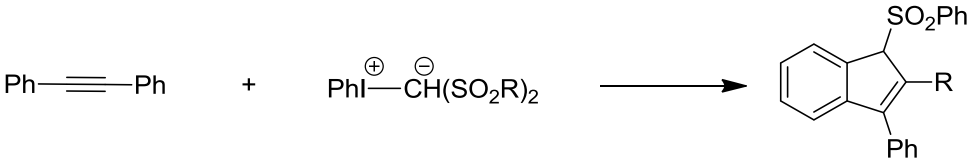
Telu S., et al. *Tetrahedron Lett.*, **2007**, 1863

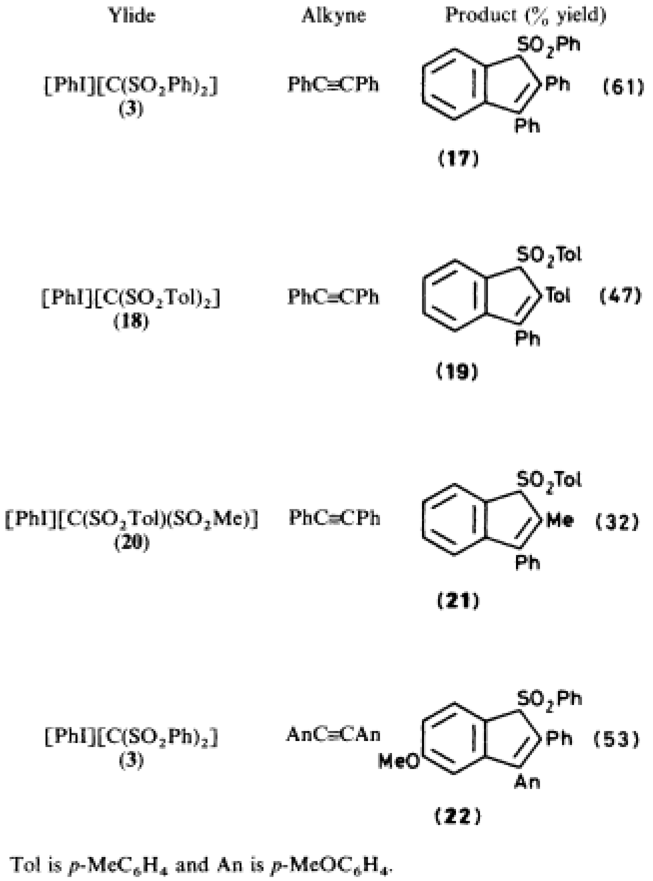
C-H bond insertion



Telu S., et al. *Tetrahedron Lett.*, **2007**, 1863

Reactions with alkynes



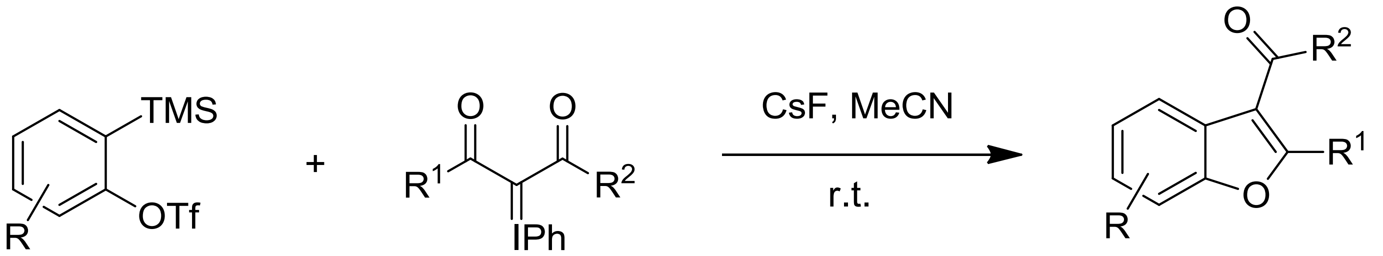


Ylide	Alkyne	Product (% yield)
[PhI][C(SO$_2$Ph)$_2$] (3)	PhC≡CPh	(17) (61)
[PhI][C(SO$_2$Tol)$_2$] (18)	PhC≡CPh	(19) (47)
[PhI][C(SO$_2$Tol)(SO$_2$Me)] (20)	PhC≡CPh	(21) (32)
[PhI][C(SO$_2$Ph)$_2$] (3)	AnC≡CAn	(22) (53)

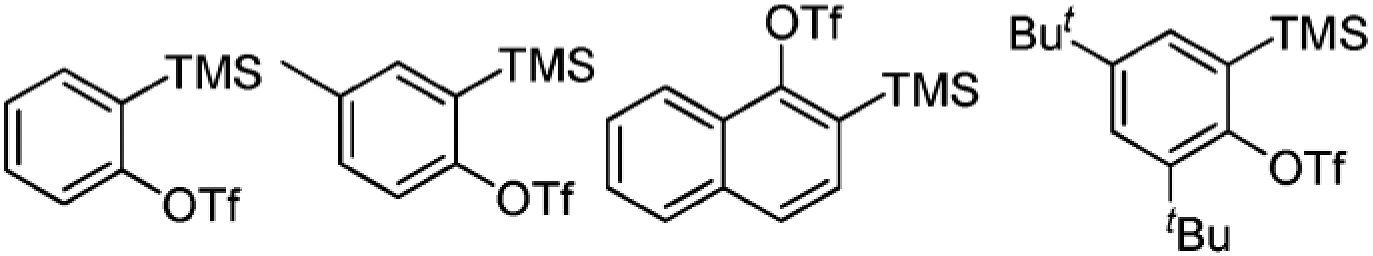
Tol is *p*-MeC$_6$H$_4$ and An is *p*-MeOC$_6$H$_4$.

Hadjiarapoglou L., et al. *J. Chem. Soc. Perkin Trans. 1*, **1988**, 2839

Cycloaddition of arynes with iodonium ylides

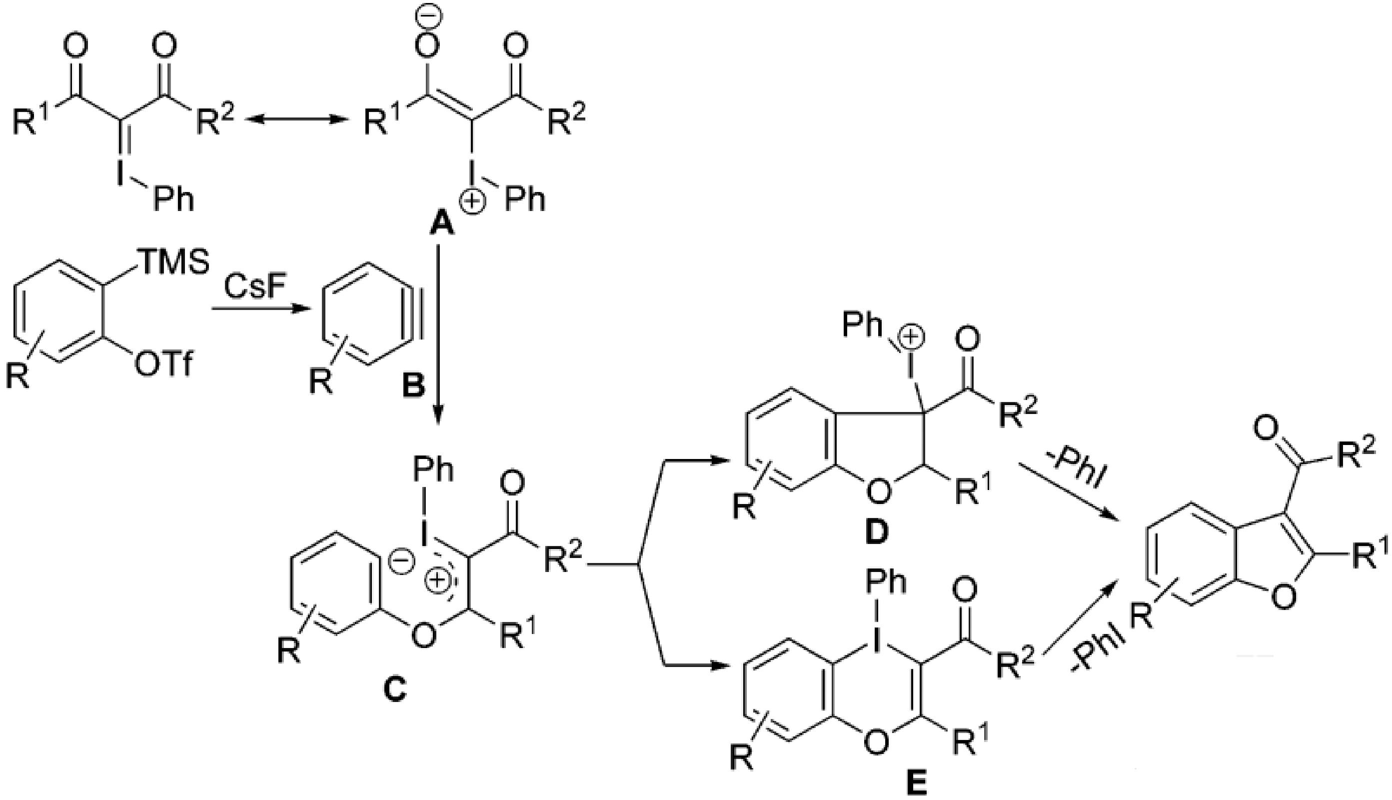


25-91%



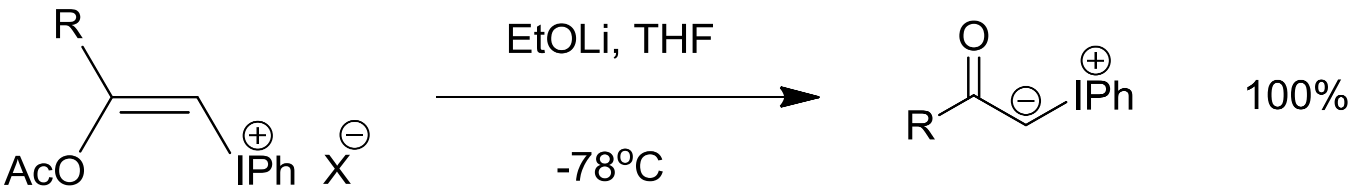
Huang X.-C. et al. *Org. Lett.*, **2008**, 1525

Cycloaddition of arynes with iodonium ylides

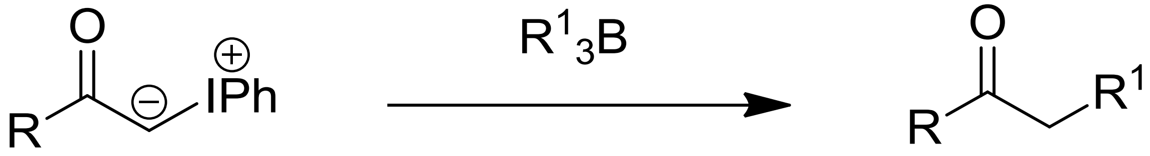


Huang X.-C. et al. *Org. Lett.*, **2008**, 1525

Carboxymethyliodonium ylides

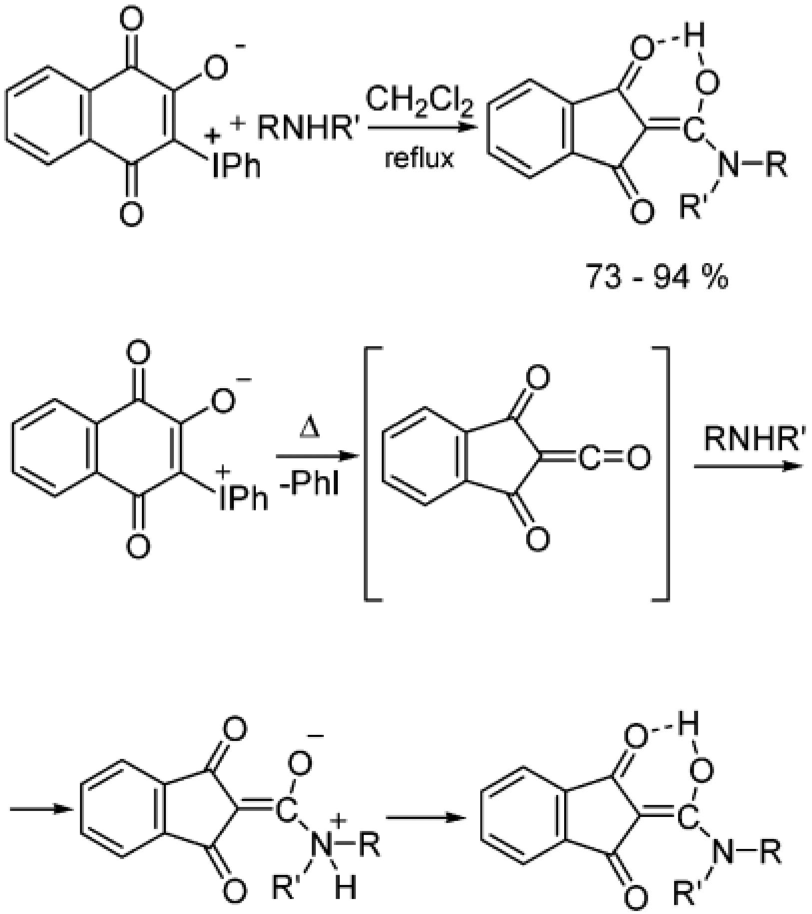


Stable up to -30°C



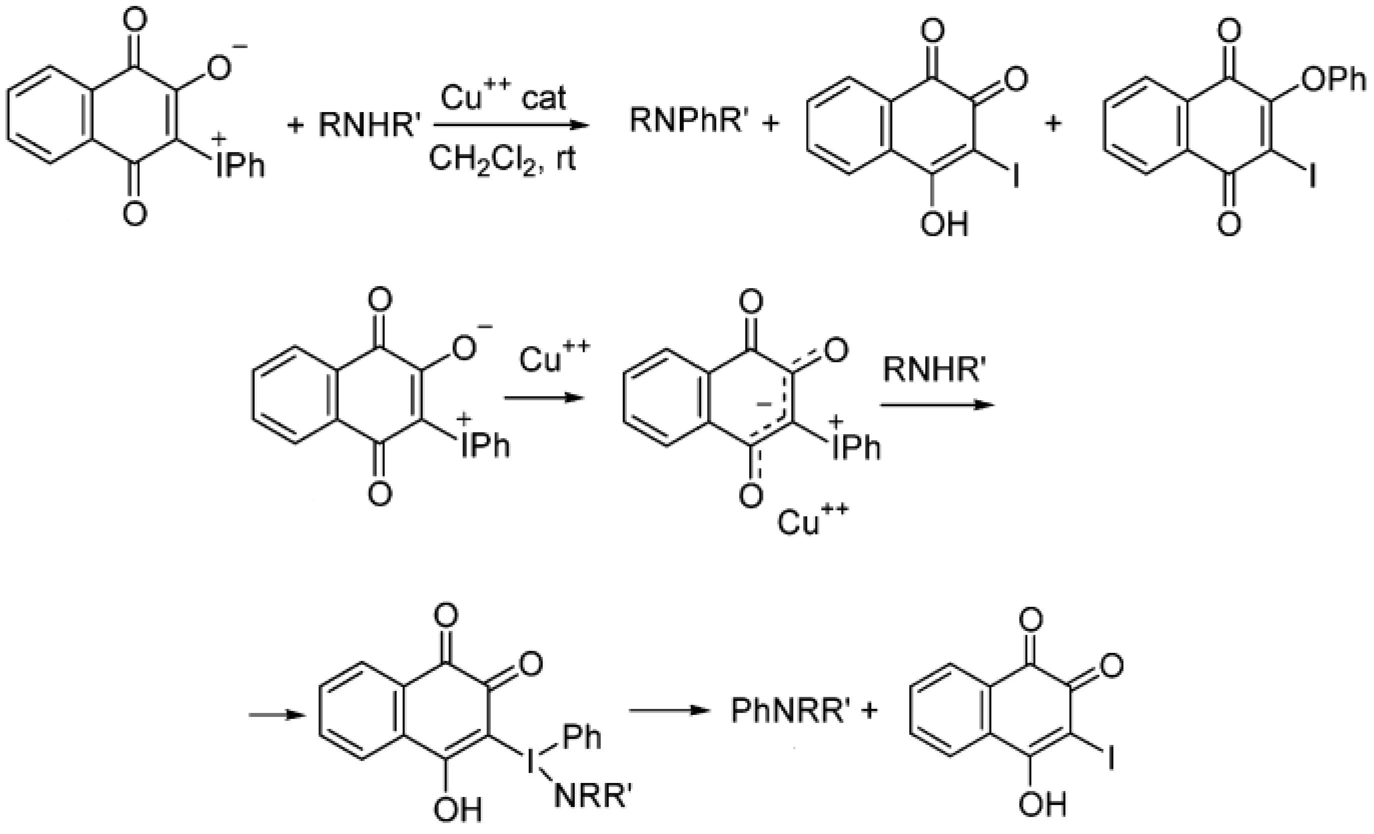
Ochiai M. et al. *Org. Lett.*, **2004**, 1505

Ylides of 2-hydroxy-1,4-naphthoquinone



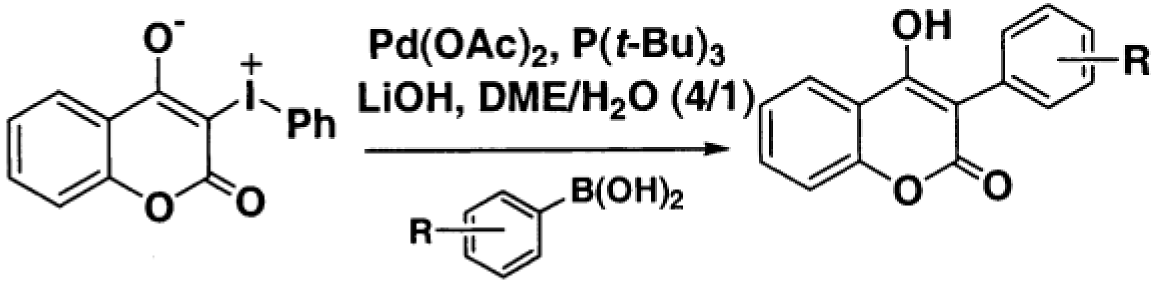
Malamidou-Xenikaki E. et al. *J. Org. Chem.*, **2003**, 5625

Ylides of 2-hydroxy-1,4-naphthoquinone



Malamidou-Xenikaki E. et al. *J. Org. Chem.*, **2003**, 5625

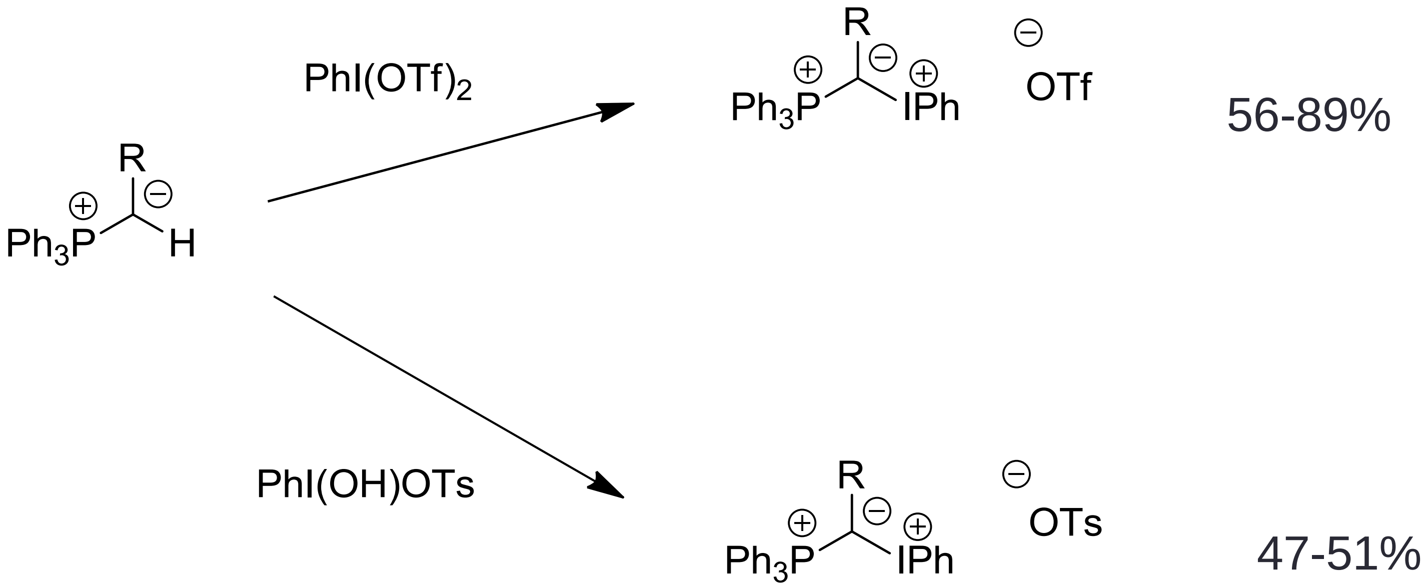
Phenyliodonium ylides in Suzuki-type reaction



46-92%

Zhu Q. et al. *Org. Lett.*, **2002**, 3333

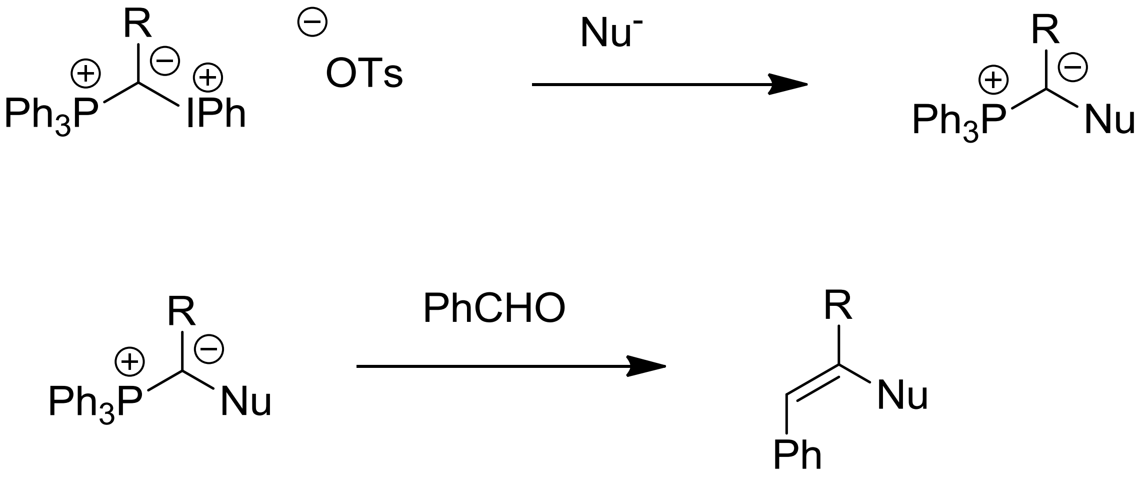
Mixed phosphonium-iodonium ylides



R=C(O)Me, CO$_2$Me, CN, CHO

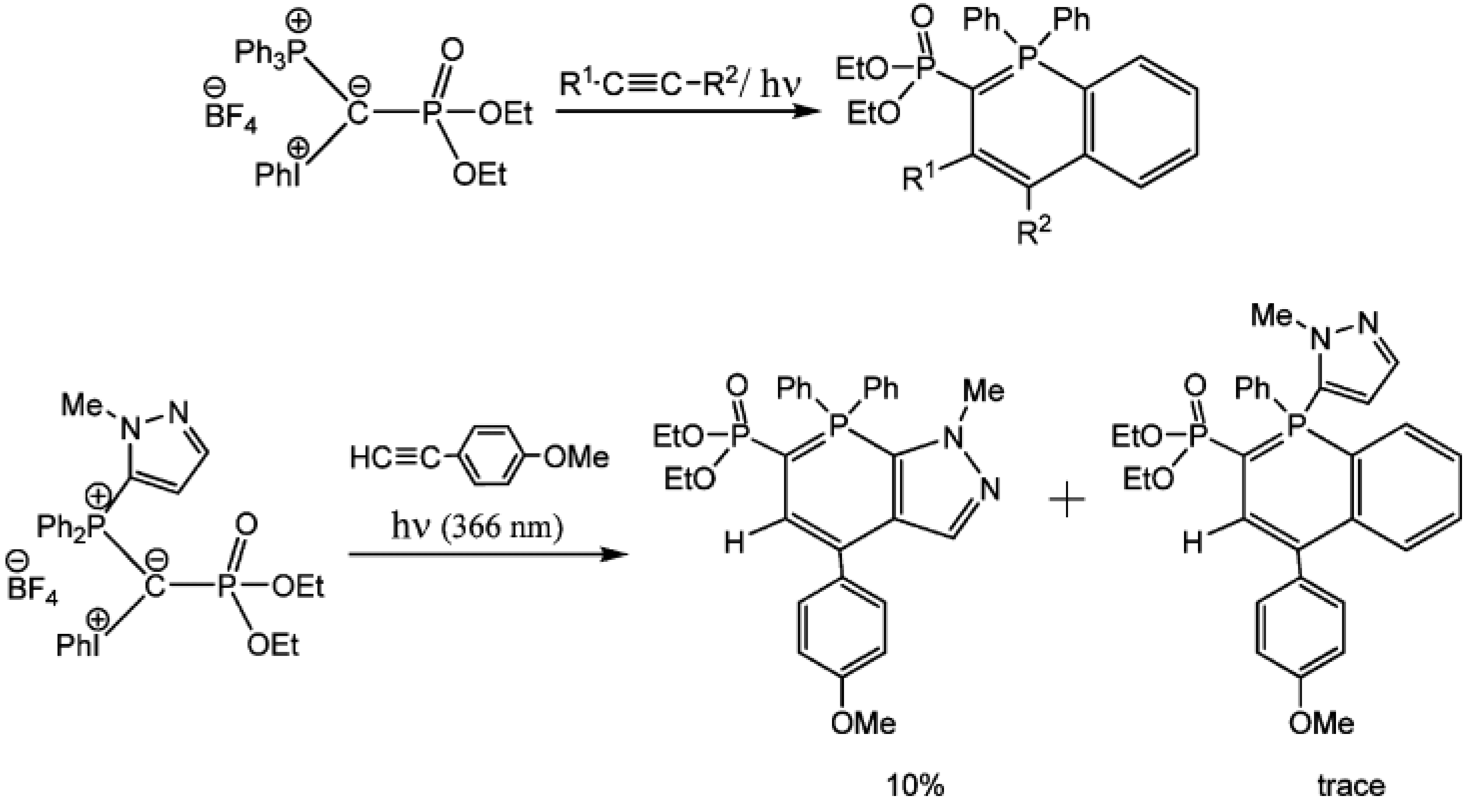
Zhdankin V. V. et al. *J. Org. Chem.*, **2003**, 1018

Mixed phosphonium-iodonium ylides



Zhdankin V. V. et al. *J. Org. Chem.*, **2003**, 1018

Mixed phosphonium-iodonium ylides



Matveeva E.D. et al. *J. Org. Chem.*, **2013**, 11691

Conclusion and future development

1. Non-toxic and safe-to-handle iodonium ylides can be prepared from a wide variety of activated substrates

2. Strong leaving ability of aryliodonium group as well as dipolar character of ylide molecule determine interesting reactivity of iodonium ylides

Future:

1. New reagents (mixed ylides), new reactivity
2. Transition metal-catalysed reactions

Thank you for your attention

Questions for the public

1. What are preparation methods for iodonium ylides?

2. What reactivity do iodonium ylides exhibit?