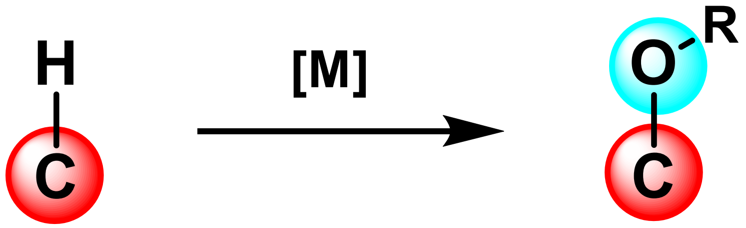
Frontiers in Chemical Synthesis I
Towards Sustainable Chemistry

Seminar Program
June 1, BCH 4310
June 2, BCH 5310

	Speaker	**Title**
	June 1, 2017, BCH 4310	
	Session I: (Philipp Greenwood)	
13h00-14h00	Coralie Duchemin	*Transition metal catalyzed oxidative C-H functionalization strategy for C-O bond formation*
14h00-15h00	Philipp Seeberger	*Advances in Ag(I)-catalyzed C-H bond functionalization*
15h00-16h00	Abdusalom Suleymanov	*Recent Advances in Non-activated C(Sp3)-H Bond Functionalization*
16h00-17h00	Marko Stojanovic	*C-H Activation as an Alternative Tool for the Synthesis of Organic Electronic and Photonic Materials*
17h00-18h00	Mao Runze	*Joining Photoredox and Transition-Metal Catalysis*
	June2, 2017, BCH 5310	
	Session II: (Coralie Duchemin)	
9h00-10h00	Yun Suk Jang	*Recent Developments in Asymmetric Cooperative Catalysis of Transition Metals and Chiral Bronsted Acids*
10h00-11h00	Marion Garreau	*Radical Reactions in Water*
11h00-12h00	Budai Balazs	*Recent Progress on the Use of Bismuth in Organic Synthesis*
	Session III: (Marko Stojanovic)	
15h00-16h00	Phillip Greenwood	*Recent Progress for the Incorporation of Carbon Dioxide into Organic Molecules via Transition Metal Catalysis*
16h00-17h00	Fink Cornel	*Catalytic Reduction of Carbon Dioxide*

Transition metal catalyzed oxidative C-H functionalization strategy for C-O bond formation



Coralie Duchemin

Questions

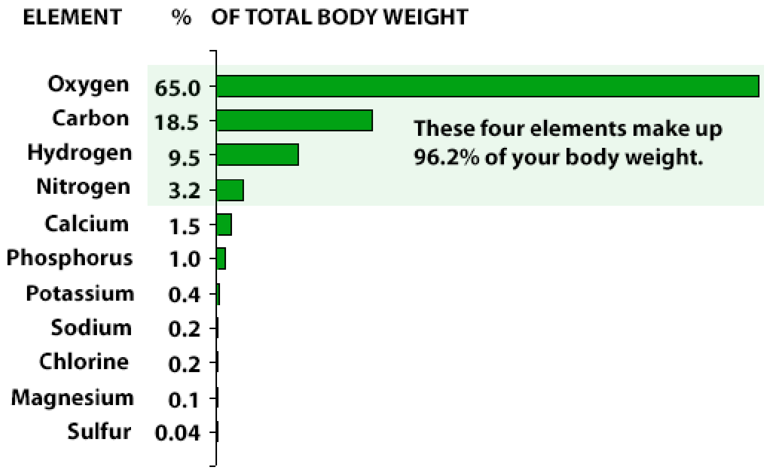
1. Enonce one method to avoid the use of stoechiometric amount of oxidant in oxidative Pd^{II} catalyzed oxygenation

2. Why is alkoxylation more challenging than acetoxylation ?

Intro

- Aside from nitrogen, oxygen is the most abondant heteroatom in man-made organic products

- Pharmaceuticals, agrochemicals, polymers



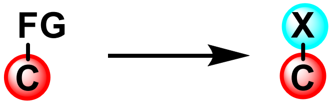
- Transformation of feedstock alkanes

- Formation of oxygen-carbon bonds is one of the most fondamental transformation in organic synthesis

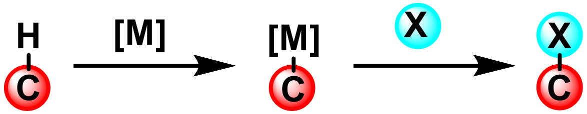
Intro

What ?

“The selective transformation of ubiquitous but inert C–H bonds to other functional groups”



Fonctional group transformation



C-H activation

Why ?

elegant, atom- and step-economic solution

Improve retrosynthetic analysis

How ?

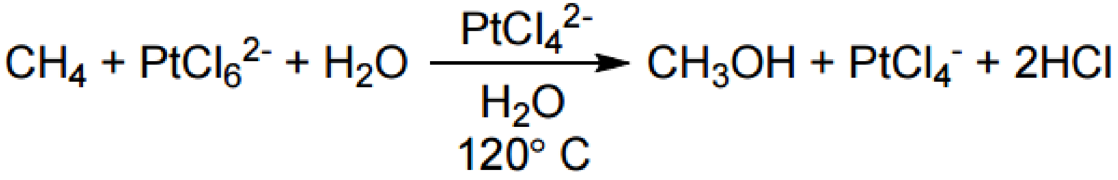
Selectivity

Group functionalities tolerance

Pioneering work

Pioneering work in oxygenation of methane and benzene

- Shilov process 1970’s



$$CH_4 + PtCl_6^{2-} + H_2O \xrightarrow[H_2O \\ 120° C]{PtCl_4^{2-}} CH_3OH + PtCl_4^{-} + 2HCl$$

- Selective to primary alkane

Shilov *Chem. Rev.* **1997**, *97*, 2879-2932, Periana *et al. Science* **1998**, *280*(5363), 560-564, Y. Fujiwara *Chemistry Letters* **1987** *16*(9), 1865-1868

Pioneering work

Pioneering work in oxygenation of methane and benzene

- Shilov process 1970’s

$$CH_4 + PtCl_6^{2-} + H_2O \xrightarrow[H_2O \\ 120° C]{PtCl_4^{2-}} CH_3OH + PtCl_4^{-} + 2HCl$$

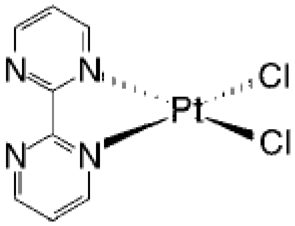
- Stoechiometric
- Selective to primary alkane

- Periana improvement 1998

$$CH_4 + 2H_2SO_4 \xrightarrow[100° C]{(bpym)PtCl_2} CH_3OSO_3H + 2H_2O + SO_2$$

72% yield

- Catalytic
- Product protected from overoxidation



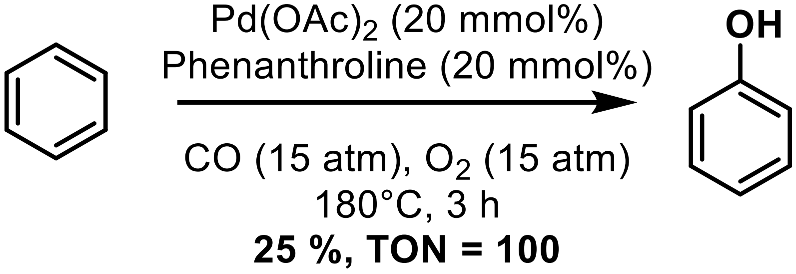
$(bpym)PtCl_2$

Shilov *Chem. Rev.* **1997**, *97*, 2879-2932, Periana *et al. Science* **1998**, *280*(5363), 560-564, Y. Fujiwara *Chemistry Letters* **1987** *16*(9), 1865-1868

Pioneering work

Pioneering work in oxygenation of methane and benzene

- Palladium Catalyzed Hydroxylation of Benzene with O_2

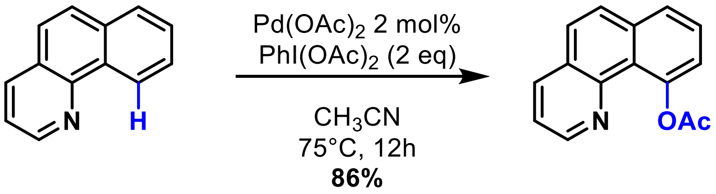


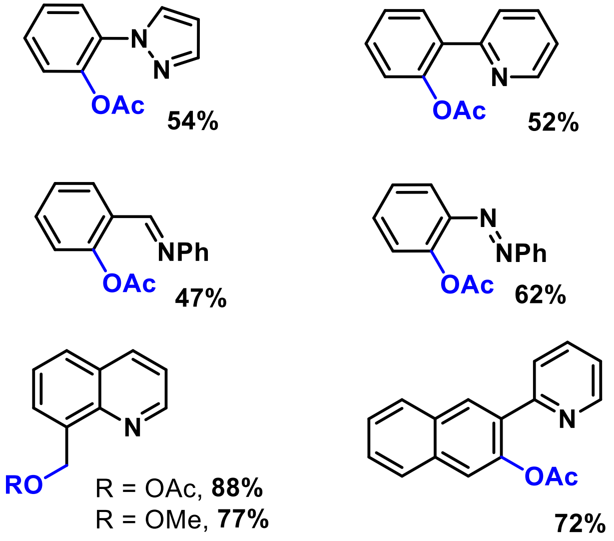
$Pd(OAc)_2$ (20 mmol%)
Phenanthroline (20 mmol%)
CO (15 atm), O_2 (15 atm)
180°C, 3 h
25 %, TON = 100

Shilov *Chem. Rev.* **1997**, *97*, 2879-2932, Periana *et al. Science* **1998**, *280*(5363), 560-564, Y. Fujiwara *Chemistry Letters* **1987** *16*(9), 1865-1868

Pioneering work

A Highly Selective Catalytic Method for the Oxidative Functionalization of C-H Bonds

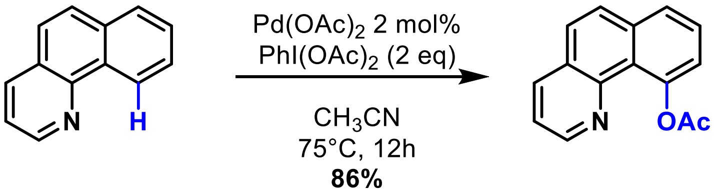


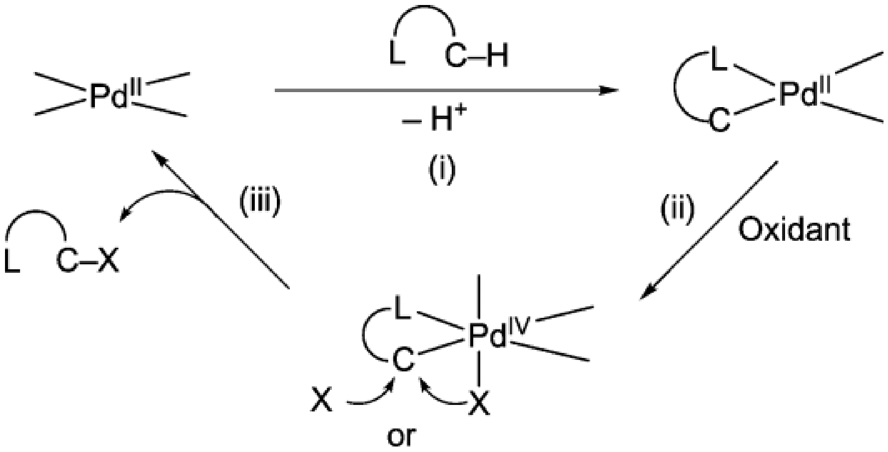


A. R. Dick , K. L. Hull , and M. S. Sanford *J. Am. Chem. Soc*. **2004**, *126*(8) 2300-2301

Pioneering work

A Highly Selective Catalytic Method for the Oxidative Functionalization of C-H Bonds





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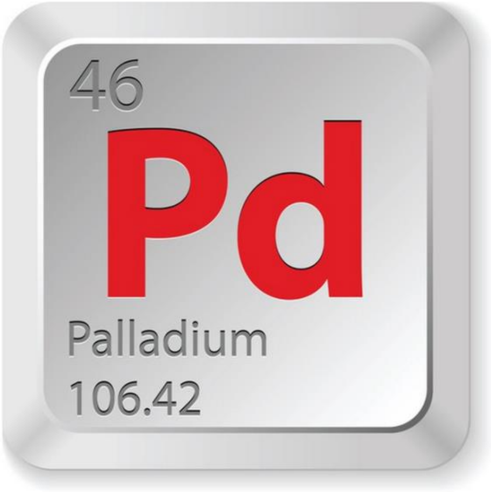
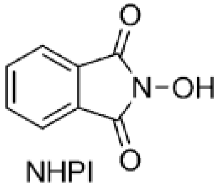
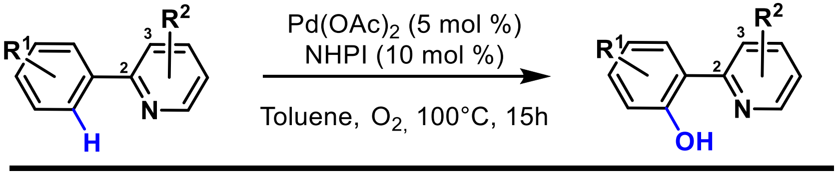
Pd(II) catalyzed C-H bonds oxygenation



Pd(II) catalyzed aromatic C-H bonds oxygenation

PdCl$_2$ and N-Hydroxyphthalimide Co-catalyzed C(Sp^2)-H Hydroxylation by Dioxygen Activation



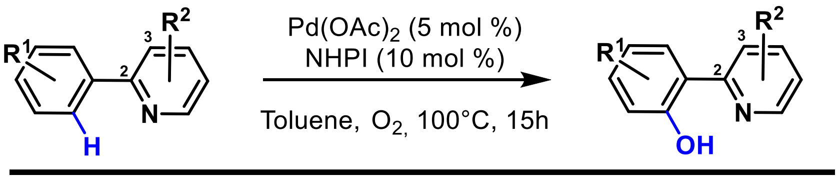


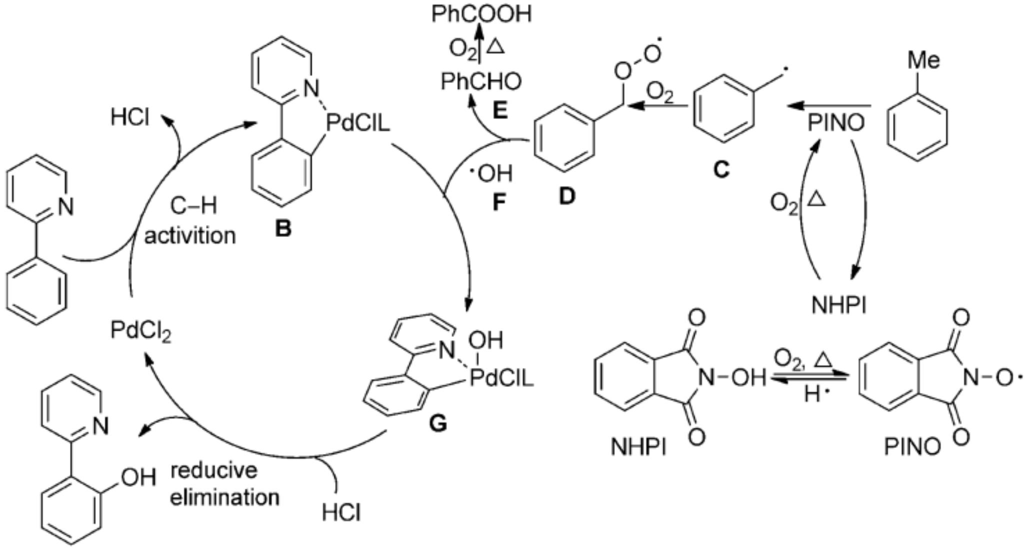
entry	R^1	R^2	yield (%)
1	H	H	72
2	*p*-Cl	H	68
3	*p*-Ph	H	73
4	*p*-CF_3	H	63
5	*m*-OPh	H	36
6	H	*3*-OMe	53

Yan, Y., Feng, P., Zheng, Q.-Z., Liang, Y.-F., Lu, J.-F., Cui, Y. and Jiao, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 5827 –5831

Pd(II) catalyzed aromatic C-H bonds oxygenation

PdCl$_2$ and N-Hydroxyphthalimide Co-catalyzed C(Sp^2)-H Hydroxylation by Dioxygen Activation





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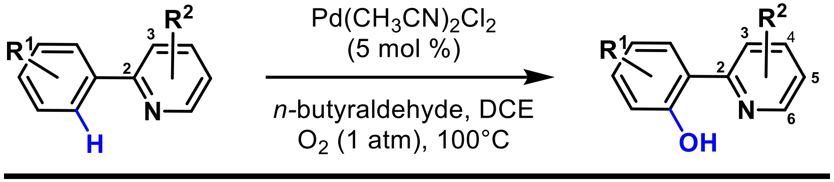
Pd(II) catalyzed aromatic C-H bonds oxygenation

Aerobic Direct C(sp²)-H Hydroxylation of 2-Arylpyridines by Palladium Catalysis Induced with Aldehyde Auto-Oxidation

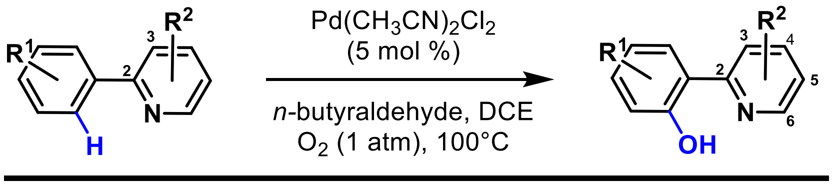


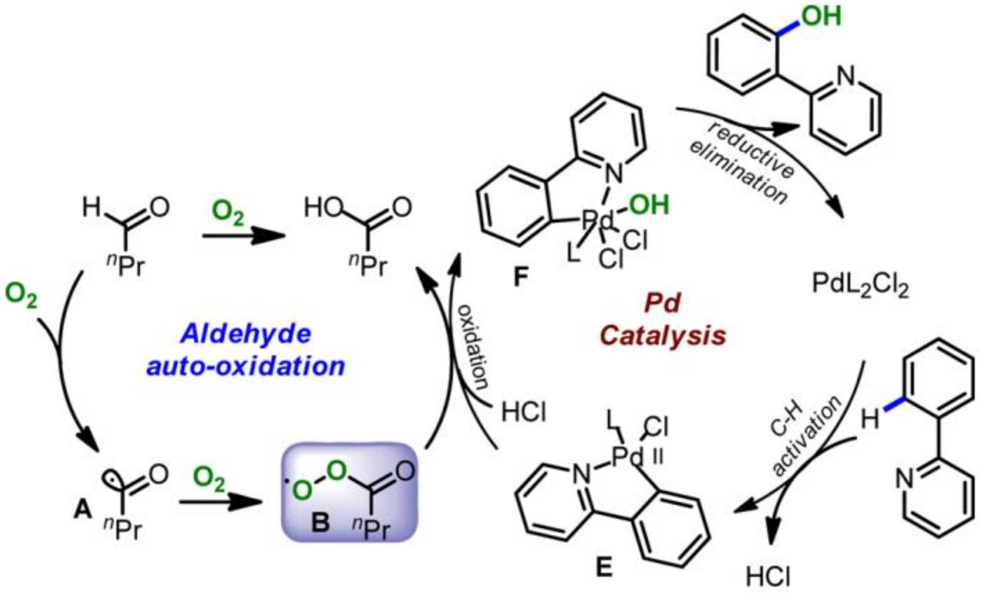
entry	R1	R2	yield (%)	t (h)
1	H	H	72	8
2	p-Ph	H	66	8
3	p-CN	H	72(a)	16
4	p-Cl	H	72(a)	16
5	o-F	H	67(b)	36
6	H	6-NHAc	53	8
7	H	5-CO_2Et	80	8
8	H	5-NO_2	76	8
9	H	4-CN	66	8
10	H	4-Ac	68	8

Prasenjit Das, Debajyoti Saha, Dibyajyoti Saha, and Joyram Guin *ACS Catal.* **2016**, *6* (9), 6050−6054

Pd(II) catalyzed aromatic C-H bonds oxygenation

Aerobic Direct C(sp^2)-H Hydroxylation of 2-Arylpyridines by Palladium Catalysis Induced with Aldehyde Auto-Oxidation



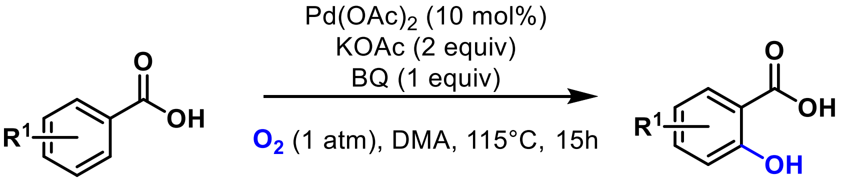


Inexpensive and nontoxic dioxygen activator

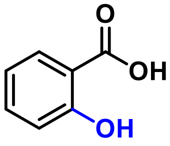
Prasenjit Das, Debajyoti Saha, Dibyajyoti Saha, and Joyram Guin *ACS Catal.* **2016**, *6* (9), 6050−6054

Pd(II) catalyzed aromatic C-H bonds oxygenation

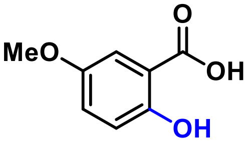
Pd(II)-Catalyzed Hydroxylation of Arenes with 1 atm of O2 or Air



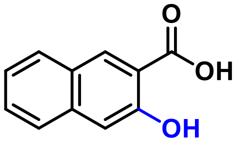
isolated



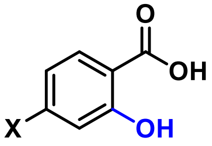
74 %



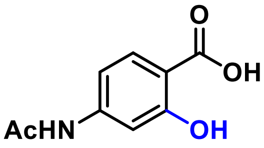
73 %



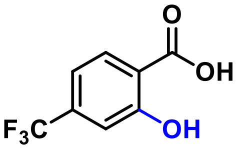
62 %



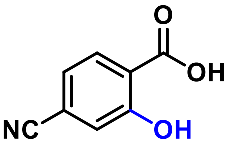
X = F, 82 %
X = Cl, **78 %**



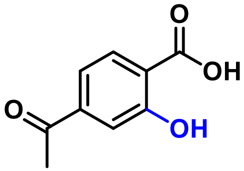
52 %



50 %
86 % (5 atm O_2)



50 %

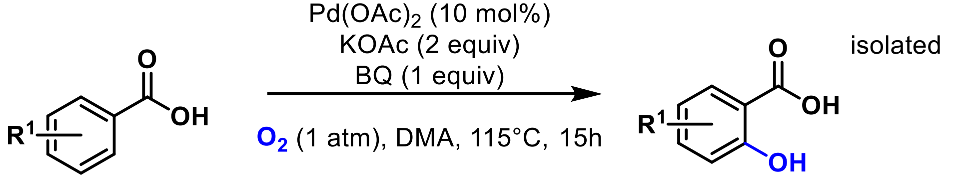


51 %
63 % (5 atm O2)

J.-Q. Yu *J. Am. Chem. Soc.* **2009** *131* (41), 14654-14655; Dong, G. *Angew. Chem. Int. Ed.* **2012**, *51* (52), 13075 –13079; Rao, Y. *Angew. Chem. Int. Ed.* **2012**, *51* (52), 13070 –13074

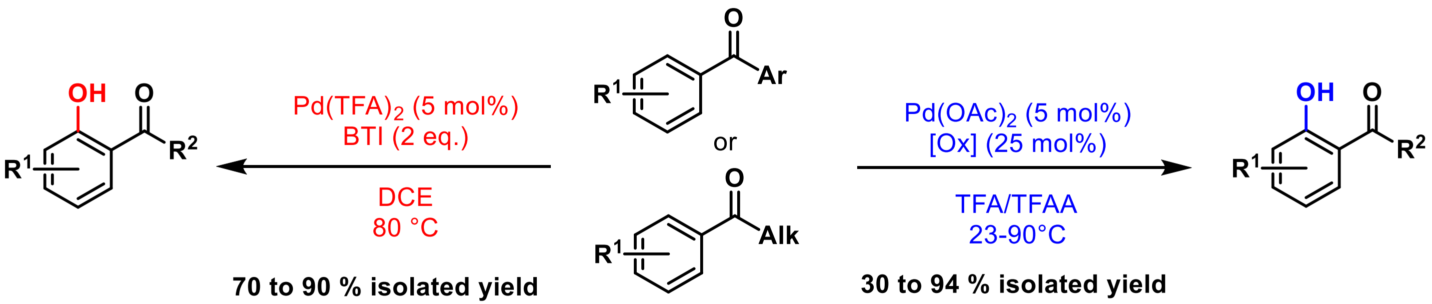
Pd(II) catalyzed aromatic C-H bonds oxygenation

Pd(II)-Catalyzed Hydroxylation of Arenes with 1 atm of O2 or Air



Pd(OAc)$_2$ (10 mol%)
KOAc (2 equiv)
BQ (1 equiv)
O_2 (1 atm), DMA, 115°C, 15h

isolated



Pd(TFA)$_2$ (5 mol%)
BTI (2 eq.)
DCE
80 °C

70 to 90 % isolated yield

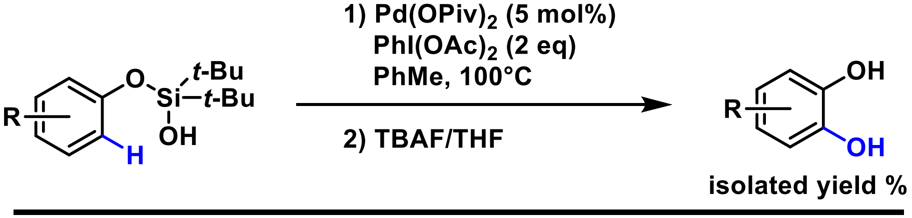
Pd(OAc)$_2$ (5 mol%)
[Ox] (25 mol%)
TFA/TFAA
23-90°C

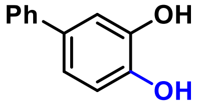
30 to 94 % isolated yield

J.-Q. Yu *J. Am. Chem. Soc.* **2009** *131* (41), 14654-14655; Dong, G. *Angew. Chem. Int. Ed.* **2012**, *51* (52), 13075 –13079; Rao, Y. *Angew. Chem. Int. Ed.* **2012**, *51* (52), 13070 –13074

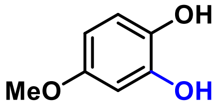
Pd(II) catalyzed aromatic C-H bonds oxygenation

Synthesis of Catechols from Phenols via Pd-Catalyzed Silanol-Directed CH Oxygenation

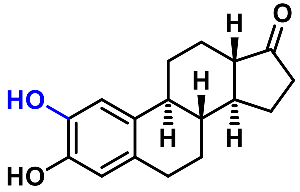




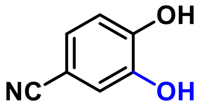
87%



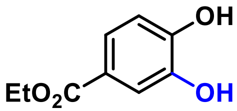
57%*



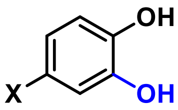
88%



1.5 eq [Ox] in $PhCF_3$ at 120°C, **29%***



24% (NMR yield)
1.5 eq [Ox] in $PhCF_3$ at 120°C, **76%***



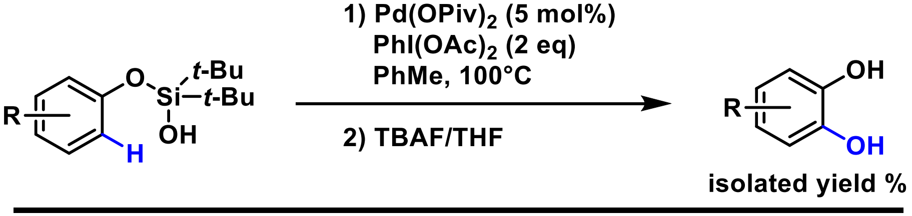
1.5 eq [Ox] in $PhCF_3$ at 120°C,
R = Cl, **84%***
R = Br, **83%** *
R = F, **60%***

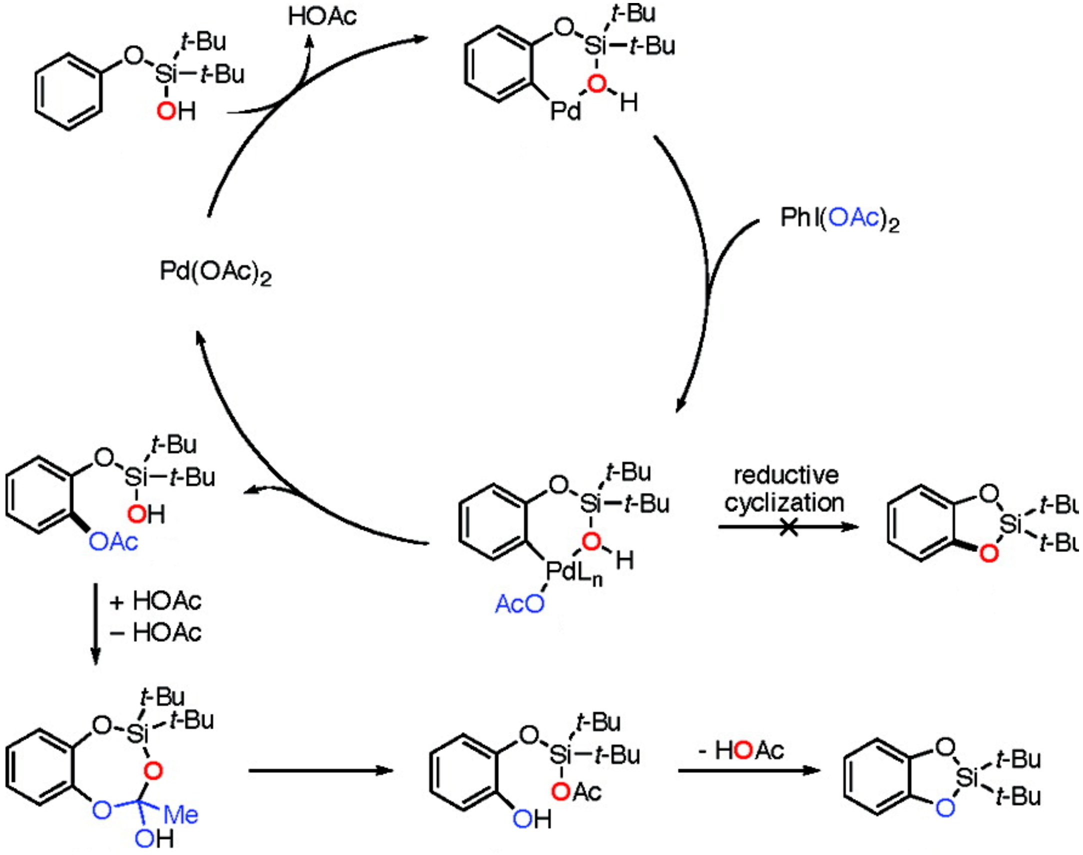
* isolated as bis-acetates by further treatement of the catechols with Ac2O and pyridine in the same pot

C. Huang, N. Ghavtadze, B. Chattopadhyay, and V.Gevorgyan *J. Am. Chem. Soc.*, **2011**, *133* (44), 17630–17633

Pd(II) catalyzed aromatic C-H bonds oxygenation

Synthesis of Catechols from Phenols via Pd-Catalyzed Silanol-Directed CH Oxygenation

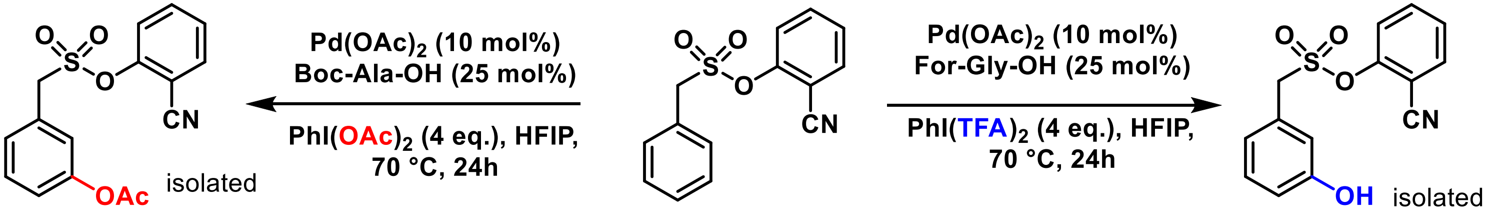




C. Huang, N. Ghavtadze, B. Chattopadhyay, and V.Gevorgyan *J. Am. Chem. Soc.*, **2011**, *133* (44), 17630–17633

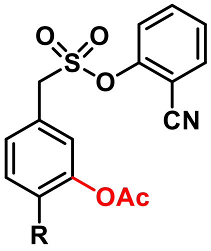
Pd(II) catalyzed aromatic C-H bonds oxygenation

Directing group assisted meta-hydroxylation by C–H activation

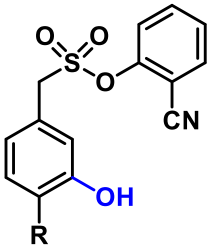


$Pd(OAc)_2$ (10 mol%)
Boc-Ala-OH (25 mol%)
$PhI(OAc)_2$ (4 eq.), HFIP,
70 °C, 24h

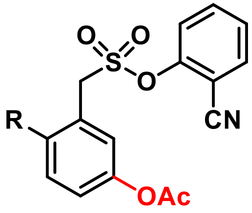
$Pd(OAc)_2$ (10 mol%)
For-Gly-OH (25 mol%)
$PhI(TFA)_2$ (4 eq.), HFIP,
70 °C, 24h



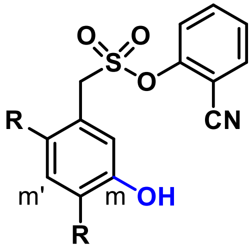
R = H; **71%** (25:1)
R = *i*Pr; **61%** (14:1)
R = OCF_3; **56%** (16:1)
R = Cl; **55%** (11:1)
R = F; **55%** (26:1)



R = H; **74%** (32:1)
R = *i*Pr; **77%** (18:1)
R = OCF_3; **51%** (19:1)
R = F; **74%** (15:1)
R = Br; **55%** (15:1)



R = Me; **75%** (8:1)
R = OCF_3; **57%** (10:1)
R = Cl; **63%** (10:1)
R = F; **51%** (19:1)

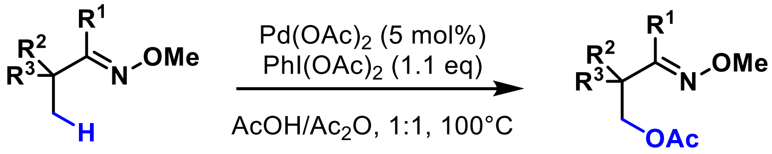


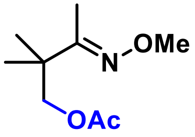
R = Cl; **65%** (m:m' = 18:1)
R = Br; **63%** (m:m' = 25:1)

Arun Maji, Bangaru Bhaskararao, Santanu Singha, Raghavan B. Sunoj and Debabrata Maiti *Chem. Sci.*, **2016**, *7* (5), 3147–3153

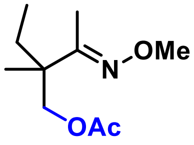
Pd(II) catalyzed aliphatic C-H bonds oxygenation

Palladium-Catalyzed Oxygenation of Unactivated C(sp^3)-H Bonds

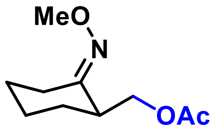




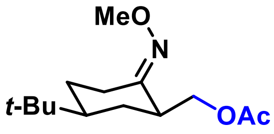
3h, **74%**



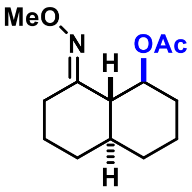
3.5h, **74%**



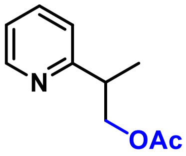
1.5 eq Ox, 1.5h, **81%**



5min**, 86%**



1.5 eq Ox, 80°C, 5h, **81%**

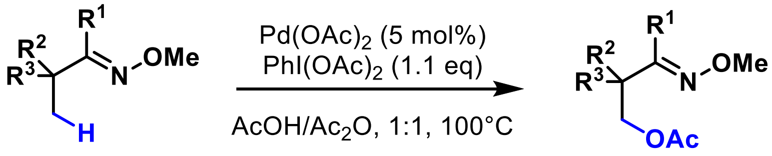


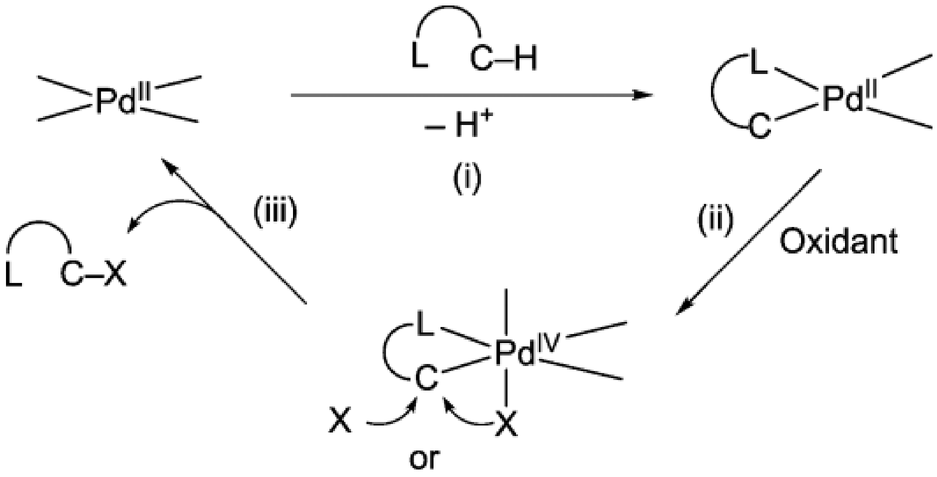
1.5 eq Ox, in DCM, 12h, **42%**

Lopa V. Desai , Kami L. Hull , and Melanie S. Sanford *J. Am. Chem. Soc.*, **2004**, *126* (31), 9542–9543

Pd(II) catalyzed aliphatic C-H bonds oxygenation

Palladium-Catalyzed Oxygenation of Unactivated C(sp^3)-H Bonds

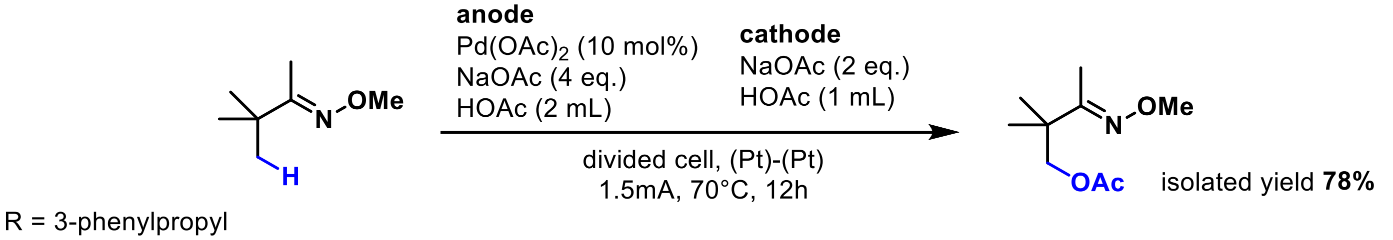


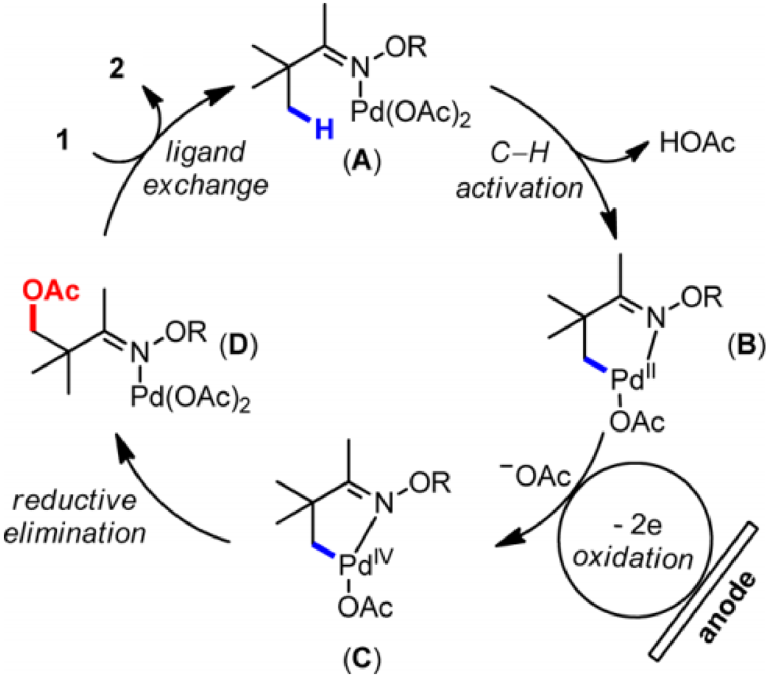


Lopa V. Desai , Kami L. Hull , and Melanie S. Sanford *J. Am. Chem. Soc.*, **2004**, *126* (31), 9542–9543

Pd(II) catalyzed aliphatic C-H bonds oxygenation

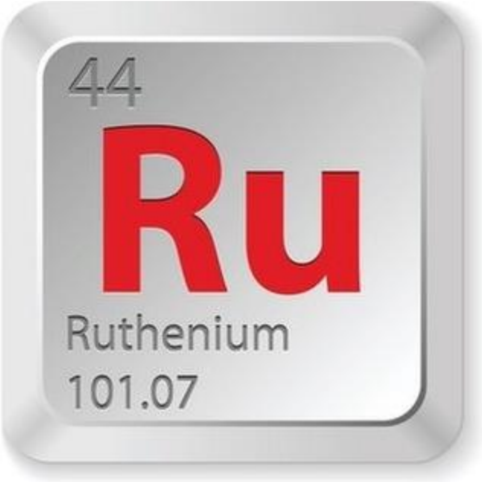
Palladium-Catalyzed C(sp^3)-H Oxygenation via Electrochemical Oxidation





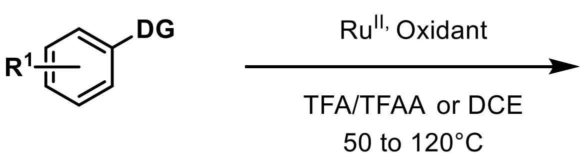
T.-S. Mei *et al. J. Am. Chem. Soc.* **2017**, *139*, 3293−3298

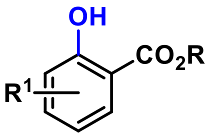
Ru(II) catalyzed C-H bonds oxygenation



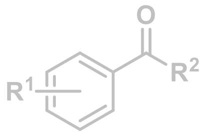
Ru(II) catalyzed aromatic C-H bonds oxygenation

Ruthenium(II)-Catalyzed Synthesis of Hydroxylated Arenes with diverse directing groups

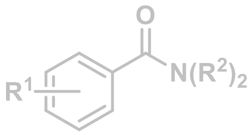




Rao ***2012***

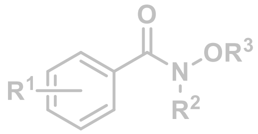


Ackermann ***2012***

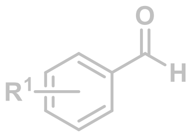


Ackermann ***2012***

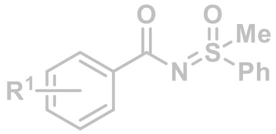
1st hydroxylation of arene with an ester as directing group
new catalytic system Ru^{II} / Oxidant / TFA/TFAA
High yielding and good functional group tolerance



Ackermann ***2013***



Ackermann ***2014***

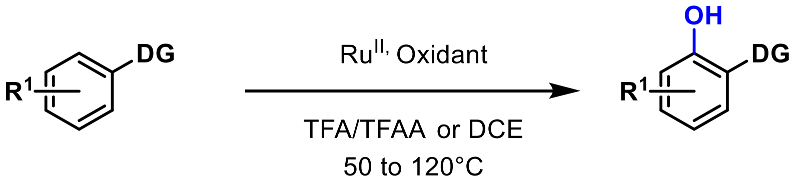


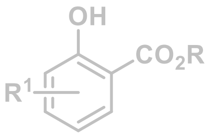
Ackermann ***2017***

Yiqing Yang, Yun Lin, and Yu Rao *Org. Lett.*, **2012**, *14* (11), 2874–2877

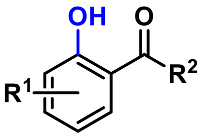
Ru(II) catalyzed aromatic C-H bonds oxygenation

Ruthenium(II)-Catalyzed Synthesis of Hydroxylated Arenes with diverse directing groups

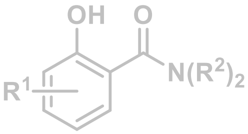




Rao ***2012***

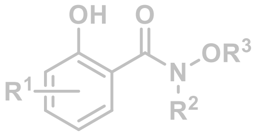


Ackermann ***2012***

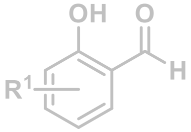


Ackermann ***2012***

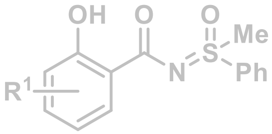
Good functional group tolerance
Chemo and site selective



Ackermann ***2013***



Ackermann ***2014***

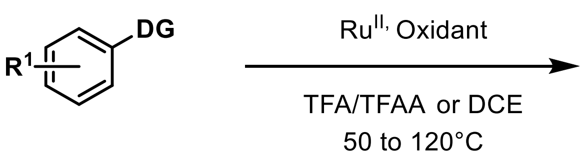


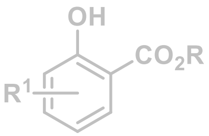
Ackermann ***2017***

Vedhagiri S. Thirunavukkarasu and Lutz Ackermann *Org. Lett.*, **2012**, *14* (24), 6206–6209

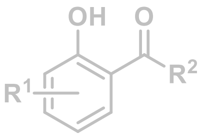
Ru(II) catalyzed aromatic C-H bonds oxygenation

Ruthenium(II)-Catalyzed Synthesis of Hydroxylated Arenes with diverse directing groups

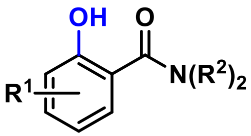




*Rao **2012***

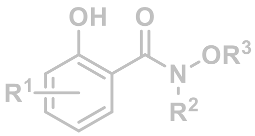


*Ackermann **2012***

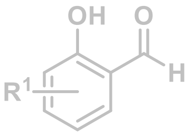


*Ackermann **2012***

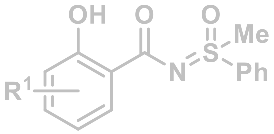
1st hydroxylation of arene with an amide as directing group
low catalyst loading (1 mol%)



*Ackermann **2013***



*Ackermann **2014***

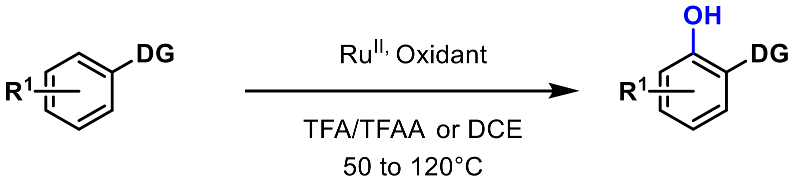


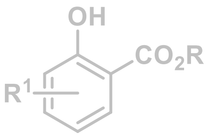
*Ackermann **2017***

Vedhagiri S. Thirunavukkarasu, Jonathan Hubrich, and Lutz Ackermann *Org. Lett.* **2012**, *14* (16), 4210–4213

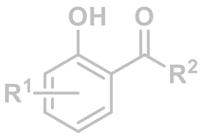
Ru(II) catalyzed aromatic C-H bonds oxygenation

Ruthenium(II)-Catalyzed Synthesis of Hydroxylated Arenes with diverse directing groups

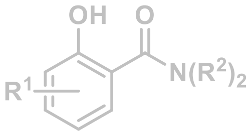




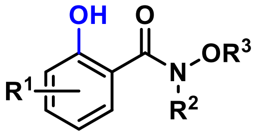
*Rao **2012***



*Ackermann **2012***

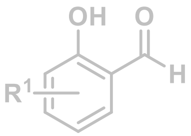


*Ackermann **2012***

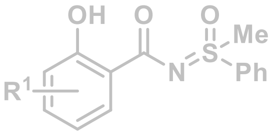


*Ackermann **2013***

Mild reaction conditions (50°C)
Chemo and site selective
Acces to the corresponding ketone and aldehyde



*Ackermann **2014***

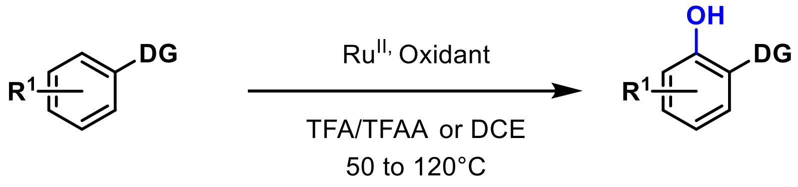


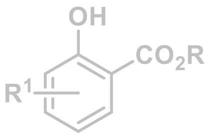
*Ackermann **2017***

Fanzhi Yang and Lutz Ackermann *Org. Lett.*, **2013**, *15* (3), 718–720

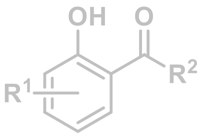
Ru(II) catalyzed aromatic C-H bonds oxygenation

Ruthenium(II)-Catalyzed Synthesis of Hydroxylated Arenes with diverse directing groups

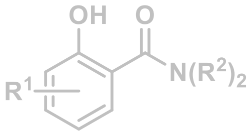




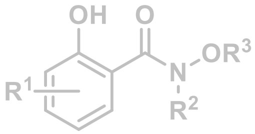
Rao ***2012***



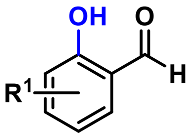
Ackermann ***2012***



Ackermann ***2012***

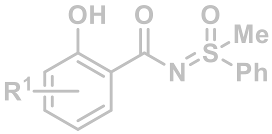


Ackermann ***2013***



Ackermann ***2014***

Very weakly coordinating group
Convertible into valuable heterocycles

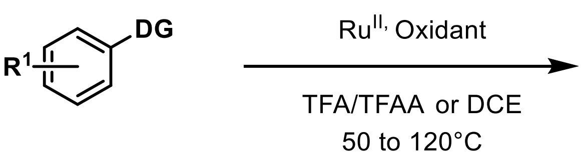


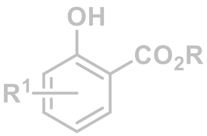
Ackermann ***2017***

Yang, F., Rauch, K., Kettelhoit, K. and Ackermann, L. *Angew. Chem. Int. Ed.* **2014**, *53* (42), 11285 –11288

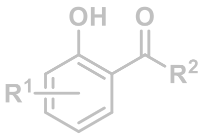
Ru(II) catalyzed aromatic C-H bonds oxygenation

Ruthenium(II)-Catalyzed Synthesis of Hydroxylated Arenes with diverse directing groups

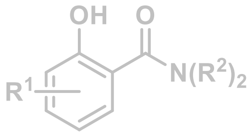




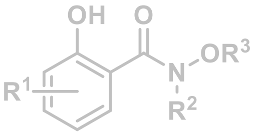
Rao ***2012***



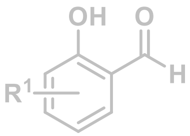
Ackermann ***2012***



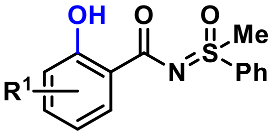
Ackermann ***2012***



Ackermann ***2013***



Ackermann ***2014***

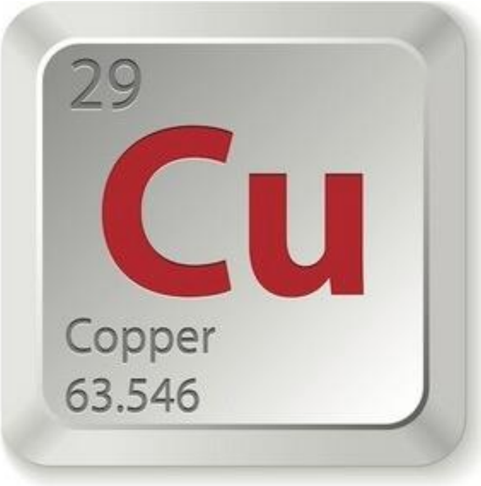


Ackermann ***2017***

Removable and reusable
Chemo and site selective

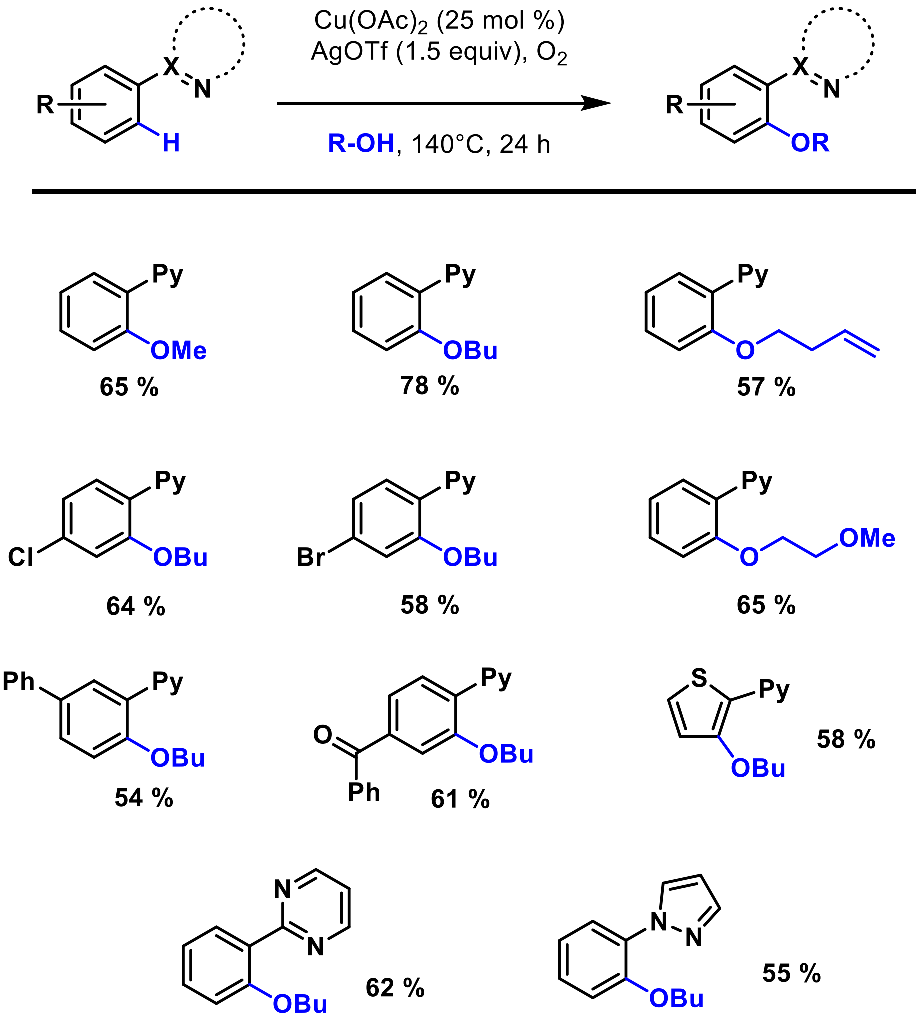
Keshav Raghuvanshi, Daniel Zell, and Lutz Ackermann *Org. Lett.* **2017**, *19* (6), 1278–1281

Cu(II) catalyzed C-H bonds oxygenation



Cu(II) catalyzed aromatic C-H bonds oxygenation

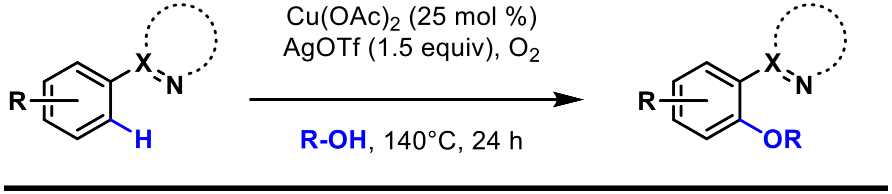
Copper-Catalyzed Dehydrogenative Coupling of Arenes with Alcoholsc

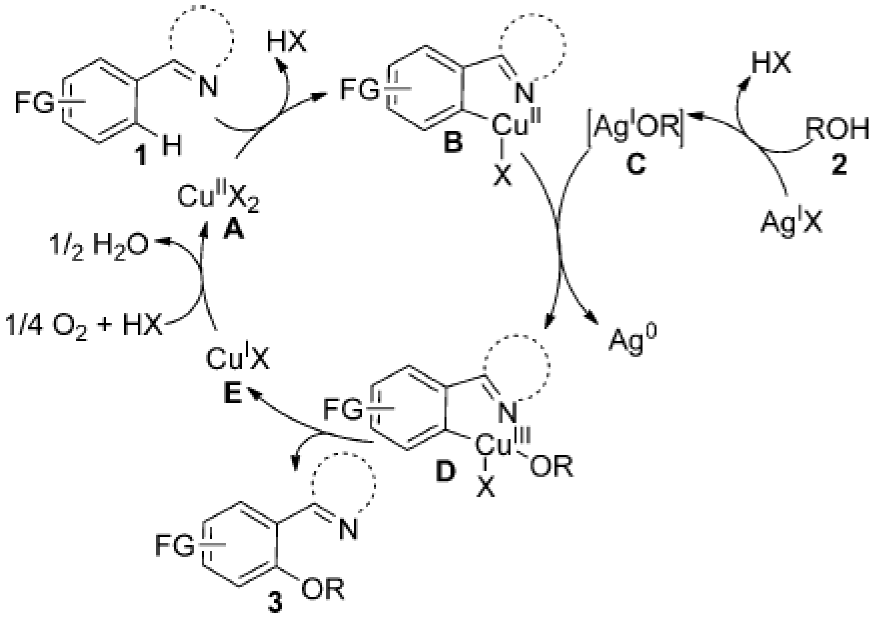


Bhadra, S., Matheis, C., Katayev, D. and Gooßen, L. J. *Angew. Chem.* **2013**, *125* (35), 9449 –9453

Cu(II) catalyzed aromatic C-H bonds oxygenation

Copper-Catalyzed Dehydrogenative Coupling of Arenes with Alcoholsc

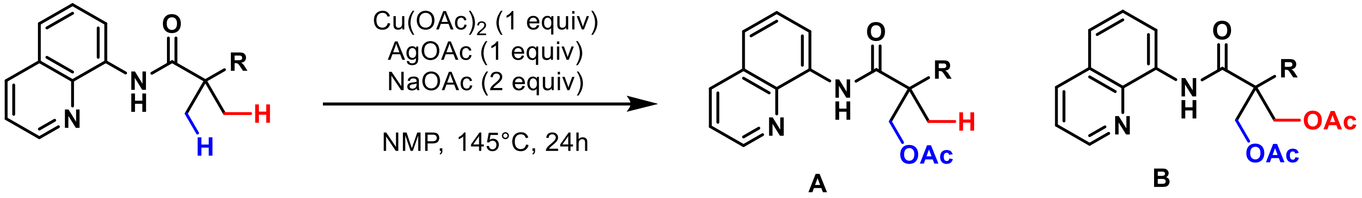




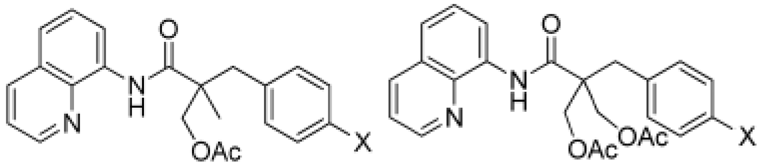
Bhadra, S., Matheis, C., Katayev, D. and Gooßen, L. J. *Angew. Chem.* **2013**, *125* (35), 9449 –9453

Cu(II) catalyzed aliphatic C-H bonds oxygenation

Copper-Mediated Direct C(sp^3)–H and C(sp^2)–H Acetoxylation



R^1 = Me	39	38
R^1 = $^nC_3H_7$	55	23
R^1 = $(CH_2)_2Ph$	55	21
R^1 = CH_2OCH_2Ph	54	22
R^1 = CF_3	73	<1

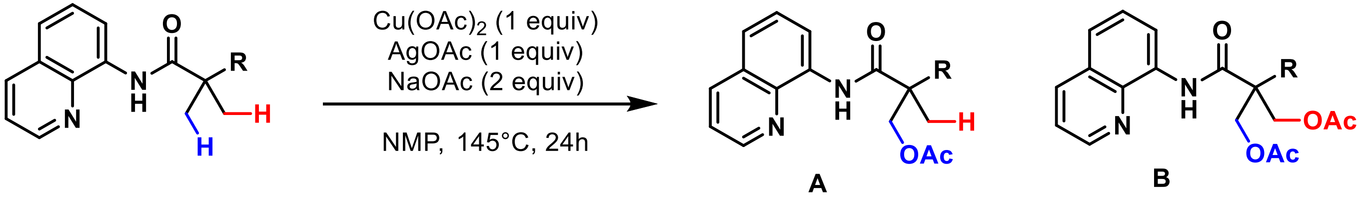


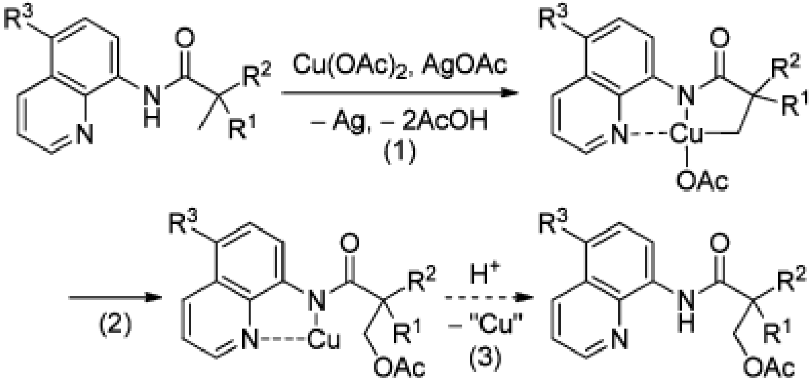
X = OMe	67	<1
X = Me	71	<1
X = H	74	<1
X = Br	62	<1
X = Cl	78	<1
X = F	81	<1
X = CF_3	83	<1

Z. Wang, Y. Kuninobu and M. Kanai *Org. Lett.* **2014**, *16* (18), pp 4790–4793

Cu(II) catalyzed aliphatic C-H bonds oxygenation

Copper-Mediated Direct C(sp^3)−H and C(sp^2)−H Acetoxylation

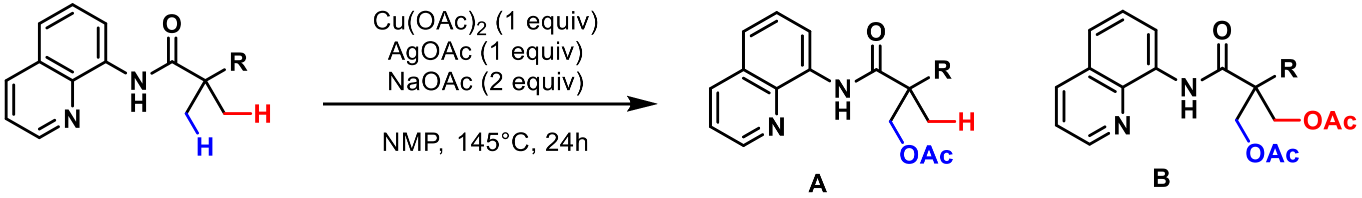


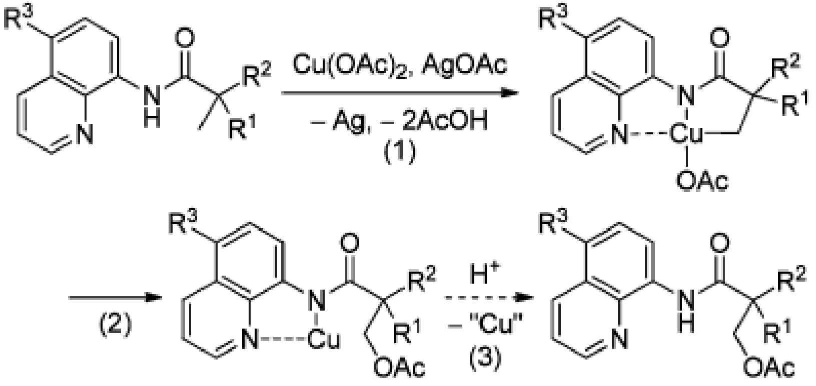


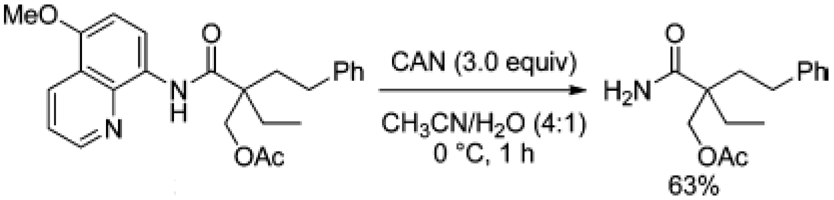
Z. Wang, Y. Kuninobu and M. Kanai *Org. Lett.* **2014**, *16* (18), pp 4790–4793

Cu(II) catalyzed aliphatic C-H bonds oxygenation

Copper-Mediated Direct C(sp^3)–H and C(sp^2)–H Acetoxylation

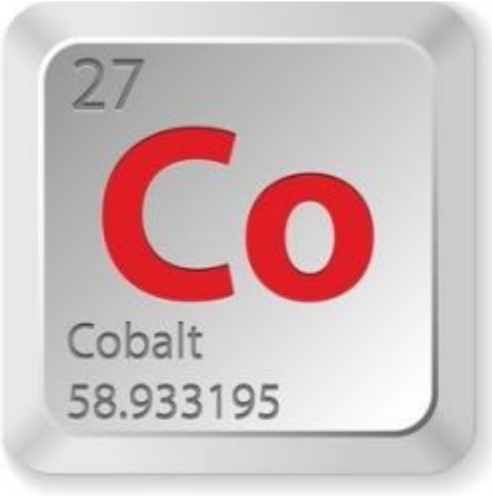






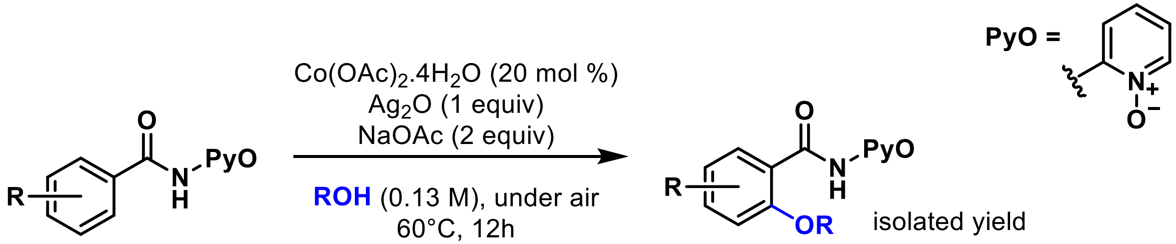
Z. Wang, Y. Kuninobu and M. Kanai *Org. Lett.* **2014**, *16* (18), pp 4790–4793

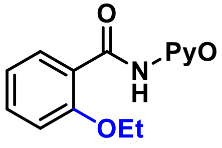
Co(II) catalyzed aromatic C-H bonds oxygenation



Cobalt catalyzed aromatic C-H bonds oxygenation

Cobalt-Catalyzed C(sp²⁾H Alkoxylation of Aromatic and Carboxamides

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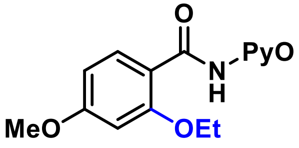
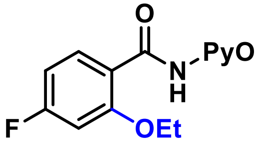
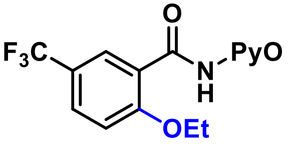
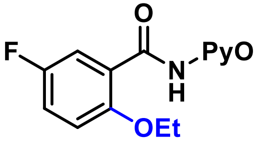
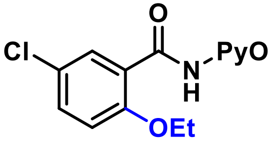
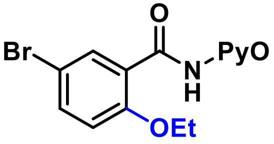

83 %

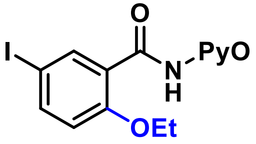

69 %

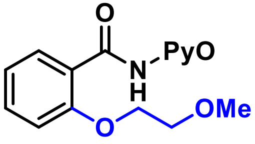

34 %

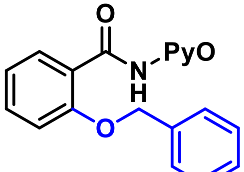

51 %

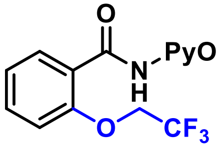

68 %

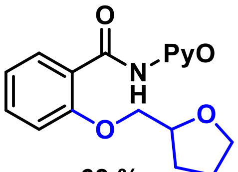

53 %


52 %


69 %


56 %

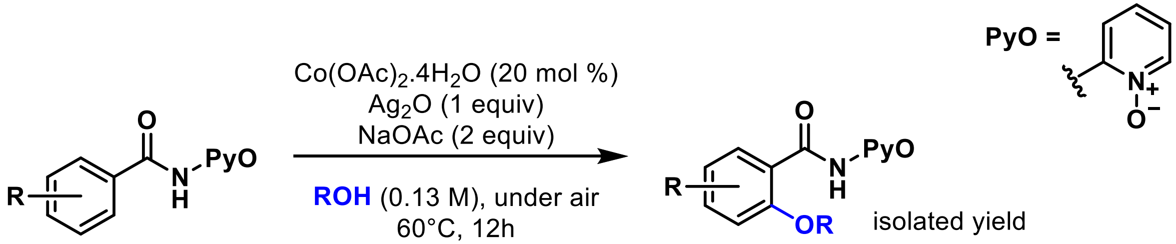

67 %

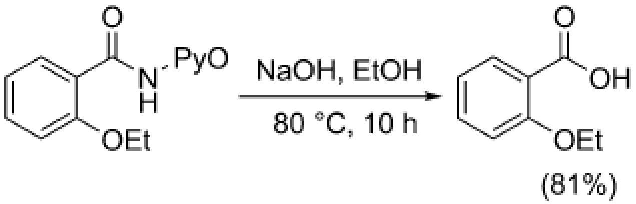

68 %

Song, M.-P. *et al. Angew. Chem.* **2015**, *127* (1), 274 –277

Cobalt catalyzed aromatic C-H bonds oxygenation

Cobalt-Catalyzed C(sp$^{2)}$H Alkoxylation of Aromatic and Carboxamides





Song, M.-P. *et al. Angew. Chem.* **2015**, *127* (1), 274 –277

Conclusion

✓ Since 2004, Hot topic

✓ Effort in developping ecofriendly catalytic system

✓Many method developed to extend the functionalities tolerance

→ Further investigation on mechanistic studies

→ Improved catalytic activity for cheaper metal catalysts

Answers

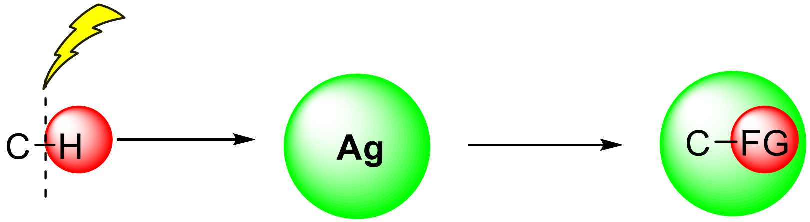
1. Enonce one method to avoid the use of stoechiometric amount of oxidant in oxidative Pd^{II} catalyzed oxygenation

Use of dioxygen activator such as a cocatalyst (NHPI)

2. Why is alkoxylation more challenging than acetoxylation ?

Alkoxyl-metal intermediate formed tend to undergo beta-H elimination

Advances in Ag(I)-catalyzed C-H bond funcitonalization



Philipp Seeberger

Table of content

Why silver?

- Coinage metals
  - ➡ d^{10} electronic configuration

- Formation of stable complexes:
  - Interaction with π-donor- and n-donor ligands

- Neglected metal:

✖ Low catalytic efficiency

✖ Moderate Lewis acidity

Why silver?

- Economics

New York Spot Price

MARKET IS OPEN
(Will close in 6 hrs. 34 mins)

Metals	Date	Time (EST)	Bid	Ask	Change		Low	High
GOLD	05/31/2017	10:27	39.50	39.53	-0.07	-0.18%	39.40	39.64
SILVER	05/31/2017	10:26	0.54	0.54	-0.01	-0.96%	0.54	0.55
PLATINUM	05/31/2017	10:27	29.37	29.53	+0.01	+0.03%	29.16	29.78
PALLADIUM	05/31/2017	10:27	25.44	25.60	+0.25	+0.98%	25.06	25.67
RHODIUM	05/31/2017	08:34	26.50	29.62	-0.13	-0.50%	26.47	29.72

- Low toxicity

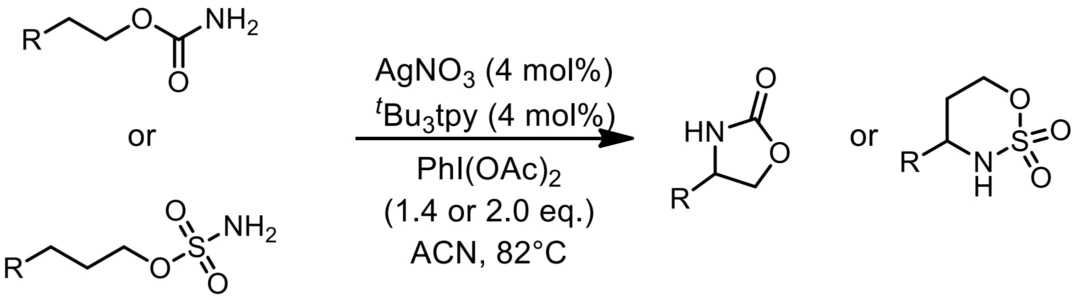
http://www.kitco.com/market/

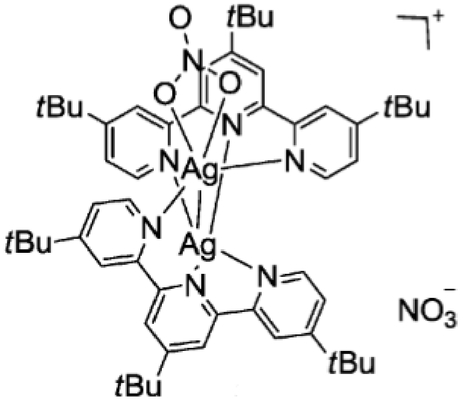
Silver-catalyzed Csp^3-H functionalization

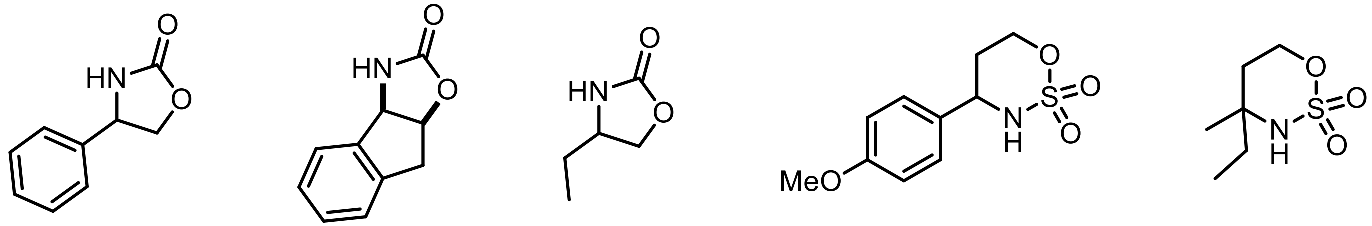
First examples

C-N bond formation

- **2004, He *et al.*:**





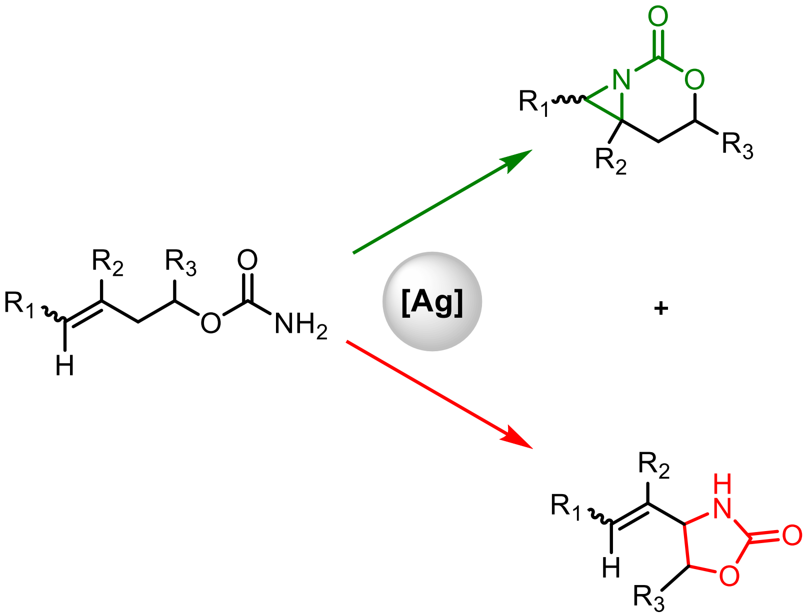


81% 83% 58% 78% 90%

Mechanism presumed to proceed via silver-nitrene intermediate

Cui, Y.; He, C. *Angew. Chem.* **2004**, *116*, 4306.

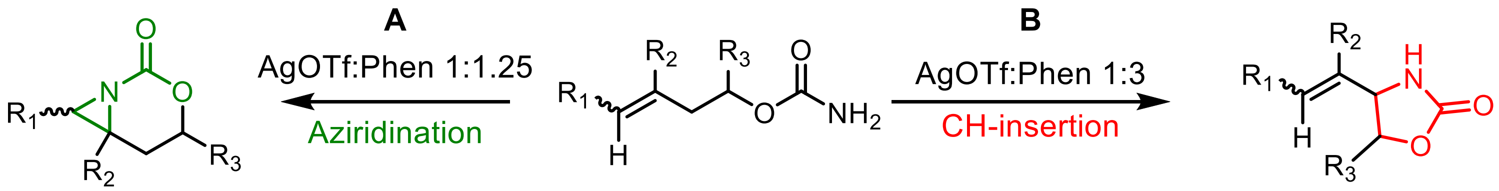
Challenges: Chemoselectivity



- Presence of both reactive C-H and C=C
- Selectivity often substrate controlled

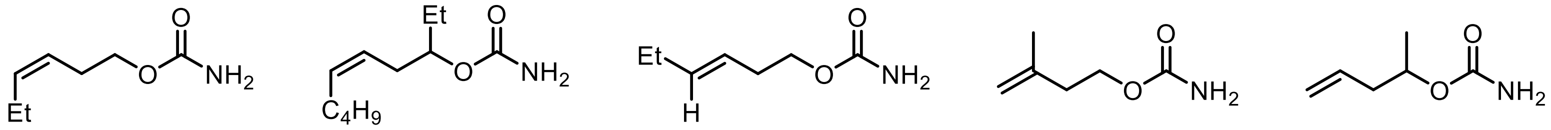
Recent developments

- **2013, Schomaker *et al.*:**



A: AgOTf (20 mol%), 1,10-phenanthroline (25 mol%), PhIO (2 eq.), 4 Å, DCM
B: AgOTf (10 mol%), 1,10-phenanthroline (30 mol%), PhIO (2 eq.), 4 Å, DCM

- Substrate controlled selectivity largely overcome

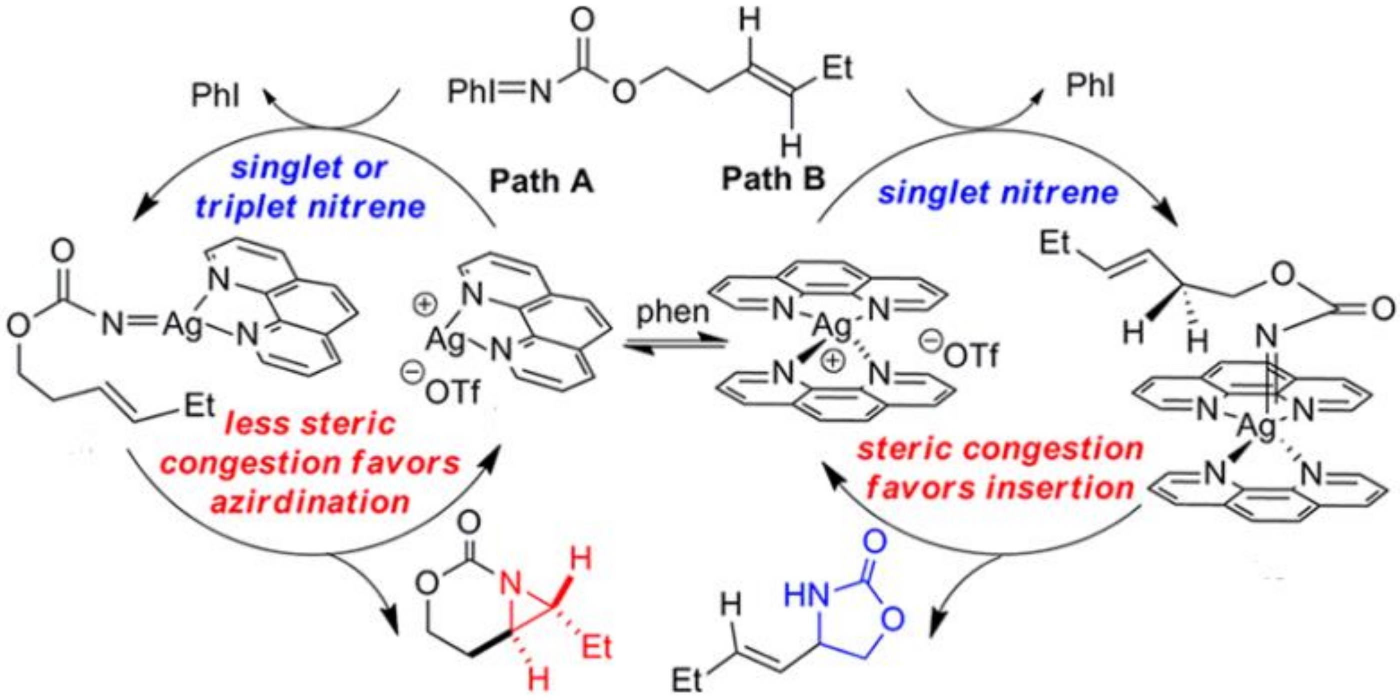


A: 16.8:1	**A:** 9.9:1	**A:** 29:1	**A:** 99:1	**A:** 1.4:1
B: 0:100	**B:** 1:22	**B:** 1:6.6	**B:** 1:2.9	**B:** 0:100

Rigoli, J. W.; Weatherly, C. D.; Alderson, J. M.; Vo, B. T.; Schomaker, J. M. *J. Am. Chem. Soc.* **2013**, *135*, 17238.

Recent developments

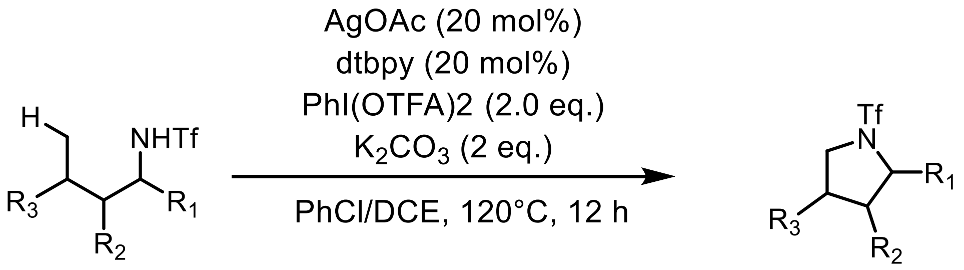
Mechanism

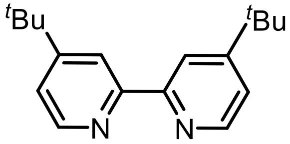


Rigoli, J. W.; Weatherly, C. D.; Alderson, J. M.; Vo, B. T.; Schomaker, J. M. *J. Am. Chem. Soc.* **2013**, *135*, 17238.

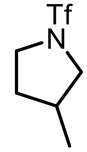
Recent developments

- **2014, Shi *et al.*:** *Activation of primary Csp^3-H-bonds*

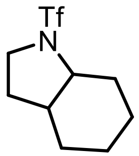




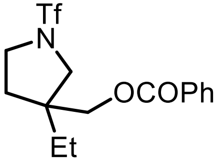
4,4'-di-*tert*-butyl-2,2'-bypridine (dtbpy)



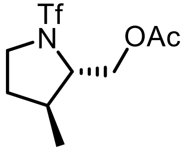
70%



60 %, dr=60:40



72 %



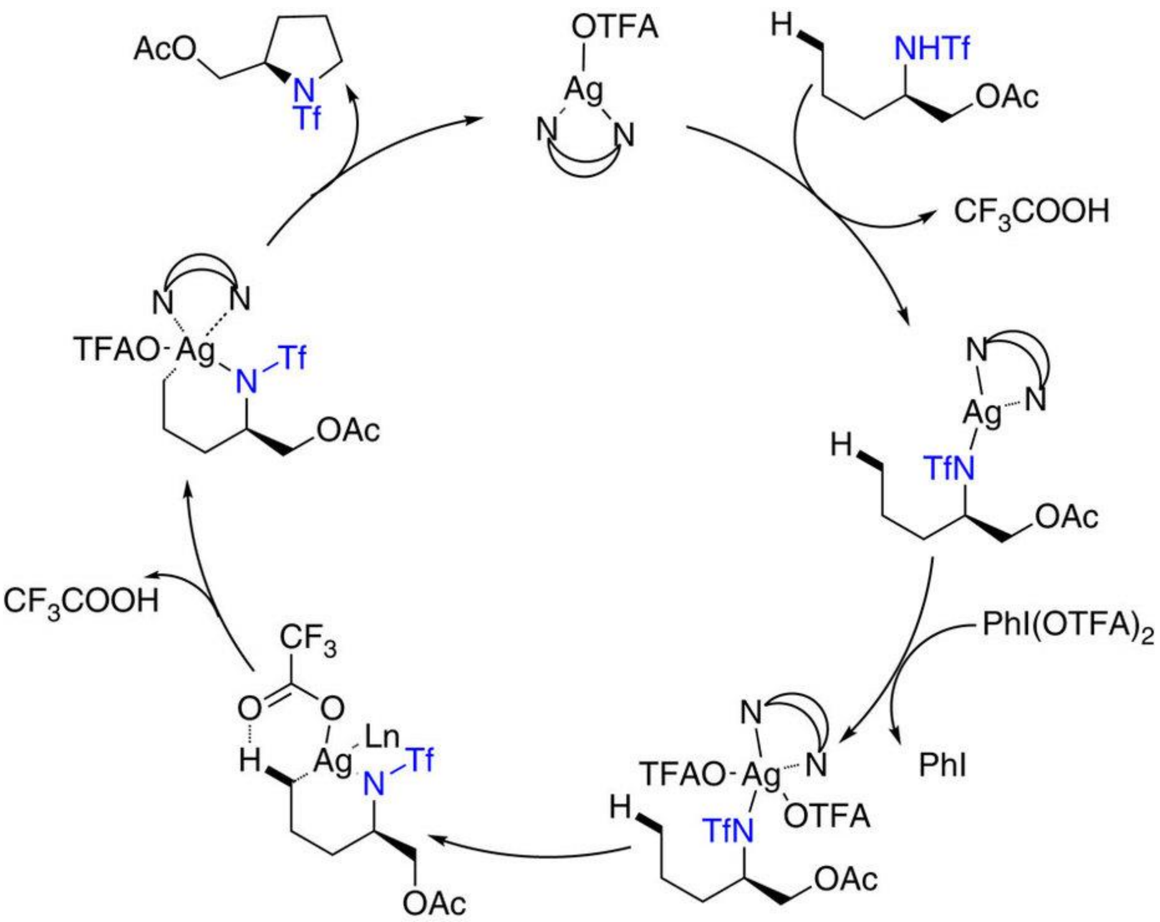
54%, dr 93:7

➡ Proceeds without the need for further directing groups

Yang, M.; Su, B.; Wang, Y.; Chen, K.; Jiang, X.; Zhang, Y.-F.; Zhang, X.-S.; Chen, G.; Cheng, Y.; Cao, Z.; Guo, Q.-Y.; Wang, L.; Shi, Z.-J. *Nat. Commun.* **2014**, *5*, 4707.

Recent developments

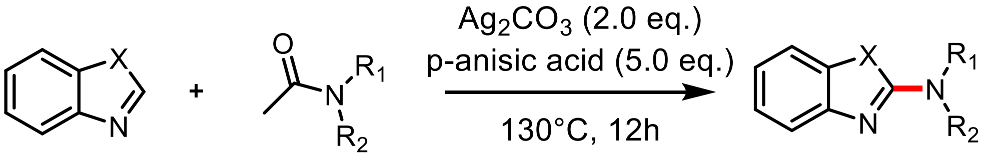
Mechanism



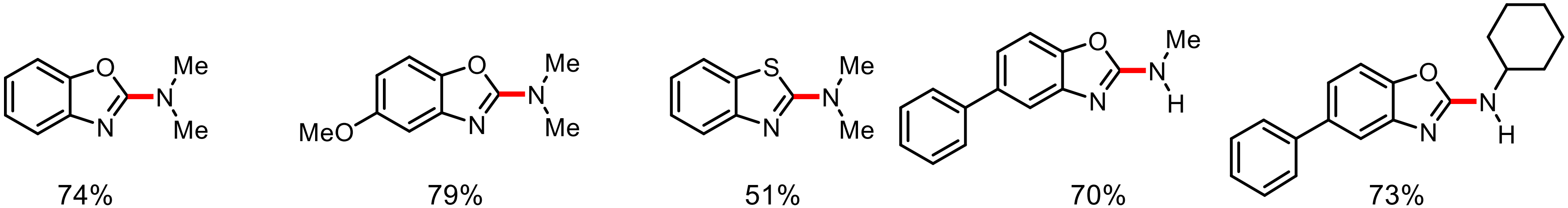
Silver-catalyzed Csp^{2}H-functionalization

C-N bond formation

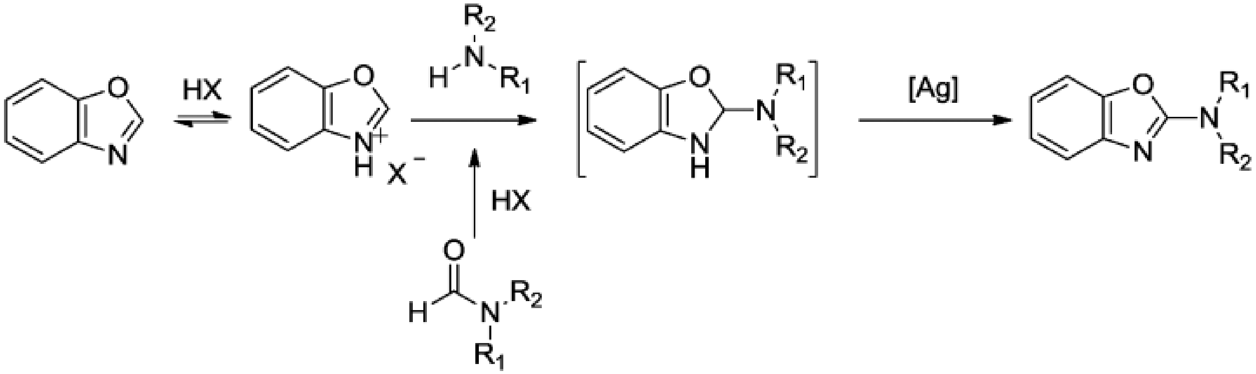
2009, Chang *et al.*: *First silver-mediated amination of benzoxazoles*



Ag_2CO_3 (2.0 eq.)
p-anisic acid (5.0 eq.)
130°C, 12h



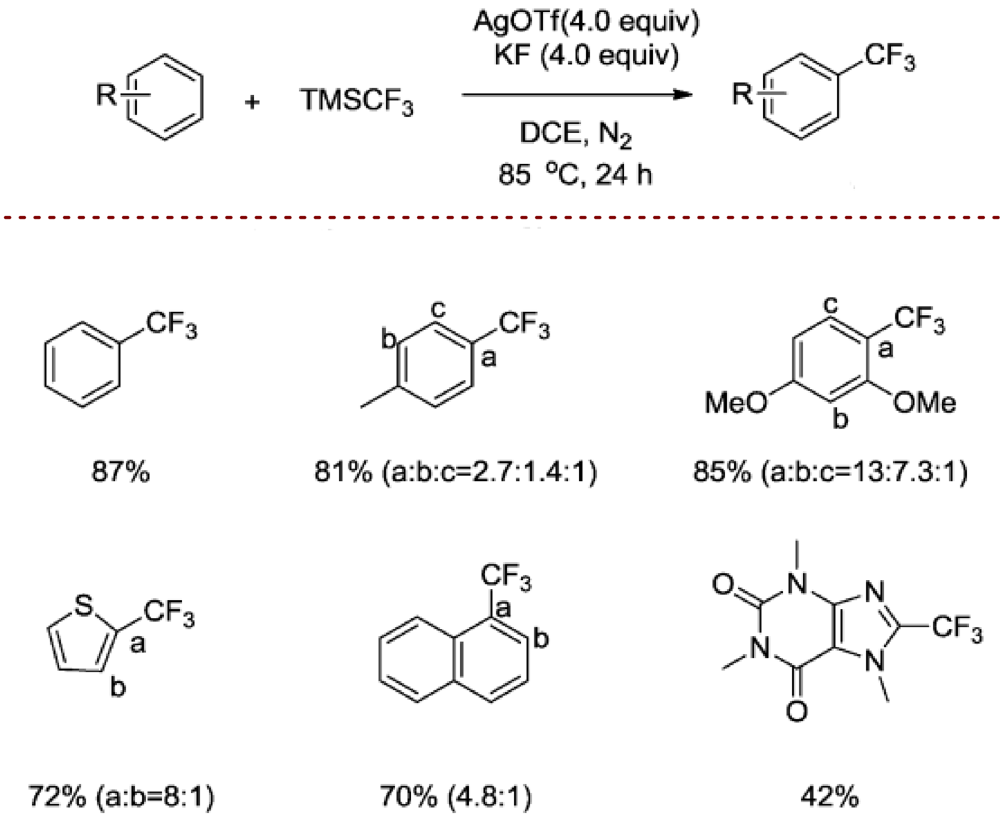
74% 79% 51% 70% 73%



Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 9127.

C-C bond formation: Trifluoromethylation

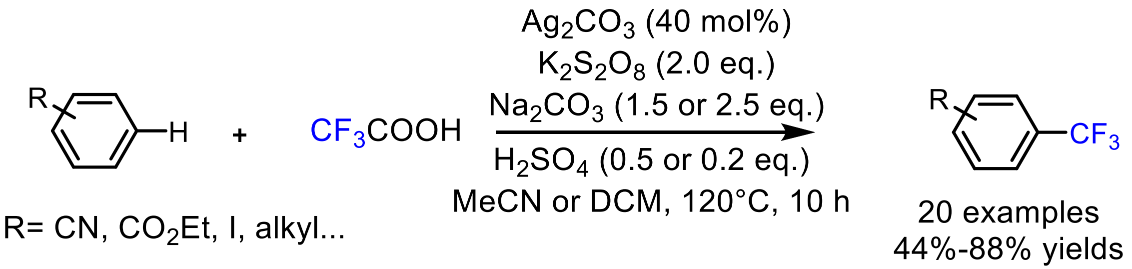
- **2009, Sanford *et al.*:**



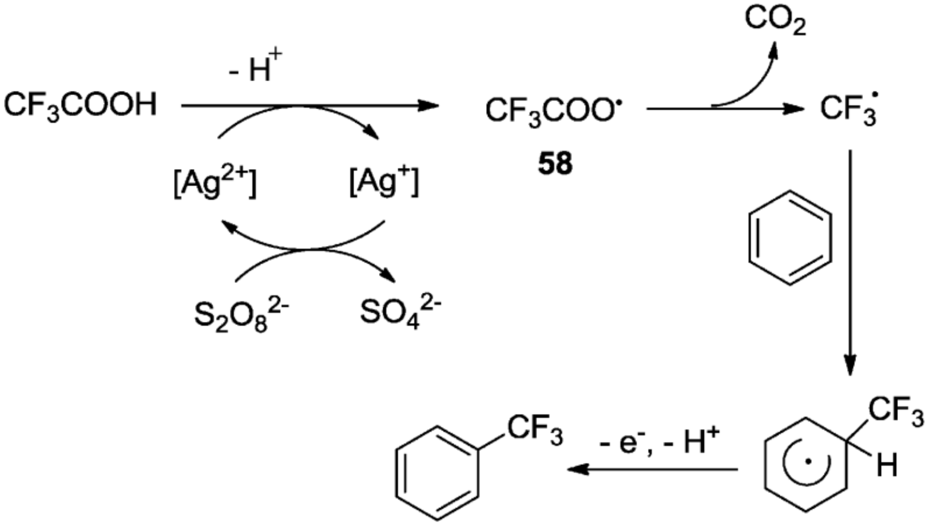
Y. Ye, S. H. Lee and M. S. Sanford, *Org. Lett.*, **2011**, *13*, 5464–5467.

Csp^2H-functionalization

- **2015, Zhang *et al.*:**



- TFA as source of –CF_3

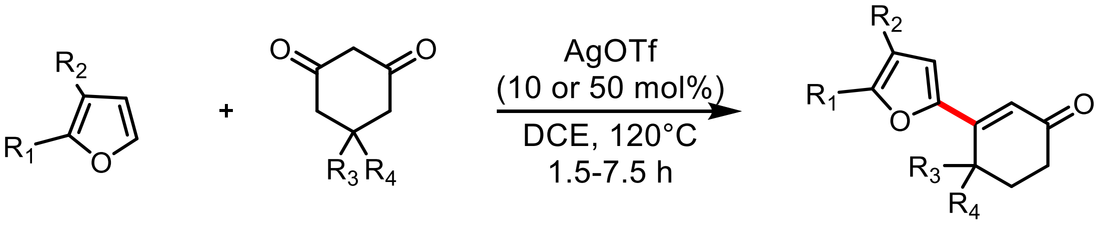


G. Shi, C. Shao, S. Pan, J. Yu and Y. Zhang, *Org. Lett.*, **2015**, *17*, 38–41.

Csp²H-functionalization

C-C bond formation: heterocycle coupling

- **2007, Arcadi *et al.*:**
- First example of direct coupling of furans with 1,3-dicarbonyls



R_1 = Me, Ph; R_2 = H, Me
R_3 = H, Me, Ph; R_4 = H, Me, Ph

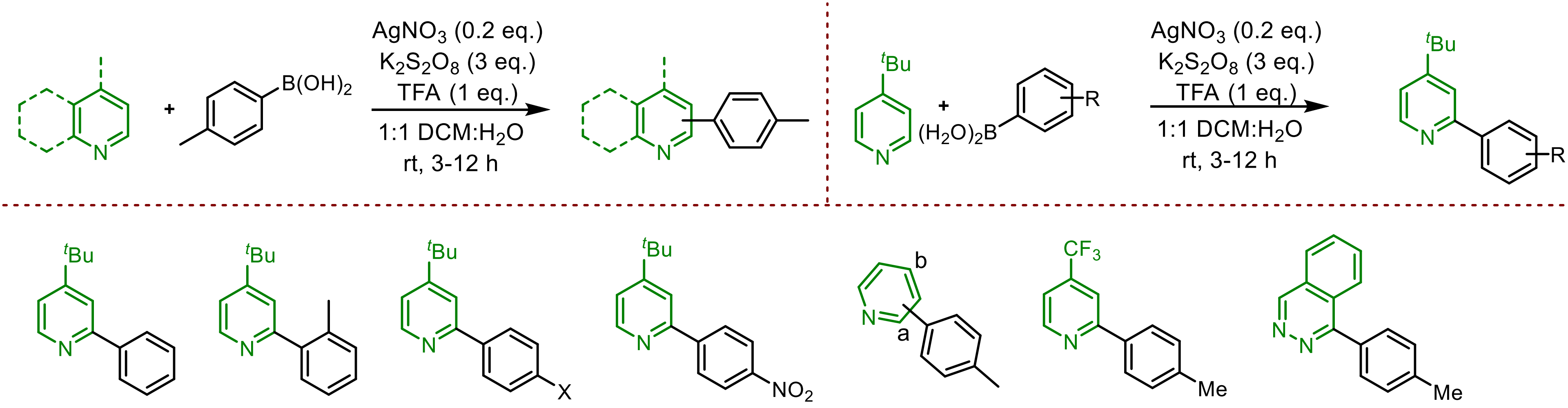
40-88% yields

- AgOTf more active than corresponding $AuBr_3$
- Previously reported procedures use Tl and Hg derivatives

A. Arcadi, M. Alfonsi and F. Marinelli, *J. Organomet. Chem.*, **2007**, *692*, 5322–5326.

Csp^{2}H-functionalization

- **2010, Baran *et al.*:**
  - Aimed to overcome the limitations of the Minisci reaction (access to aryl radicals)



57%

21%

X = Br, 44%
X = I, 42%

45%

68% (a:b = 2:1)

81%

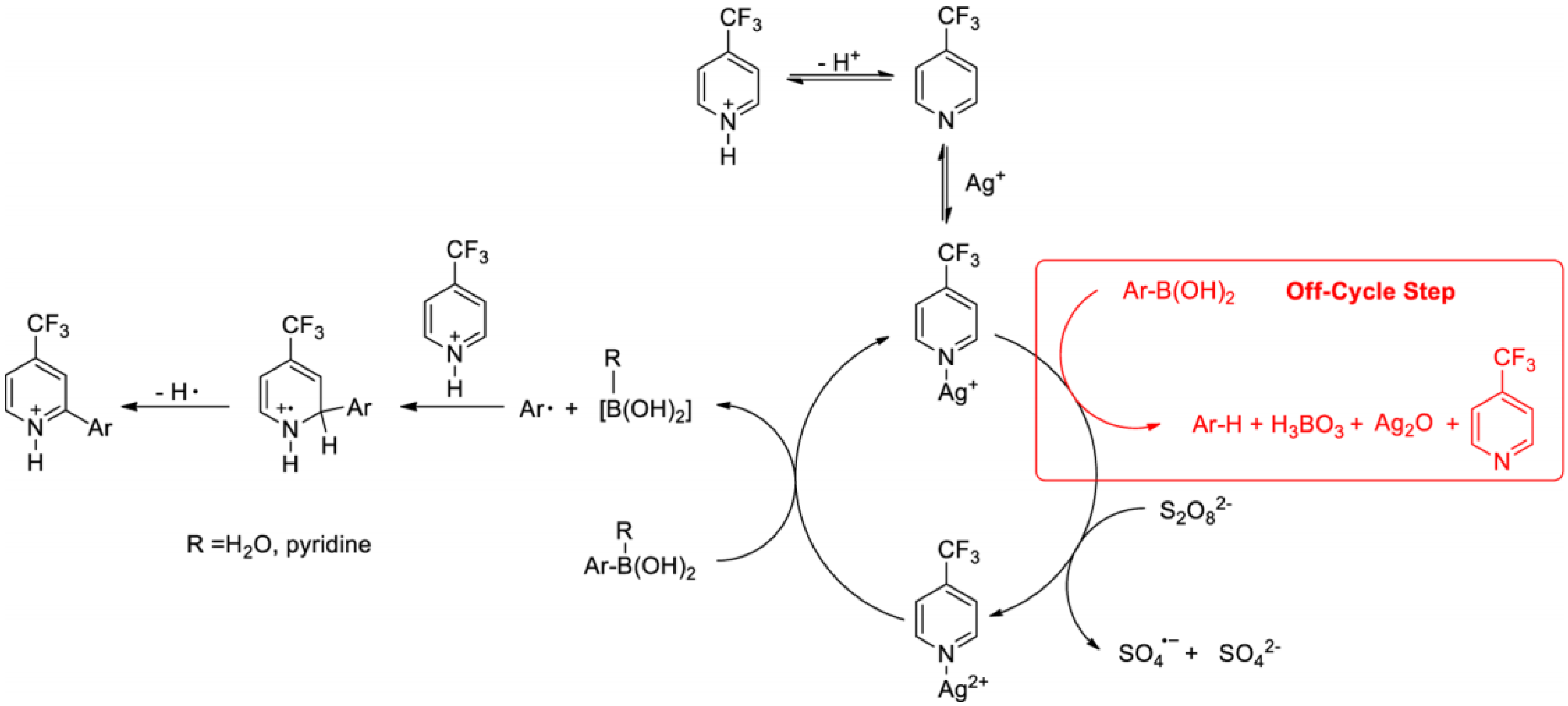
51%

- Direct arylation of electron-deficient heteroarenes using aryl radicals
- Inexpensive reagents
- Gram-scale, open flask

I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel and P. S. Baran, *J. Am. Chem. Soc.*, **2010**, *132*, 13194–13196.

Csp²H-functionalization

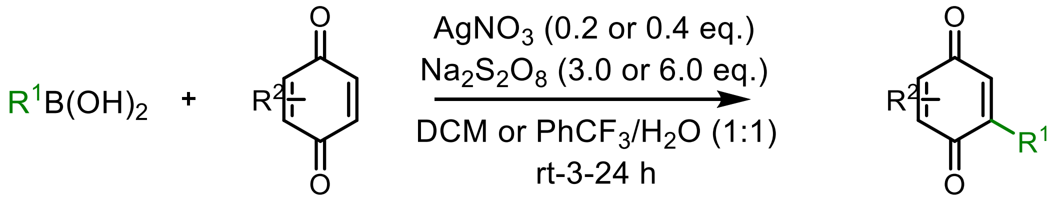
- **2013, Flowers *et al.***: *Mechanistic studies*



N. R. Patel and R. A. Flowers, *J. Am. Chem. Soc.*, **2013**, *135*, 4672–4675

Csp²H-functionalization

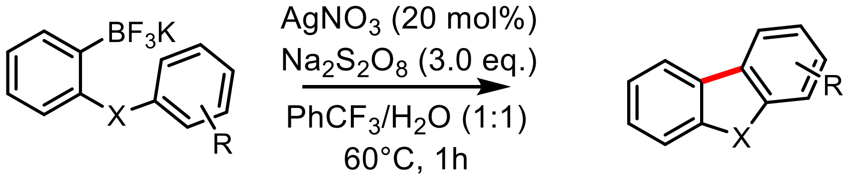
- **2011, Baran *et al.*:**[1]



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

72-91%

- **2011, Baran *et al.*:**[2] *Pschorr-type cyclization*



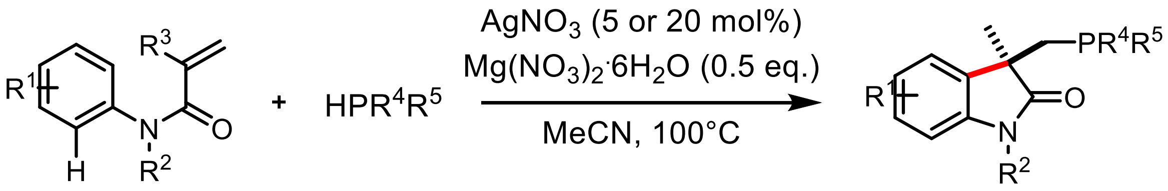
X = O, C(O)
R = H, OMe, F, CF_3, CO_2Me...

30-77% yields

---

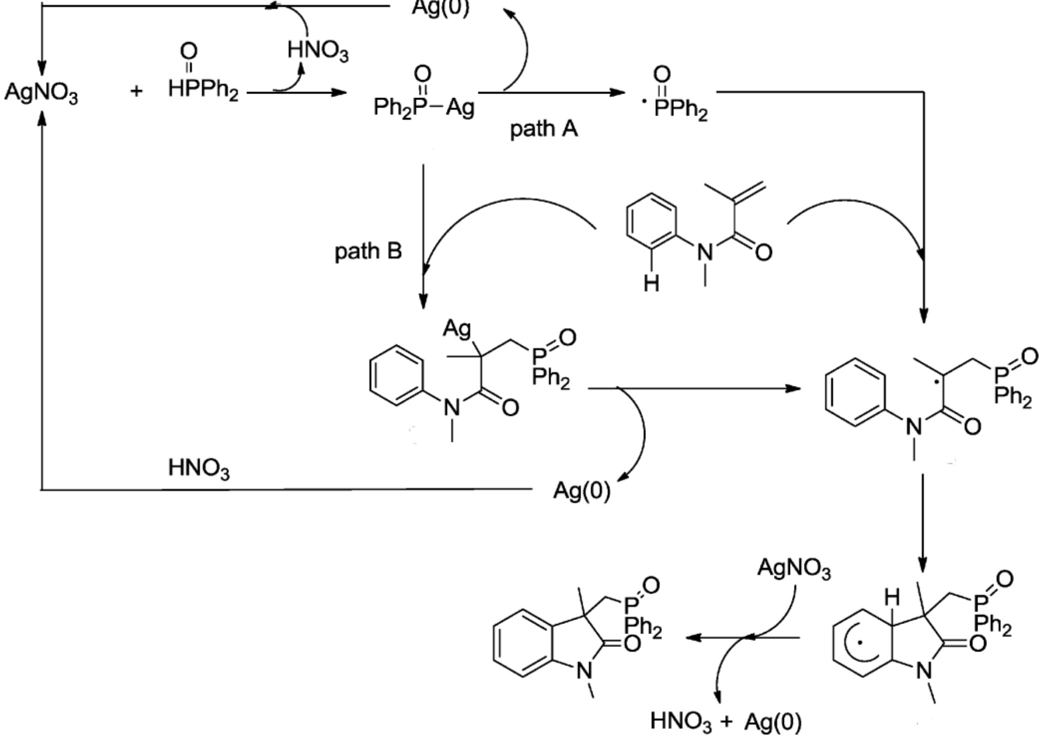
[1] Y. Fujiwara, V. Domingo, I. B. Seiple, R. Gianatassio, M. D. Bel and P. S. Baran, *J. Am. Chem. Soc.*, **2011**, *133*, 3292–3295.
[2] J. W. Lockner, D. D. Dixon, R. Risgaard and P. S. Baran, *Org. Lett.*, **2011**, *13*, 5628–5631.

Carbon phosphorylation reactions



R^1 = Me, MeO, halides; R^2= Me, Bn; R^3= Me, H.
R^4, R^5 = Ph, OEt.

43-82% yields

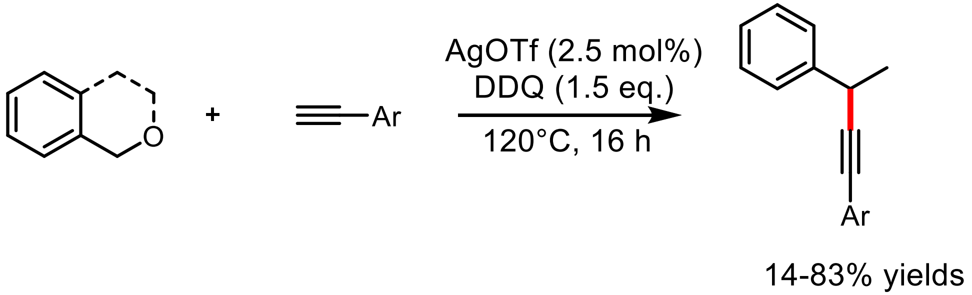


Y.-M. Li, M. Sun, H.-L. Wang, Q.-P. Tian and S.-D. Yang, *Angew. Chem., Int. Ed.*, **2013**, *52*, 3972–3976.

Silver-catalyzed Csp-H-functionalization

Csp-H-functionalization

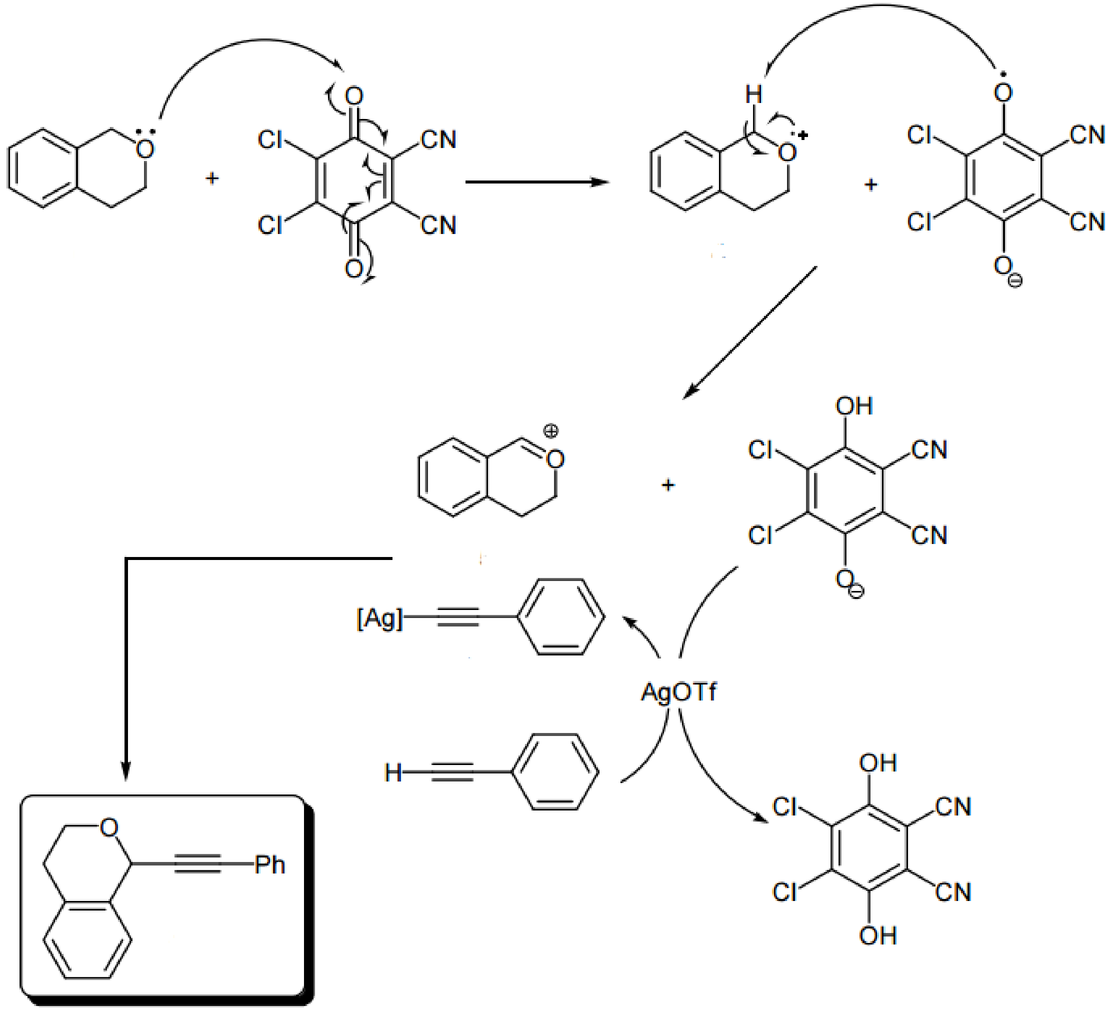
- **2010, Li *et al.*:**



- First example of oxidative coupling of terminal alkynes with benzylic ethers
- Cheap reagents

C. A. Correia and C.-J. Li, *Heterocycles*, **2010**, *82*, 555–562.

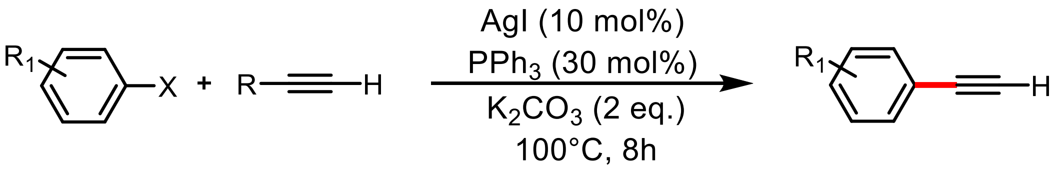
Csp-H-functionalization



C. A. Correia and C.-J. Li, *Heterocycles*, **2010**, *82*, 555–562.

Csp-H-functionalization

- **2006, Wang *et al.*:[1]** *Sonagashira coupling*

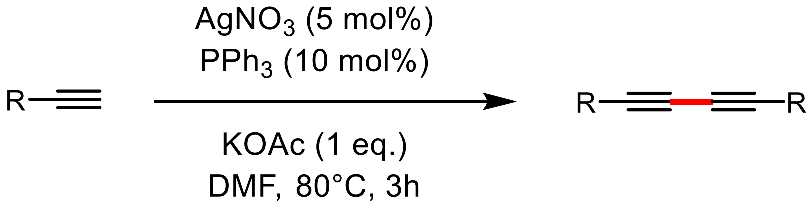


R_1 = I,Br; R = aryl, alkyl

20 examples
62-99% yield

- **No use of expensive Pd catalyst**
- **No CuI required**

- **2015, Yang *et al.*:** *Glaser coupling*



R = Aryl, 1-$C_{10}H_7$, 2-Pyridinyl, 1-Cyclohexenyl, n-C_4H_9, etc.

16 examples,
61-97% yield

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[1] P. Li and L. Wang, *Synlett*, **2006**, 2261–2265.

[2] G. Mo, Z. Tian, J. Li, G. Wen and X. Yang, *Organomet. Chem.*, **2015**, *29*, 231–233.

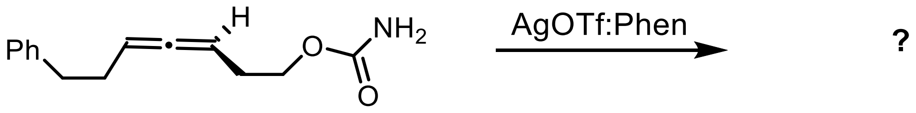
Conclusion

- **Advantages of Ag-catalyzed C-H functionalization**
  - Versatile reactivity
  - Often does not require expensive ligands
  - Cheap reagents can replace more expensive precious metals
  - Atom and step economy
  - Lower toxicity

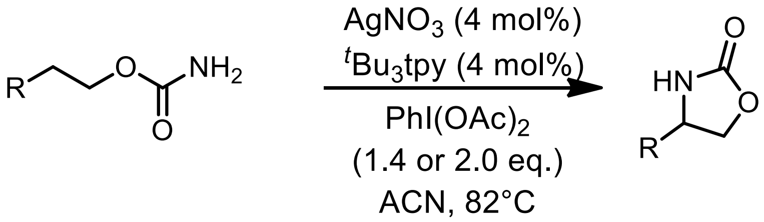
- **Challenges**
  - Sometimes requires harsh conditions
  - Highly dependent on reaction conditions
  - Poor selectivity
  - Less tunable
  - Relatively high catalyst loading→ lower TON

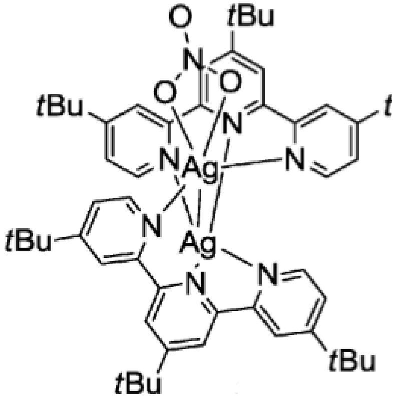
Questions

- What are the two possible outcomes for this reaction?



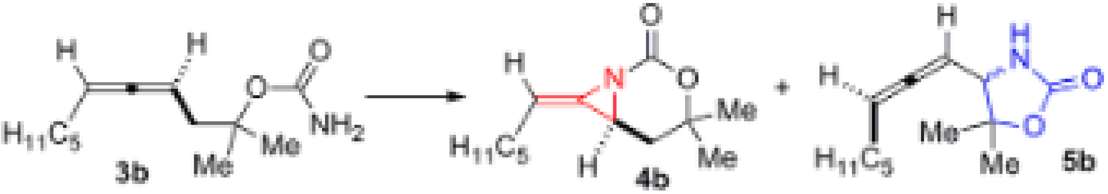
- In the following transformation, addition of a small amount of 4-tert-butyl pyridine provided better yields, while addition of an excess of this reagent had a detrimental effect on the reaction outcome. Why?





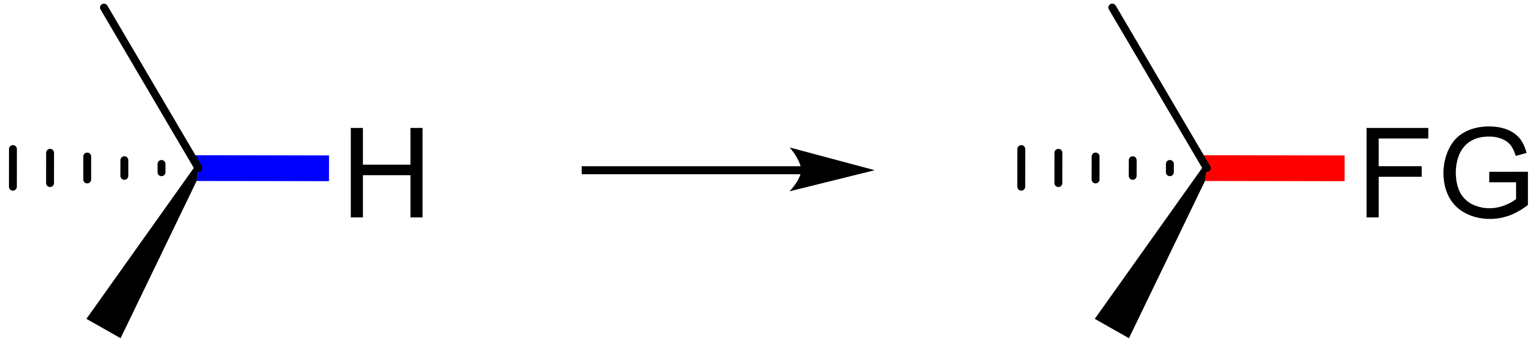
Answers

- 1.



- 2. Pyridine coordinates to one metal centre, changing the reactivity on the second. With an excess of reagent, both metal centres are coordinated, and the catalyst is poisoned.

Recent Advances in Non-Activated C(sp^3)-H Bond Functionalization



Abdusalom Suleymanov

PhD student, Laboratory of Supramolecular Chemistry, EPFL

01.06.2017

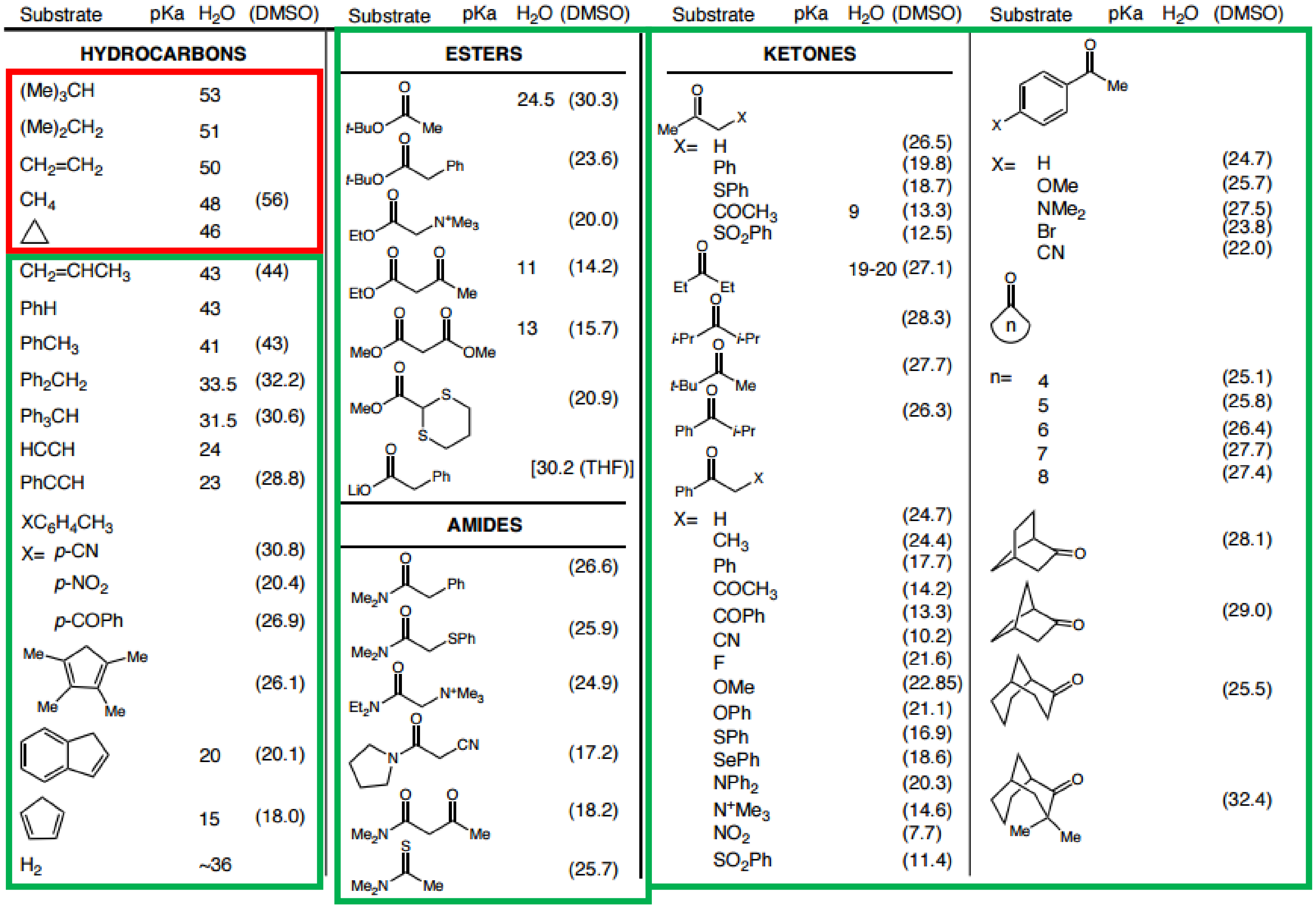
D.H. Ripin, D.A. Evans

pKa's of CH bonds in Hydrocarbons and Carbonyl Compounds

Chem 206

Non-Activated
+
(alpha C-H bond
of ethers and amines)

Activated
(benzyl, allyl,
alpha C-H bond of carbonyl
compounds)



HYDROCARBONS

Substrate	pKa H_2O	(DMSO)
$(Me)_3CH$	53	
$(Me)_2CH_2$	51	
$CH_2=CH_2$	50	
CH_4	48	(56)
△	46	
$CH_2=CHCH_3$	43	(44)
PhH	43	
$PhCH_3$	41	(43)
Ph_2CH_2	33.5	(32.2)
Ph_3CH	31.5	(30.6)
HCCH	24	
PhCCH	23	(28.8)
$XC_6H_4CH_3$		
X= *p*-CN		(30.8)
p-NO_2		(20.4)
p-COPh		(26.9)
Me Me Me Me		(26.1)
	20	(20.1)
	15	(18.0)
H_2	~36	

ESTERS

Substrate	pKa H_2O	(DMSO)
O t-BuO Me	24.5	(30.3)
O t-BuO Ph		(23.6)
O EtO N^+Me_3		(20.0)
O O EtO Me	11	(14.2)
O O MeO OMe	13	(15.7)
O MeO S S		(20.9)
O LiO Ph	[30.2 (THF)]	

AMIDES

Substrate	pKa H_2O	(DMSO)
O Me_2N Ph		(26.6)
O Me_2N SPh		(25.9)
O Et_2N N^+Me_3		(24.9)
O N CN		(17.2)
O O Me_2N Me		(18.2)
S Me_2N Me		(25.7)

KETONES

Substrate	pKa H_2O	(DMSO)
O Me X		
X= H		(26.5)
Ph		(19.8)
SPh		(18.7)
$COCH_3$	9	(13.3)
SO_2Ph		(12.5)
O Et Et	19-20	(27.1)
O i-Pr i-Pr		(28.3)
O t-Bu Me		(27.7)
O Ph i-Pr		(26.3)
O Ph X		
X= H		(24.7)
CH_3		(24.4)
Ph		(17.7)
$COCH_3$		(14.2)
COPh		(13.3)
CN		(10.2)
F		(21.6)
OMe		(22.85)
OPh		(21.1)
SPh		(16.9)
SePh		(18.6)
NPh_2		(20.3)
N^+Me_3		(14.6)
NO_2		(7.7)
SO_2Ph		(11.4)

Substrate	pKa H_2O	(DMSO)
O Me X		
X= H		(24.7)
OMe		(25.7)
NMe_2		(27.5)
Br		(23.8)
CN		(22.0)
O n		
n= 4		(25.1)
5		(25.8)
6		(26.4)
7		(27.7)
8		(27.4)
O		(28.1)
O		(29.0)
O		(25.5)
O Me Me		(32.4)

*Values <0 for H_2O and DMSO, and values >14 for water and >35 for DMSO were extrapolated using various methods.

For a comprehensive compilation of Bordwell pKa data see: http://www.chem.wisc.edu/areas/reich/pkatable/index.htm

pKa Table.3 11/4/05 1:44 PM

Unactivated $C(sp^3)$-H bond abundance

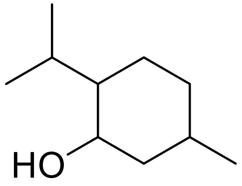
Feedstock chemicals

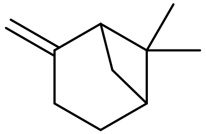
Hydrocarbons

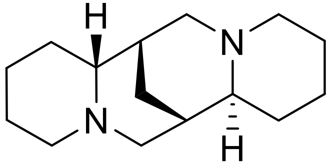
Fatty acids

Carbohydrates

Natural products

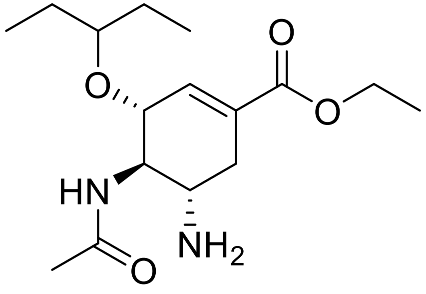

menthol


pinene

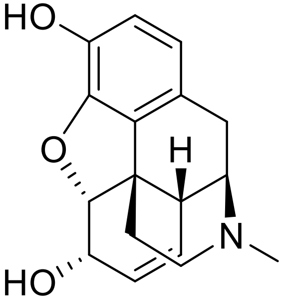


spartein

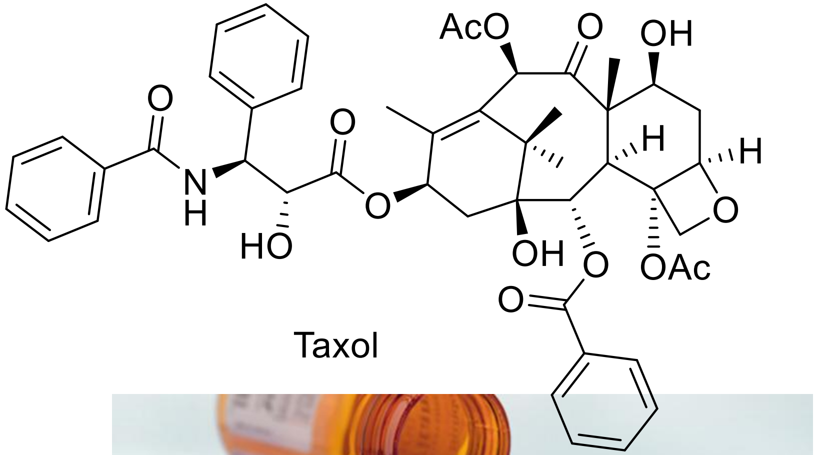
Pharmaceuticals



Tamiflu

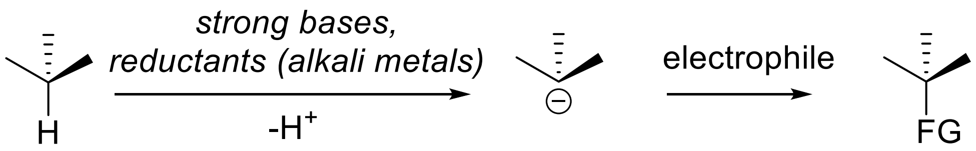


morphine



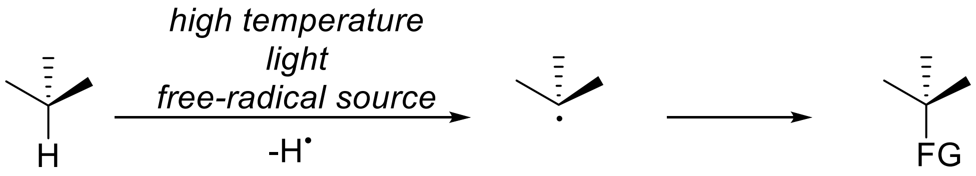
Taxol

Deprotonation



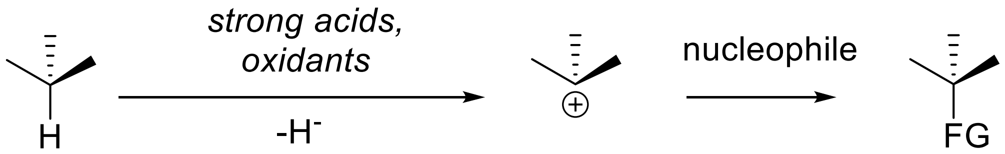
Very poor chemistry (mainly old papers)

Homolytic cleavage



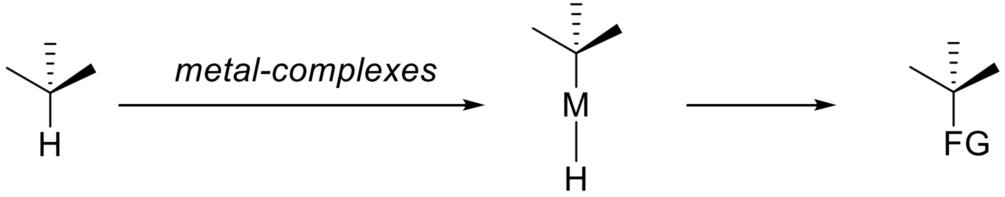
Developed chemistry (tons of papers and reviews)

Hydride abstraction



No systematic reviews. 20-30 scattered publications.

C-H insertion



Rapidly growing area. Several reviews are published.

Fundamental problems

High energy bond 90-100 kcal/mol

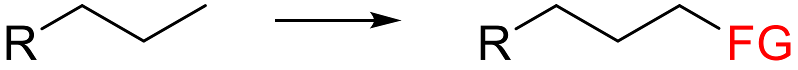
Low acidity pKa = 45-60

Unreactive molecular orbital profile

Outline

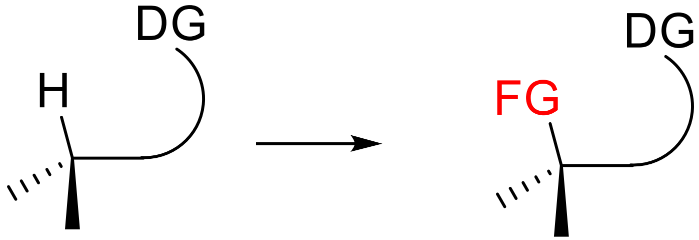
Metal-catalyzed alkane functionalization

Shilov-type C(sp^3)-H activation
Hartwig C(sp^3)-H borylation



Directed C(sp3)-H functionalization

C(sp^3)-H silylation
Carbon-Halogen bond promoted C(sp^3)-H functionalization
C(sp^3)-H activation directed by strongly coordinating ligand



Shilov reaction

$$CH_4 + H_2O + H_2PtCl_6 \longrightarrow CH_3OH + H_2PtCl_4 + 2HCl$$

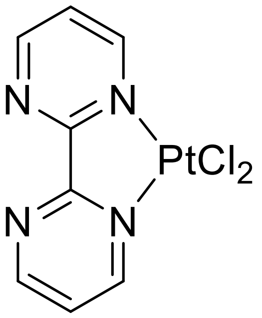
stoichiometric amount of Pt

Shilov and co-workers
Zh. Fiz. Khim. **1972**, *46*, 1353.
Coord. Chem. Rev. **1977**, *24*, 97

"Catalytica" modification

$$CH_4 + H_2SO_4 \xrightarrow[H_2SO_4]{\text{Hg(II) or Pt(II)}} CH_3HSO_4 + 2H_2O + SO_2$$

methane conversion 50-60%
selectivity 80-90%

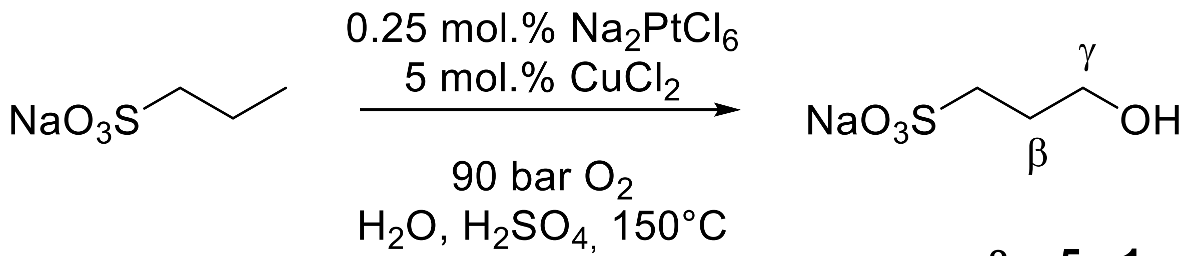


TON > 500

Periana and co-workers
Science **1993**, *259*, 340.
Science **1998**, *280*, 560

works well with methane, ethane
higher alkanes undergo further transformations

Synthetic application

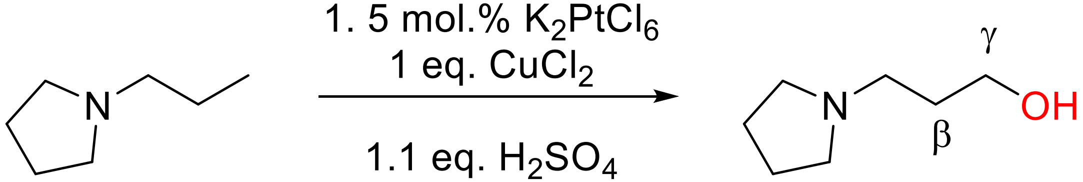


$\gamma : \beta$ = 5 : 1
TON = 52

Sen and co-workers
JACS **2001**, *123*, 1000.

Proximal CH bonds are deactivated by EWG group

Shilov-type remote C(sp3)-H hydroxylation of aliphatic amines



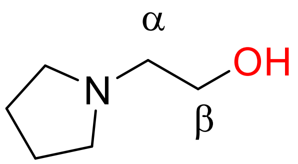
1. 5 mol.% K_2PtCl_6
1 eq. $CuCl_2$

1.1 eq. H_2SO_4
H_2O, 150°C, 24h

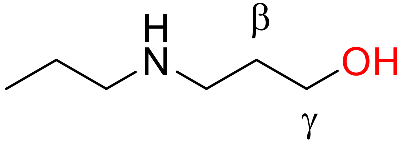
yield 85 %
γ : β = 20 : 1

Sanford and co-workers
JACS **2015**, *137*, 12796.

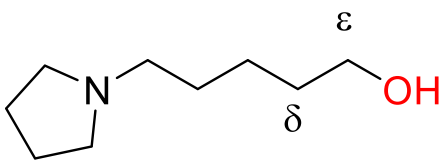
Scope & Limitations



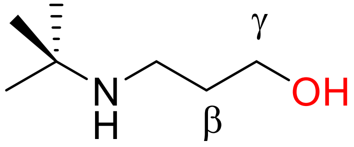
yield 35 %
β : α = >20 : 1



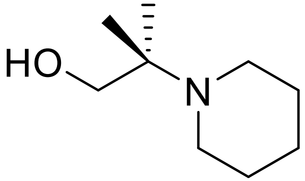
yield 97 %
γ : β = >20 : 1



yield 73 %
ε : δ = 2 : 1

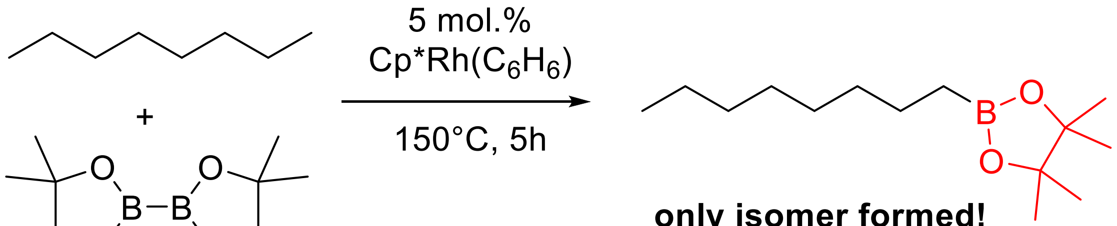


yield 46 %
γ : β = >20 : 1



yield <5 %

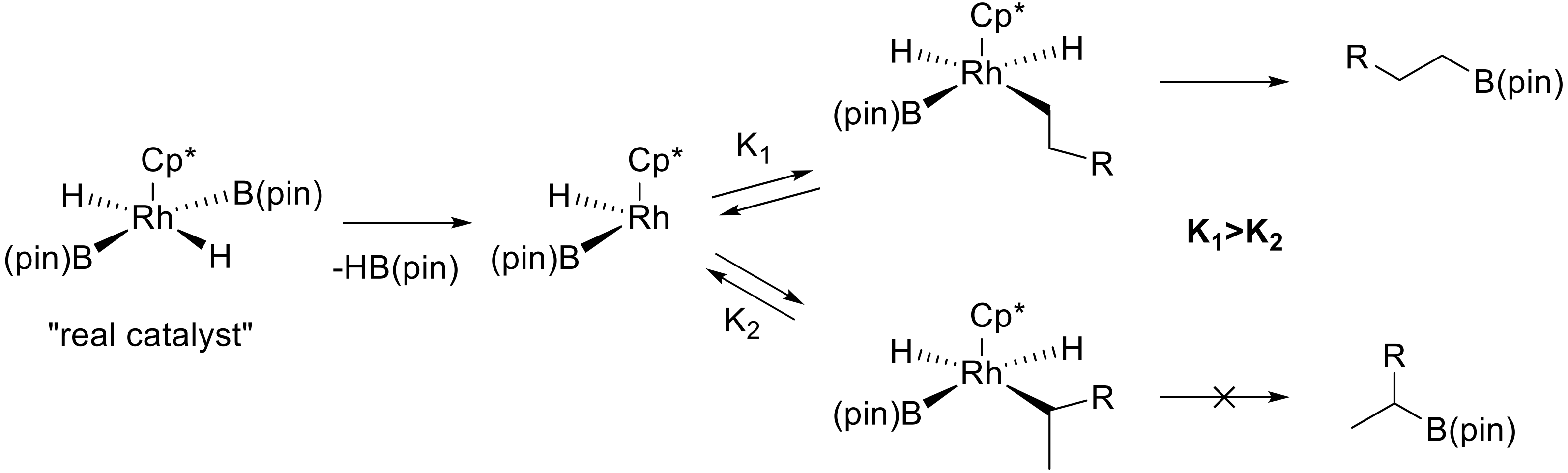
Hartwig alkane borylation



only isomer formed!
isolated yield 84%
based on B_2Pin_2

Hartwig and co-workers
Science **2000**, *287*, 1995.

Plausible mechanism

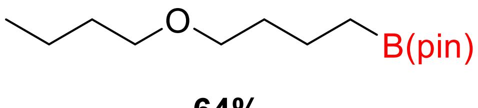


"real catalyst"

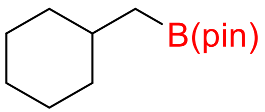
K_1>K_2

Hartwig and co-workers
JACS **2010**, *132*, 3078.

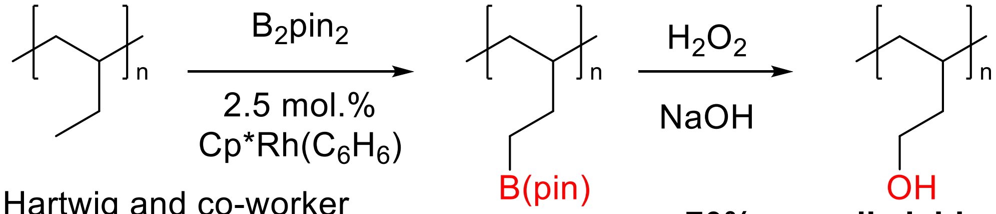
Scope & Limitations



64%
80h



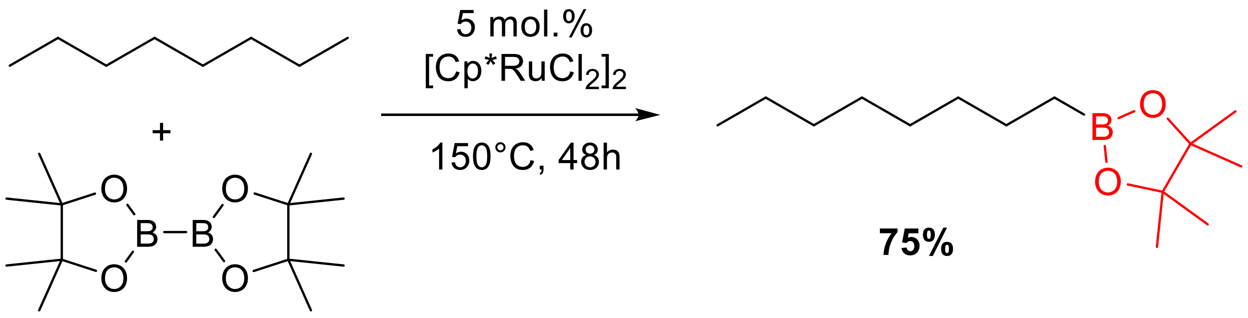
49%
80h



Hartwig and co-worker
JACS **2002**, *127*, 1164.

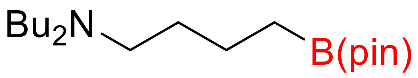
70% overall yield

Hartwig borylation (Ru catalyst)

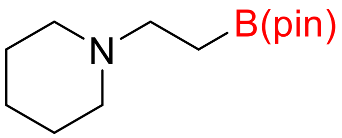


Hartwig and co-workers
JACS **2006**, *128*, 13684.

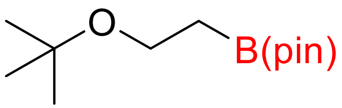
Scope & Limitations



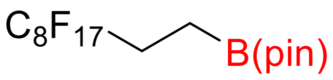
80%
24h



80%
48h



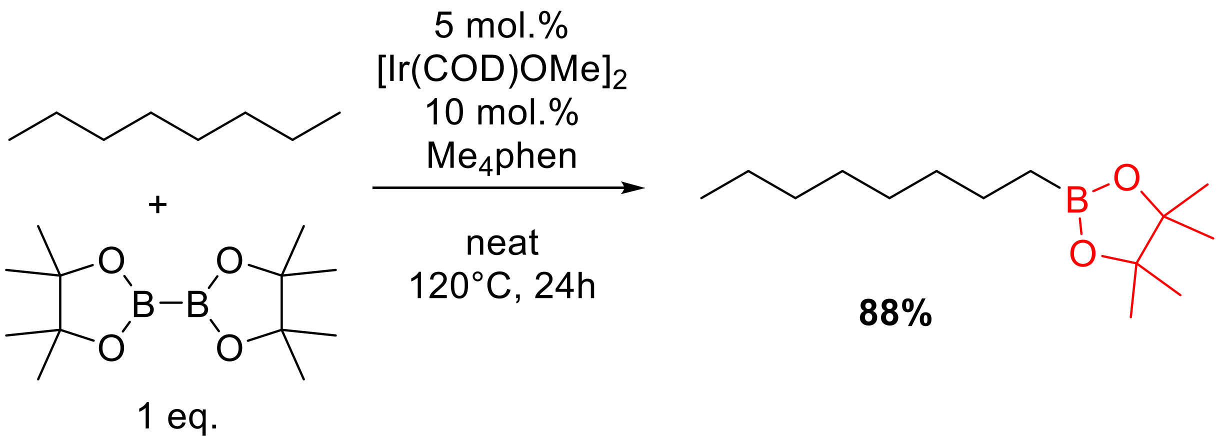
70%
48h



>90%
48h

Low functional group compatibility
Reagent used as a solvent
Only 1°-alkyl activation

Hartwig borylation (Ir catalyst)



5 mol.% $[Ir(COD)OMe]_2$
10 mol.% Me_4phen

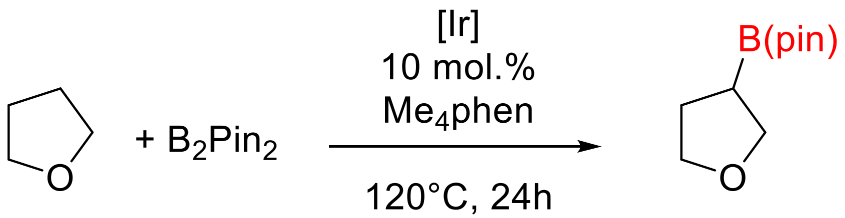
neat
120°C, 24h

1 eq.

88%

Liskey and Hartwig
JACS **2012**, *134*, 12422.

THF activation!

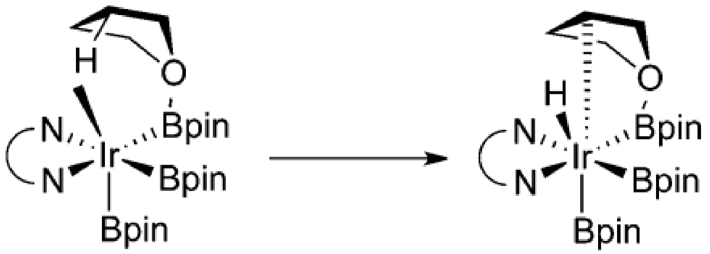


+ B_2Pin_2

[Ir]
10 mol.% Me_4phen

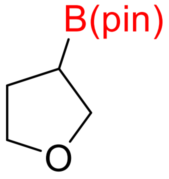
120°C, 24h

yield based on B_2pin_2
70% (10 mol.% $[Ir(COD)OMe]_2$)
104% (4 mol.% $(\eta^6\text{-mes})Ir(Bpin)_3$)

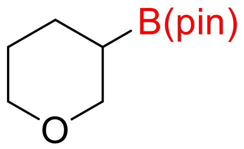


selectivity origin

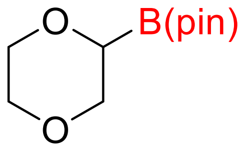
Scope & Limitations



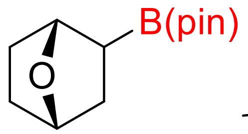
83%



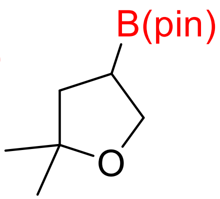
90%



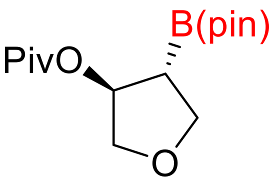
64%



63%



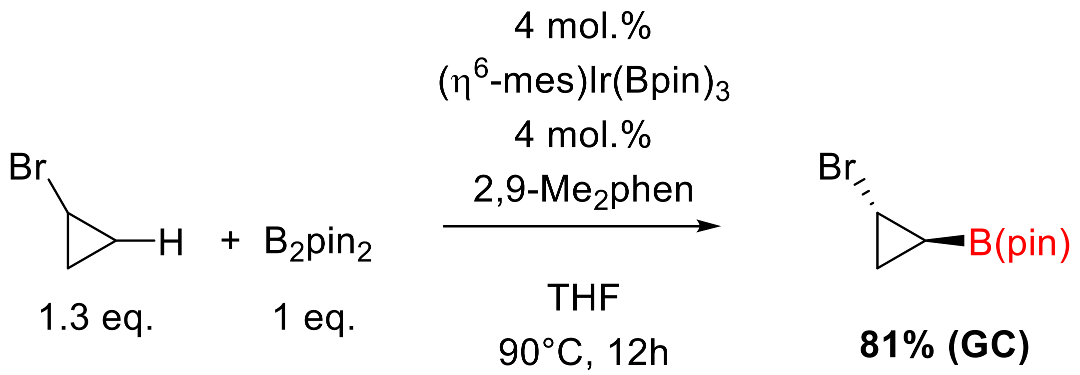
61%



40%

Hartwig borylation (Ir catalyst)

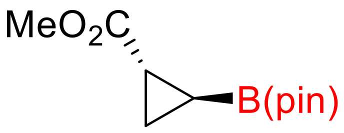
Cyclopropane borylation



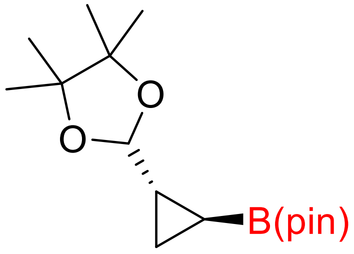
81% (GC)
48% (isolated)
d.r. 97:3

Liskey and Hartwig
JACS **2013**, *135*, 3375.

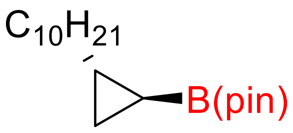
Scope & Limitations



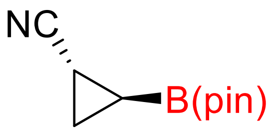
54%
d.r. 83:13



50% (GC)
d.r. 99:1

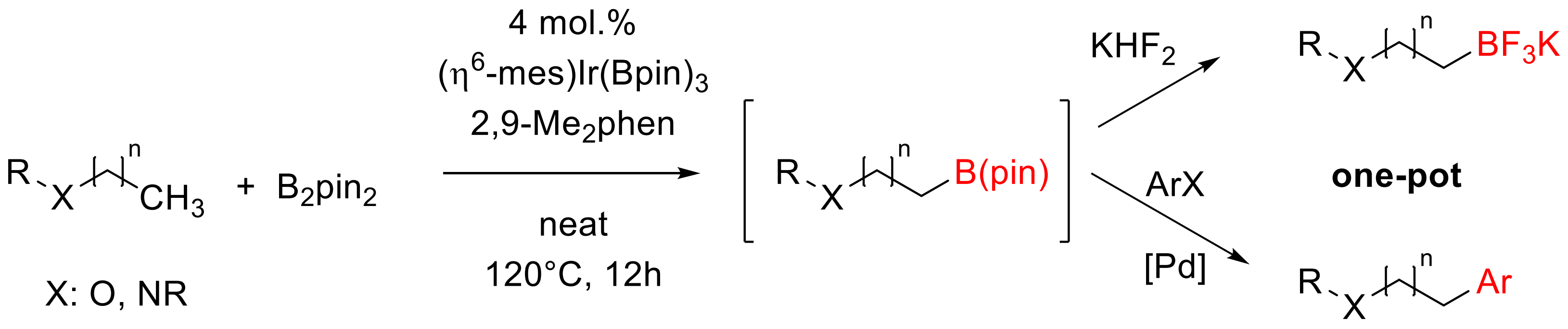


57% (GC)
d.r. 90:10



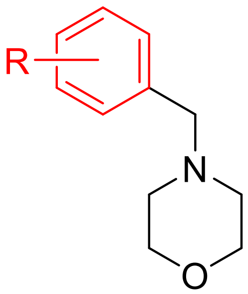
40%
d.r. 64:36

Hartwig borylation (Ir catalyst)

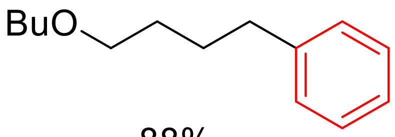


Liskey and Hartwig
JACS **2014**, *136*, 8755.

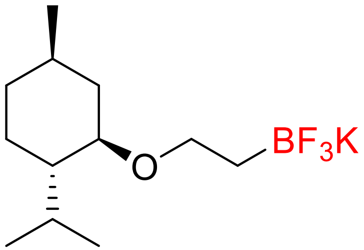
Scope & Limitations



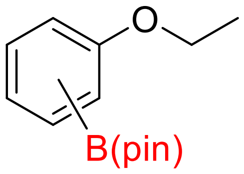
55-84%



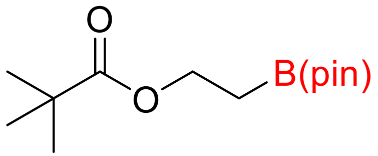
88%



56%



only aromatic ring
CH activation



60%

Methane borylation

$$CH_4 + B_2pin_2 \xrightarrow{\text{cat.}} CH_3Bpin$$

Sanford and co-workers
Science **2016**, *351*, 1421.

$$\underset{\text{35 bar}}{CH_4} + B_2pin_2 \xrightarrow[\text{cyclohexane, 150°C}]{\text{cat.}} \underset{\mathbf{1}}{CH_3Bpin} + \underset{\mathbf{2}}{CH_2(Bpin)_2}$$

Catalyst	**Loading**	**Time**	**CH_3Bpin: $CH_2(Bpin)_2$**	**Yield**	**TON**
$Cp^*RhC_6Me_6$	3 mol.%	14h	9:1	99%	33
$Cp^*RhC_6Me_6$	1.5 mol.%	14h	9:1	74%	49
$Cp^*RhC_6Me_6$	0.75 mol.%	14h	18:1	54%	68
$Cp^*RhC_6Me_6$	3 mol.%	1h	20:1	54%	18
$[Cp^*RuCl_2]_2$	3 mol.%	**6h**	**31:1**	**50%**	**17**
$[Cp^*RuCl_2]_2$	3 mol.%	14h	21:1	67%	22
$(Mes)Ir(Bpin)_3$ Me_4phen	3 mol.%	14h	4 : 1	45%	15

Mindiola and co-workers
Science **2016**, *351*, 1424.

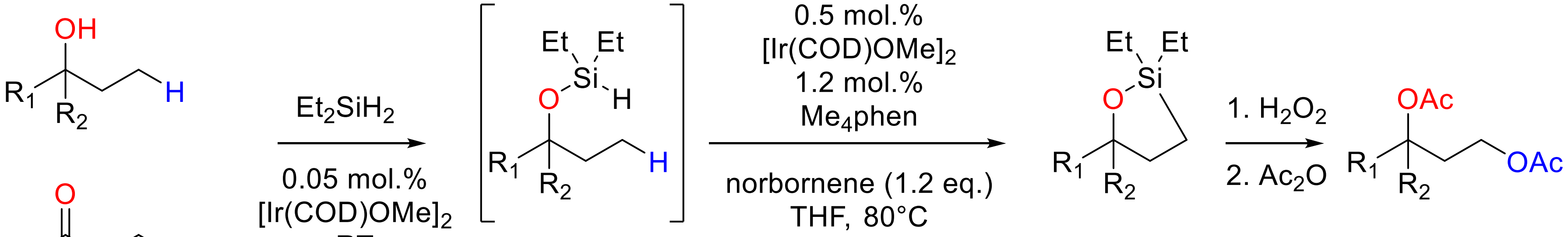
$$\underset{\text{34 bar}}{CH_4} + B_2pin_2 \xrightarrow[\text{cyclohexane, 150°C}]{[Ir(COD)Cl]_2,\ \text{dmpe}} \underset{\mathbf{1}}{CH_3Bpin} + \underset{\mathbf{2}}{CH_2(Bpin)_2}$$

Catalyst loading	**Time**	**CH_3Bpin: $CH_2(Bpin)_2$**	**Yield**	**TON**
25 mol.%	16h	9:1	9%	<1
10 mol.%	16h	5:1	14%	1
5 mol.%	16h	5:1	23%	4
1 mol.%	16h	5:1	25%	25
0.5 mol.%	16h	3:1	52%	104

Increasing the catalyst loading decreases TON !!!
Poisoning with Hg did not suppress catalysis

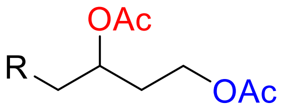
Hartwig silylation (Ir catalyst)

one-pot

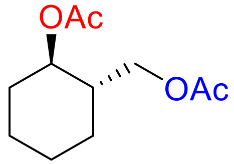


Simmons and Hartwig
Nature **2012**, *483*, 70.

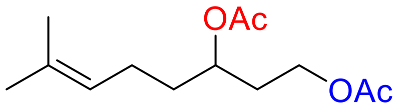
Scope & Limitations



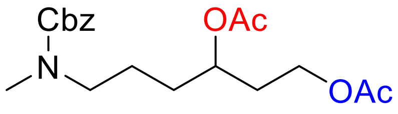
R = Ph, 53%
R = Bu, 66%



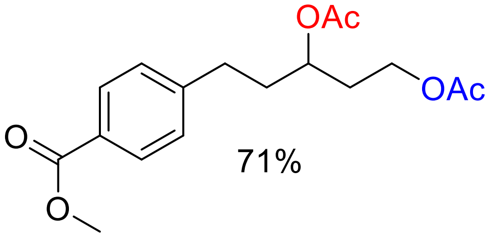
70%



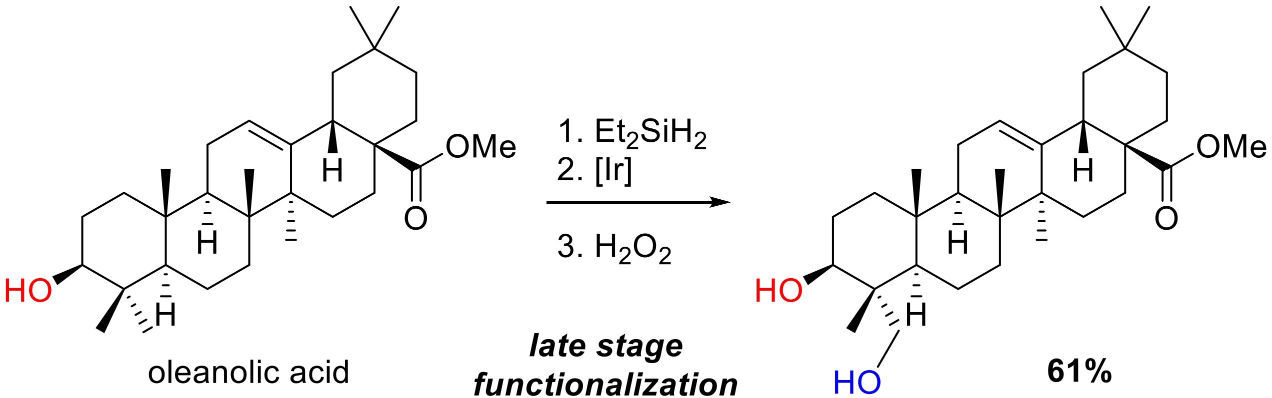
60%



70%



71%



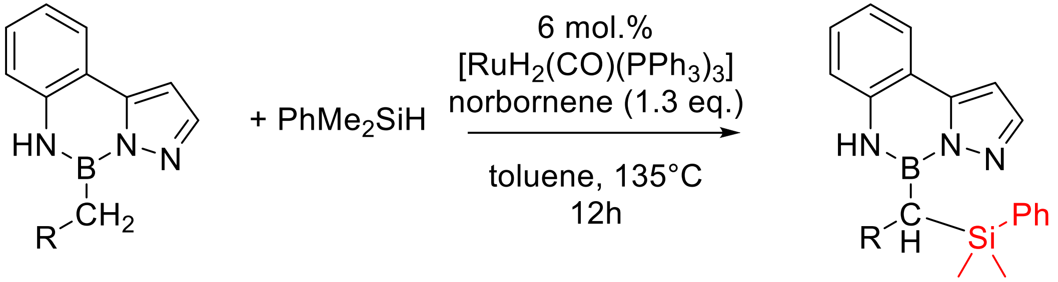
oleanolic acid
methyl ester

late stage functionalization

61%
hederagenin
methyl ester

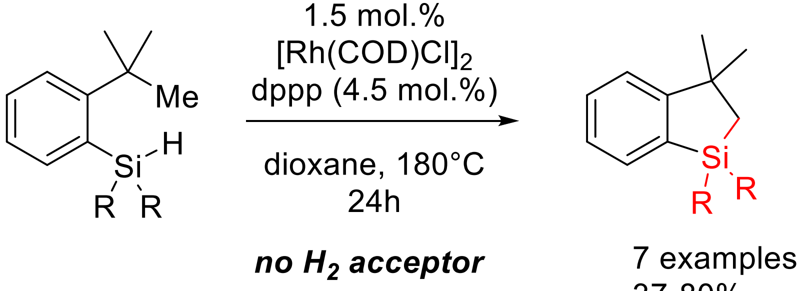
JOC **2007**, 3500
10 step synthesis from
oleanolic acid

Other silylation examples



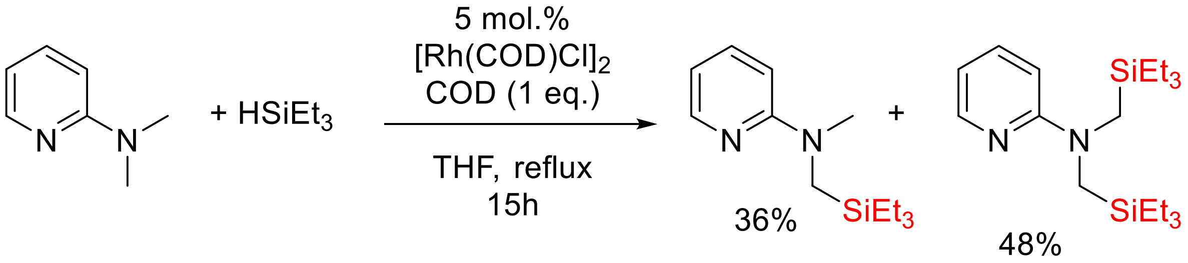
5 examples
28-85%

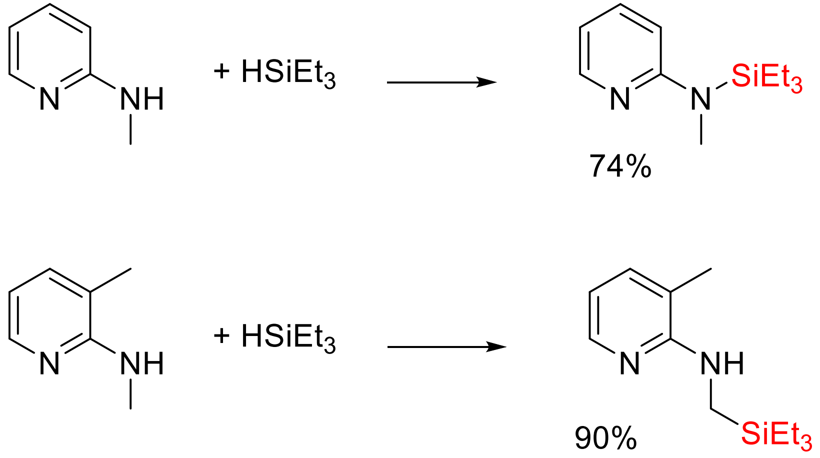
Suginome and co-workers
Chem. Lett. **2011**, *40*, 916.



7 examples
37-80%

Takai and co-workers
OL **2013**, *15*, 426.

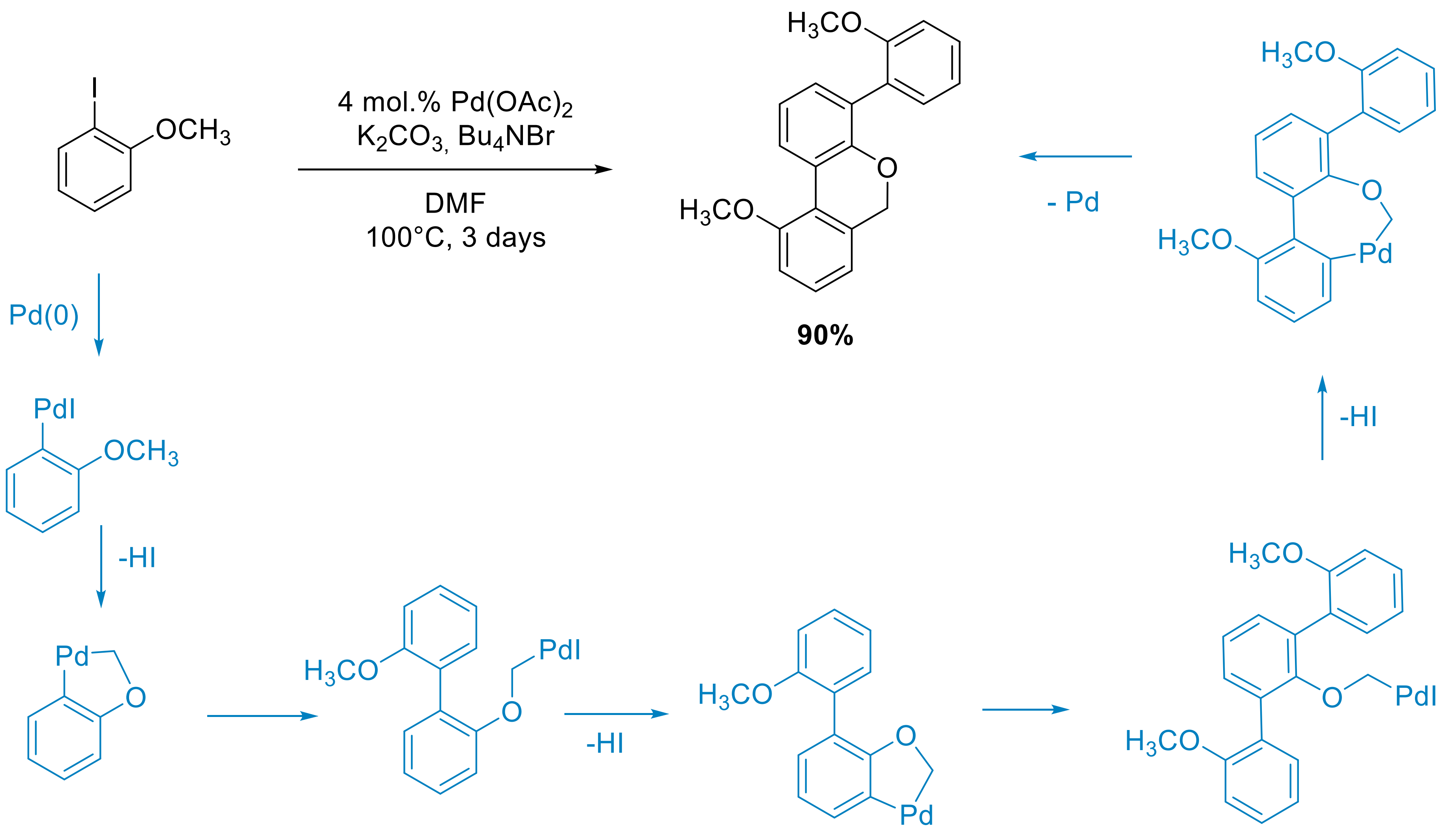




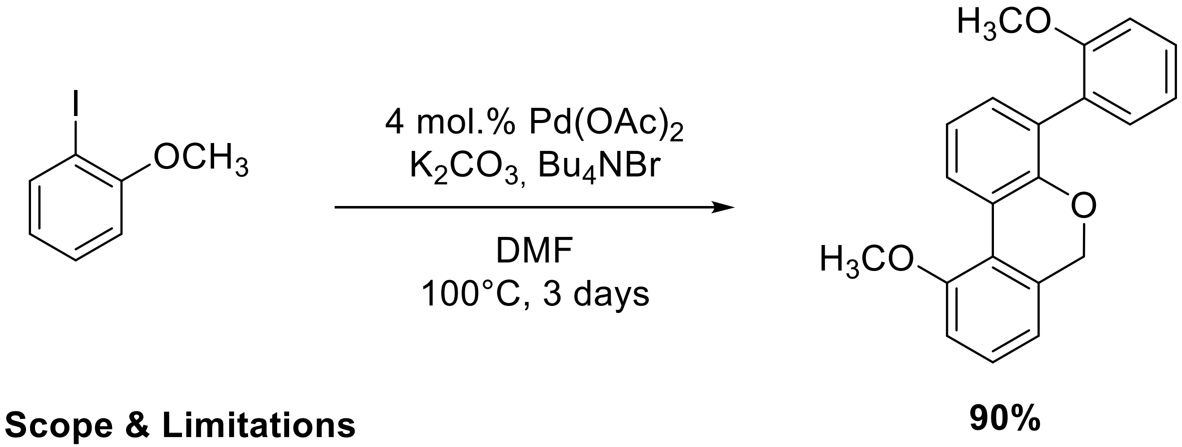
Sato and co-workers
Chem. Asian J. **2013**, *8*, 2970.

Carbon-Halogen bond promoted C(sp3)-H functionalization

Dyker
ACIE **1992**, *31*, 1023.

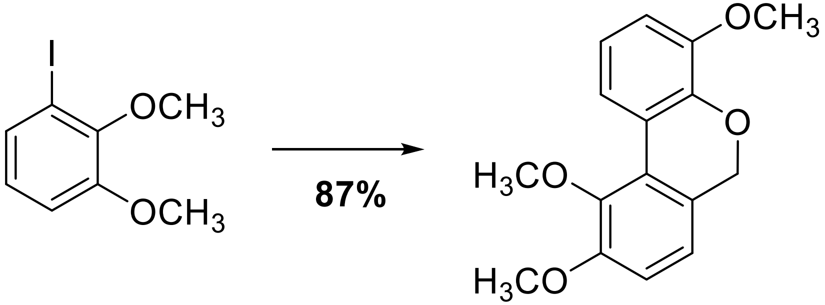


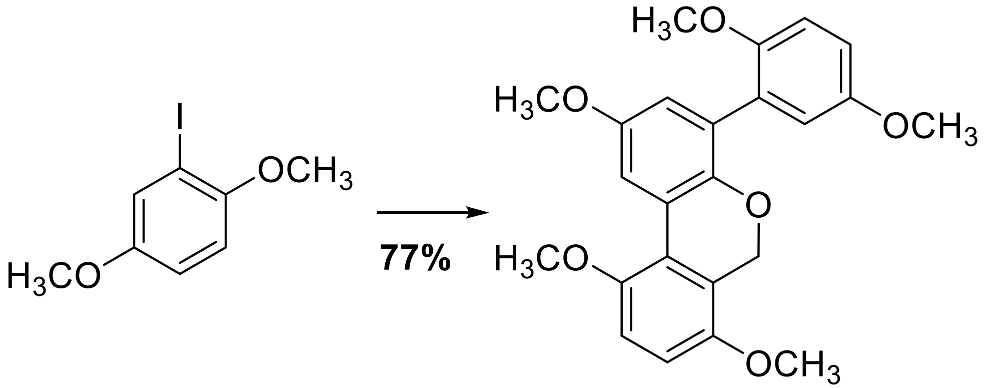
Carbon-Halogen bond promoted C(sp3)-H functionalization

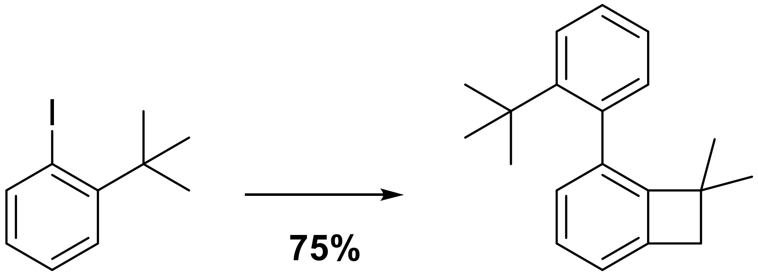


Dyker
ACIE **1992**, *31*, 1023.
JOC **1993**, *58*, 6426.
ACIE **1994**, *33*, 103.

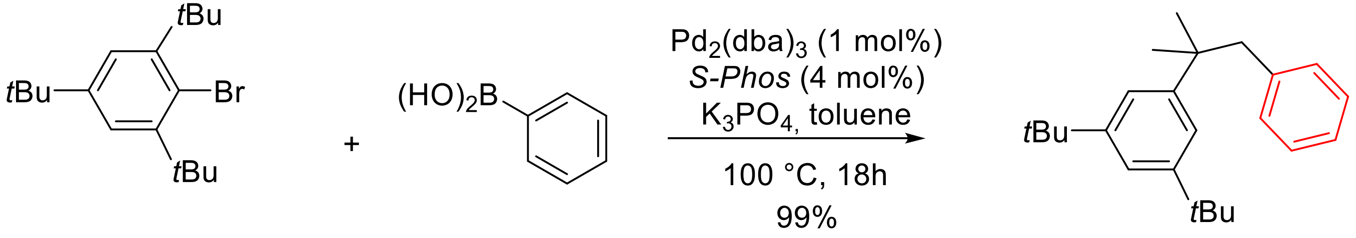
Scope & Limitations





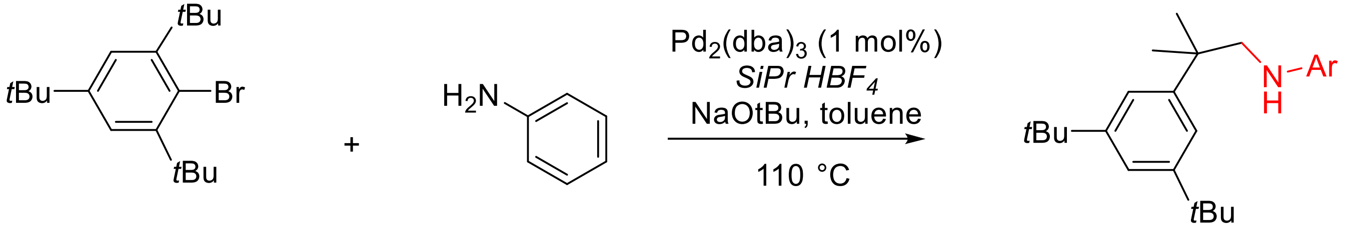


Carbon-Halogen bond promoted C(sp3)-H functionalization



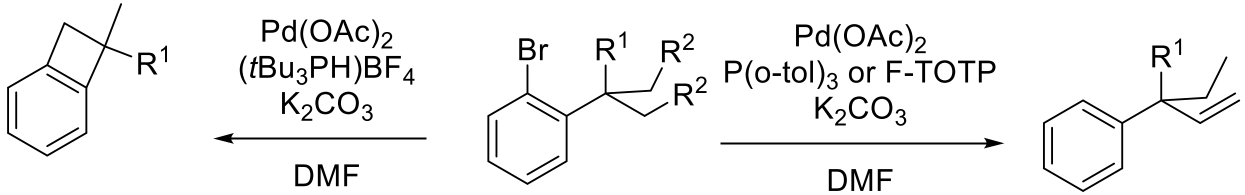
$Pd_2(dba)_3$ (1 mol%)
S-Phos (4 mol%)
K_3PO_4, toluene
100 °C, 18h
99%

Buchwald and co-workers
JACS **2005**, *127*, 4685.



$Pd_2(dba)_3$ (1 mol%)
SiPr HBF₄
NaOtBu, toluene
110 °C

Buchwald and co-workers
ACIE **2011**, *50*, 8647.



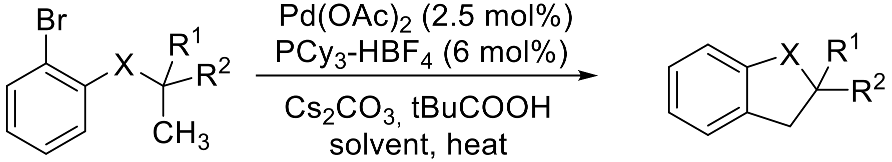
R^2 = H

$Pd(OAc)_2$
$(tBu_3PH)BF_4$
K_2CO_3
DMF
140 °C

$Pd(OAc)_2$
$P(o\text{-}tol)_3$ or F-TOTP
K_2CO_3
DMF
100-150 °C

R^1 = CN, COOR, CH_2OTIPS
R^2 = Me

Baudoin and co-workers
ACIE **2003**, *42*, 5736.
JACS **2008**, *130*, 15157.
ACIE **2009**, *48*, 179.
CEJ **2007**, *13*, 792.
Adv. Synth. Catal. **2007**, *349*, 2054.



$Pd(OAc)_2$ (2.5 mol%)
$PCy_3\text{-}HBF_4$ (6 mol%)
Cs_2CO_3, tBuCOOH
solvent, heat

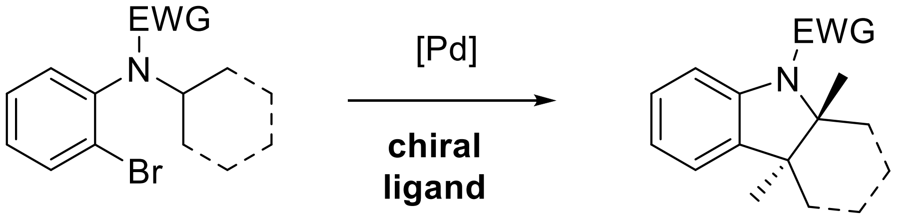
X= O, N-PG

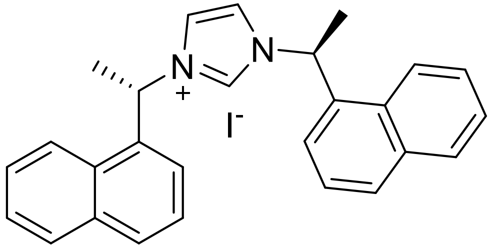
Fagnou and co-workers (X=O)
JACS **2007**, *129*, 14570.

Fujii and Ohno (X=N-PG)
OL **2008**, *10*, 1759.

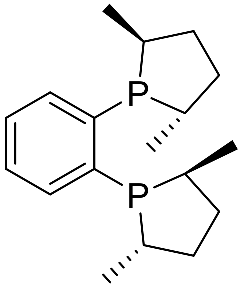
Carbon-Halogen bond promoted C(sp3)-H functionalization

Enantioselective versions

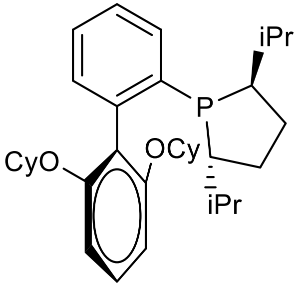




up to 95% ee
Kundig and co-workers
ACIE **2011**, *50*, 7438.



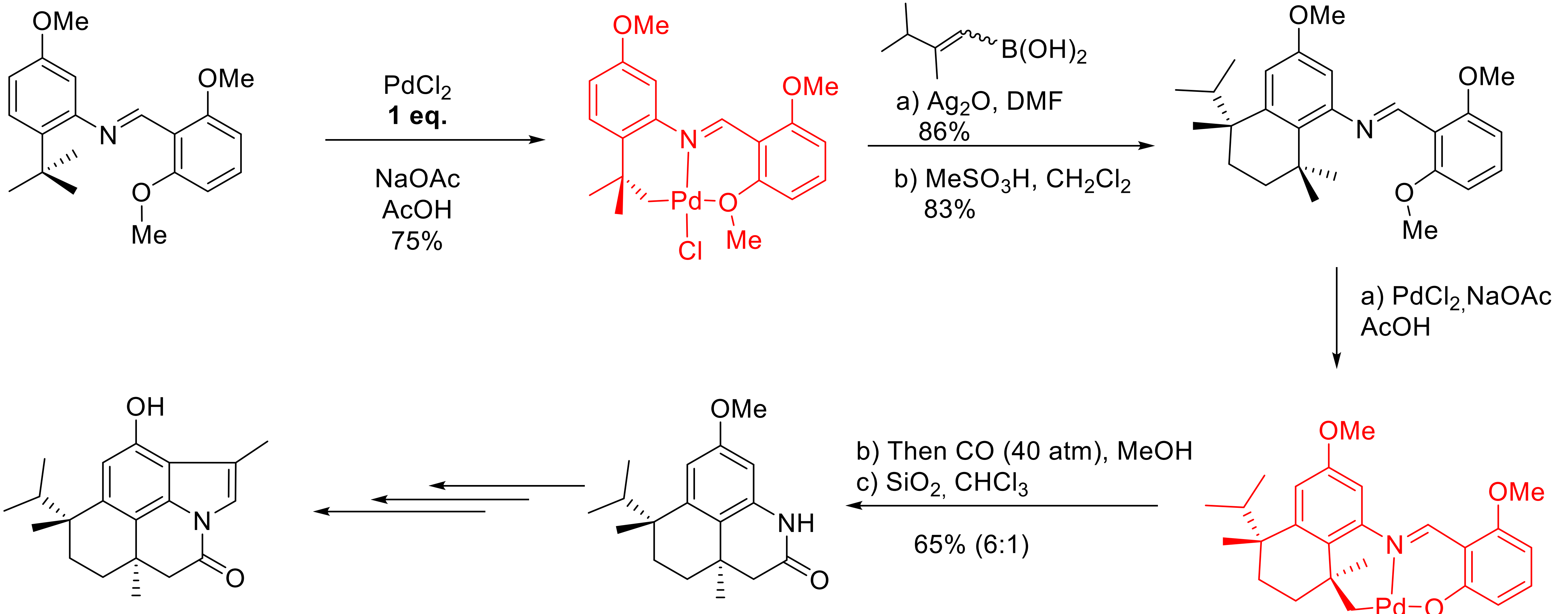
46-93% ee
Kagan and co-workers
Chem. Commun. **2011**, *47*, 11483.



up to 95% ee
Cramer and co-workers
ACIE **2012**, *51*, 2238.

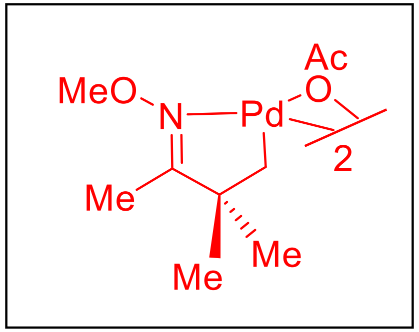
C(sp3)-H activation directed by strongly coordinating ligand

Sames and co-workers
JACS **2002**, *124*, 11856.

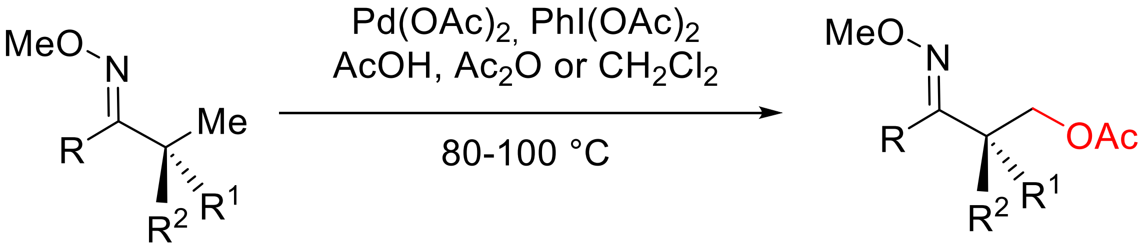


Teleocidin B-4 Core

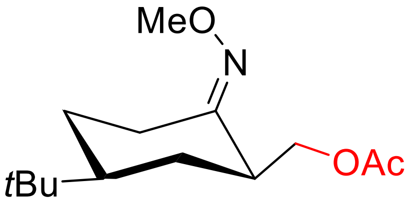
C(sp3)-H activation directed by strongly coordinating ligand
***β* CH activation**



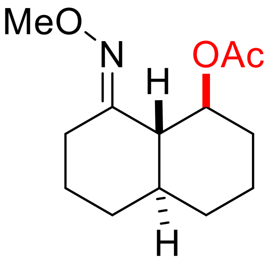
First isolated by
McDonald and Shaw
J. Chem. Soc., Dalton Trans. **1980**, 1992



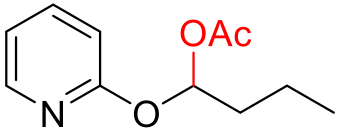
Sanford and co-workers
JACS **2004**, *126*, 14570.
OL **2010**, *12*, 532.



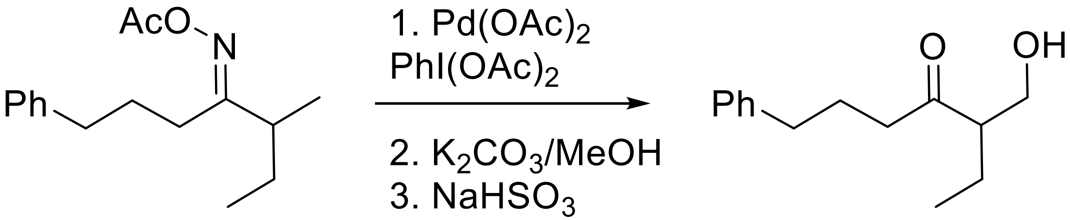
5 min, 86%



81%

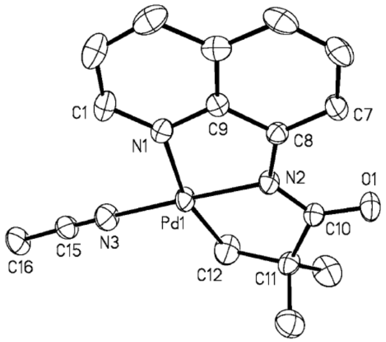


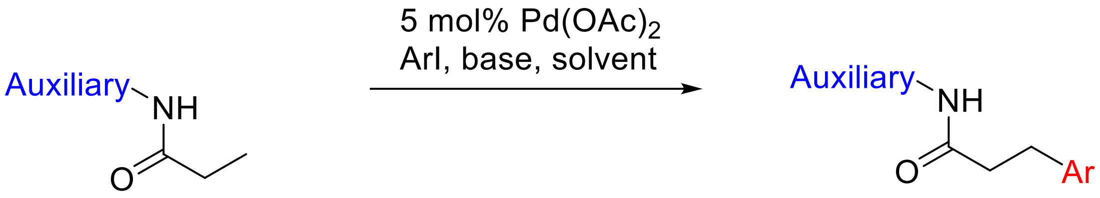
44%



one-pot 80%

C(sp3)-H activation directed by strongly coordinating ligand
***β* CH activation**



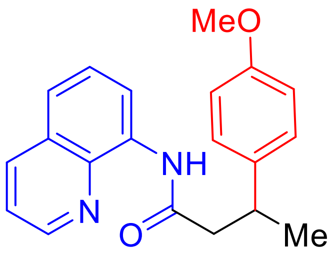


5 mol% Pd(OAc)$_2$
ArI, base, solvent

Daugulis and co-workers
JACS **2005**, *127*, 13154.
JACS **2010**, *132*, 3965.
OL **2005**, *7*, 3657.

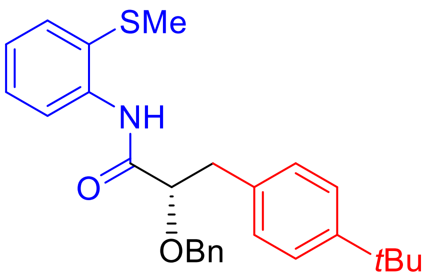
Problem: 5-20% of diarylated product forms

8-aminoquinolines



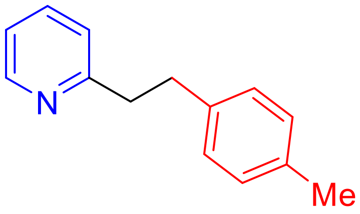
neat, AgOAc
110 °C 92%

2-methylthioaniline

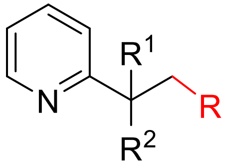


t-Amyl-OH, K_2CO_3
90 °C 65%

pyridine



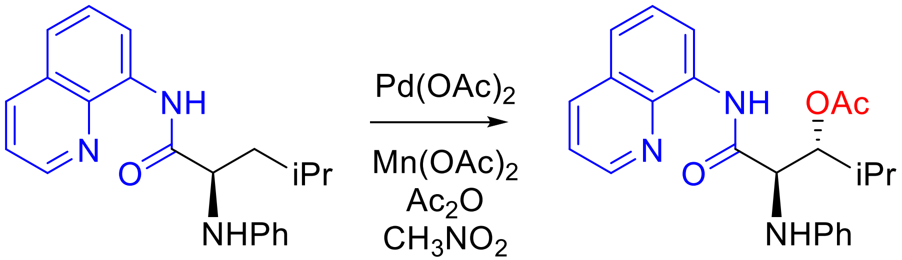
AcOH, AgOAc
110 °C 51%



10 mol% Pd(OAc)$_2$
R-B(OH)$_2$:
Ag$_2$O, BQ, 100 °C
tert-amyl alcohol

Yu and co-workers
JACS **2006**, *128*, 12634

α aminoacid functionalization



Pd(OAc)$_2$
Mn(OAc)$_2$
Ac$_2$O
CH$_3$NO$_2$
80°C

Corey and coworkers
OL **2006**, *8*, 3391.

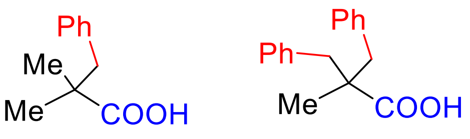
60%, d.r. 15:1

C(sp3)-H activation directed by strongly coordinating ligand

β CH activation

carboxylate

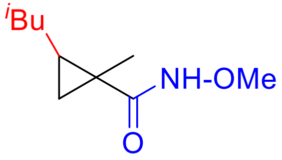
w/o NaOAc
no reaction



70%, 5:2

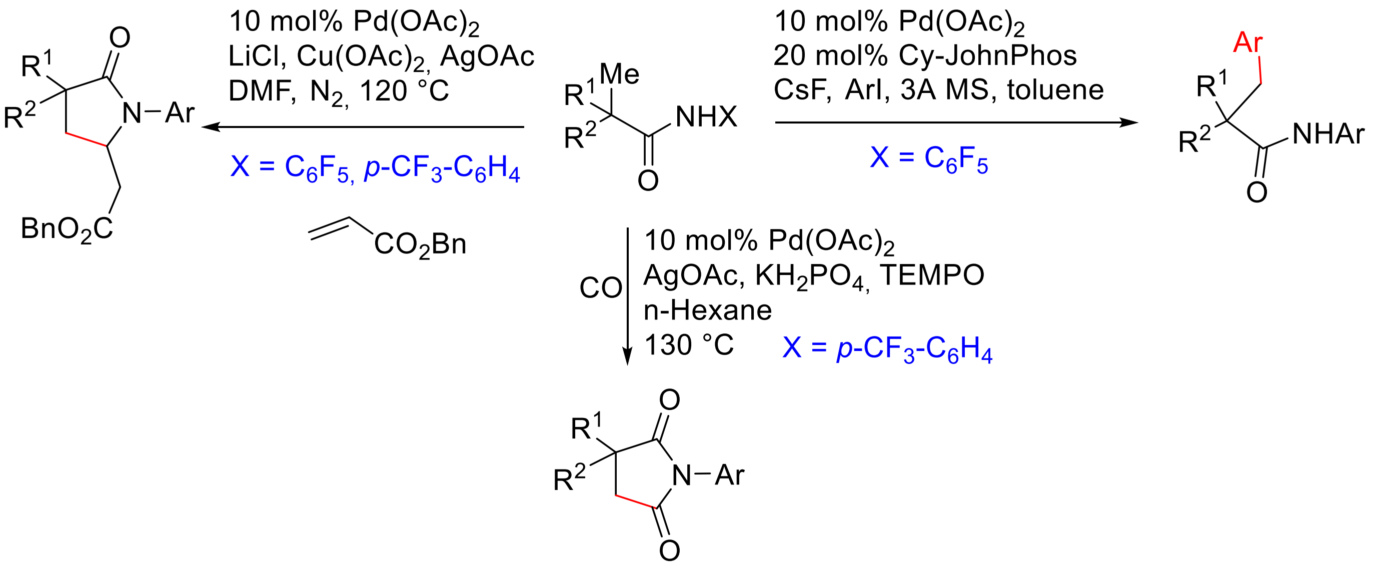
10 mol% $Pd(OAc)_2$
Ag_2CO_3, K_2HPO_4
tBuOH, **NaOAc**
130 °C, 3h
PhI

hydroxamate



10 mol% $Pd(OAc)_2$
BQ, Ag_2O, K_2CO_3
2,2,5,5-tetramethylTHF
70 °C, 18h
^{i}Bu-$B(OH)_2$
58%

carboxamide



10 mol% $Pd(OAc)_2$
LiCl, $Cu(OAc)_2$, AgOAc
DMF, N_2, 120 °C
X = C_6F_5, p-CF_3-C_6H_4

10 mol% $Pd(OAc)_2$
20 mol% Cy-JohnPhos
CsF, ArI, 3A MS, toluene
X = C_6F_5

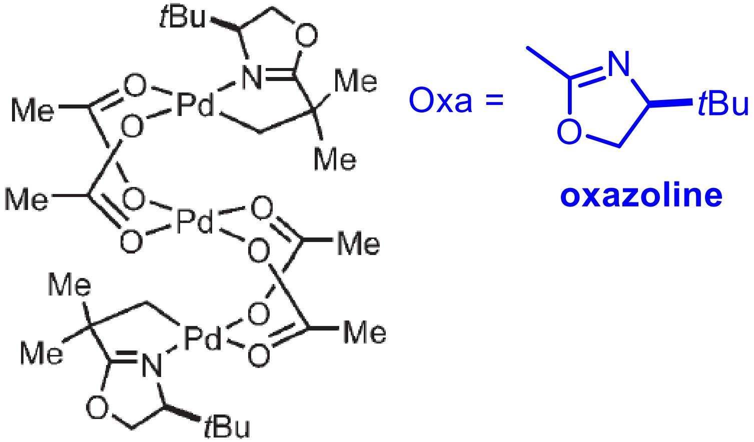
10 mol% $Pd(OAc)_2$
AgOAc, KH_2PO_4, TEMPO
n-Hexane
130 °C
X = p-CF_3-C_6H_4

Yu and co-workers
JACS **2007**, *129,* 3510.
JACS **2008**, *130,* 7190.
JACS **2009**, *131,* 9886.
JACS **2010**, *132,* 3680.
JACS **2010**, *132,* 17378.

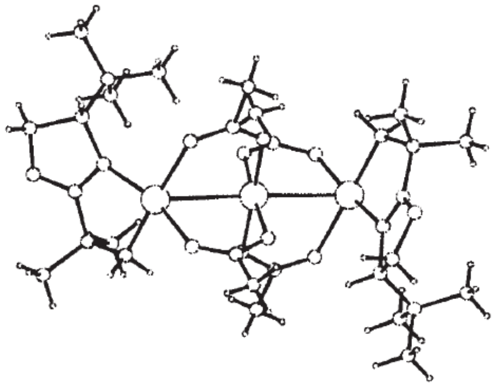
C(sp3)-H activation directed by strongly coordinating ligand

Diastereoselective β CH activation

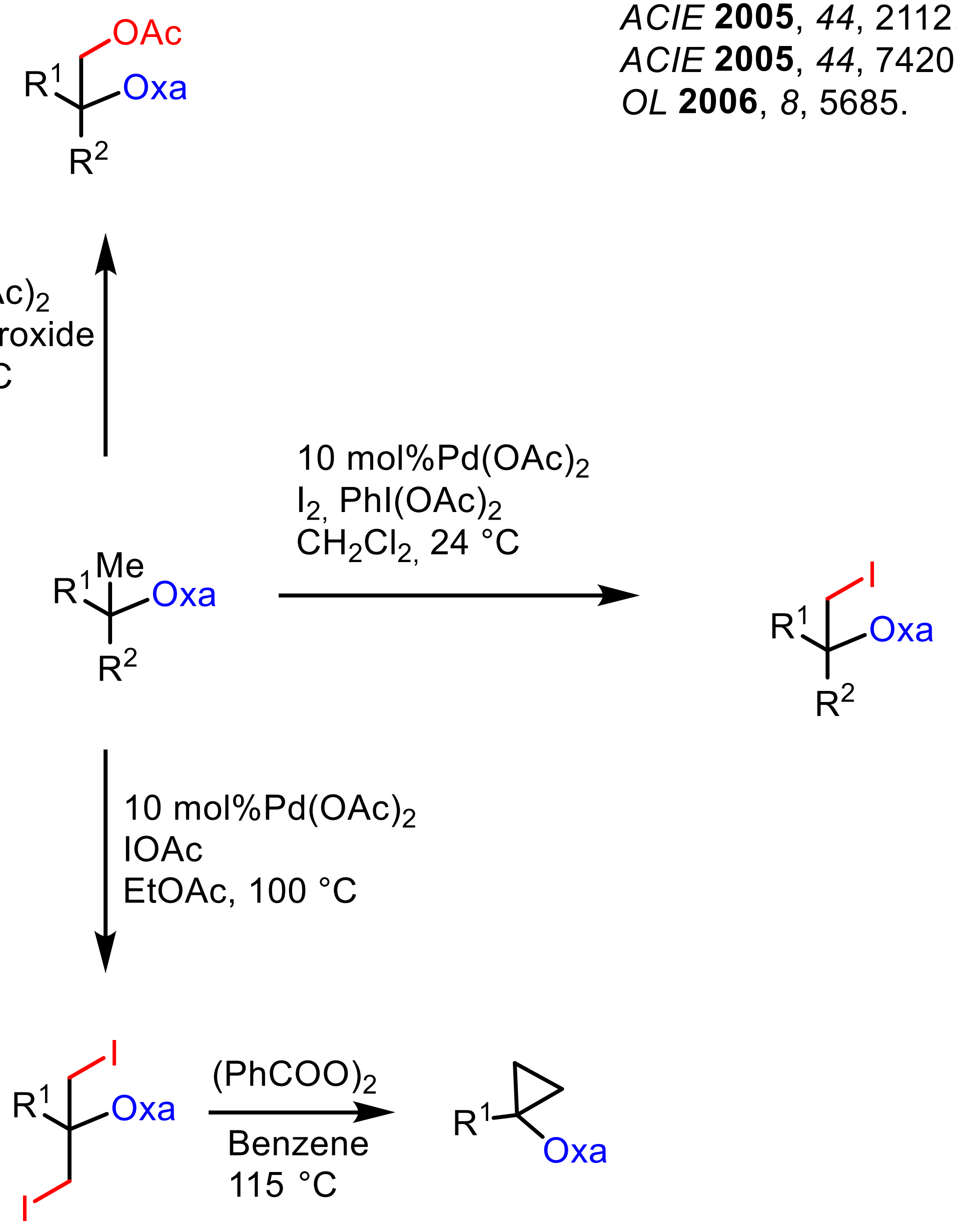
Yu and co-workers
ACIE **2005**, *44*, 2112.
ACIE **2005**, *44*, 7420.
OL **2006**, *8*, 5685.



trinuclear alkyl-Pd complex



Diastereselectivity of reactions d.r. up to 99:1



10 mol%Pd(OAc)$_2$
Dodecanoyl peroxide
Ac$_2$O, O$_2$, 50 °C

10 mol%Pd(OAc)$_2$
I$_2$, PhI(OAc)$_2$
CH$_2$Cl$_2$, 24 °C

10 mol%Pd(OAc)$_2$
IOAc
EtOAc, 100 °C

(PhCOO)$_2$
Benzene
115 °C

Conclusions

Alkane functionalization

Shilov-type electrophilic CH activation

Hartwig-type borylation

Harsh conditions (poor FG compatibility)

Early stage functionalization of relatively simple alkanes, cycloalkanes, ethers, amines

Directed C(sp^3)-H functionalization

Hartwig-type silylation

C-Hal bond promoted CH activation

Ligand promoted CH activation

Expensive noble metal catalysts
Sophisticated ligand environment
Difunctionalization

Relatively mild conditions (good FG compatibility)
Late stage functionalization

Reviews

1. Ryabov, "Mechanisms of Intramolecular Activation of C-H Bonds in Transition-Metal Complexes" *Chem. Rev.* **1990**, *90*, 403.
2. Shilov, "Activation of C–H Bonds by Metal Complexes" *Chem. Rev.* **1997**, *97*, 2879.
3. Davies, "Catalytic Enantioselective C-H Activation by Means of Metal-Carbenoid-Induced C-H Insertion" *Chem. Rev.* **2003**, *103*, 2861.
4. Sames, "C–H Bond Functionalization in Complex Organic Synthesis" *Science* **2006**, *312*, 67.
5. Davies, " Catalytic C–H Functionalization by Metal Carbenoid and Nitrenoid Insertion" *Nature* **2008**, *451*, 417.
6. Sanford, "Palladium-Catalyzed Ligand-Directed CH Functionalization Reactions" *Chem. Rev.* **2010**, *110*, 1147.
7. Baudoin, "Transition Metal-Catalyzed Arylation of Unactivated C(sp3)-H Bonds" *Chem. Soc. Rev.* **2011**, *40*, 4902.
8. Davies, (Rh-cat. Carbene insertion to CH bond) *Chem. Soc. Rev.* **2011**, *40*, 1857.
9. Hartwig, "Regioselectivity of the Borylation of Alkanes and Arenes" *Chem. Soc. Rev.* **2011**, *40*, 1992.
10. Hartwig, "Borylation and Silylation of C–H Bonds: A Platform for Diverse C–H Bond Functionalizations" *Acc. Chem. Res.* **2012**, *45*, 864.
11. Yu, "Weak Coordination as a Powerful Means for Developing Broadly Useful C-H Functionalization Reactions" *Acc. Chem. Res.* **2012**, *45*, 788.
12. Hartwig, "Evolution of C-H Bond Functionalization from Methane to Methodology" *J. Am. Chem. Soc.* **2016**, *138*, 2.
13. Goldman, "Large-Scale Selective Functionalization of Alkanes" *Acc. Chem. Res.* **2017**, *50*, 620.
14. Yu, "Palladium-Catalyzed Transformations of Alkyl C-H Bonds" *Chem. Rev.* **2017**, *ASAP* (10.1021/acs.chemrev.6b00622).

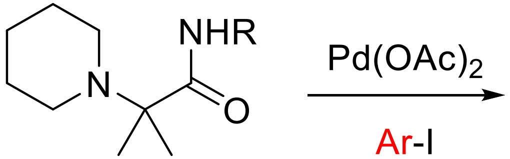
Thank you for your attention!

Question

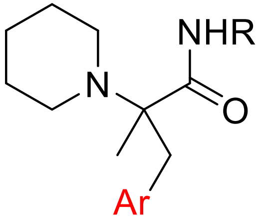
Examples in catalysis where decreasing the catalyst loading increases the rate (TON, yield)?
What is an explanation of this phenomenon?

Problem

Choose the product of C-H activation



a



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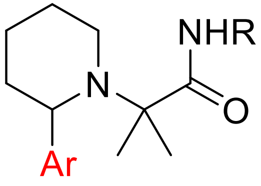
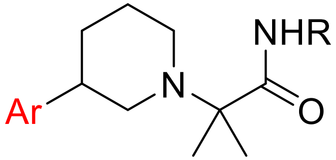
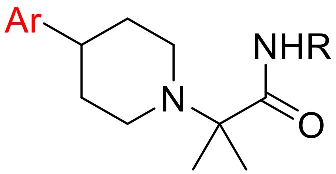
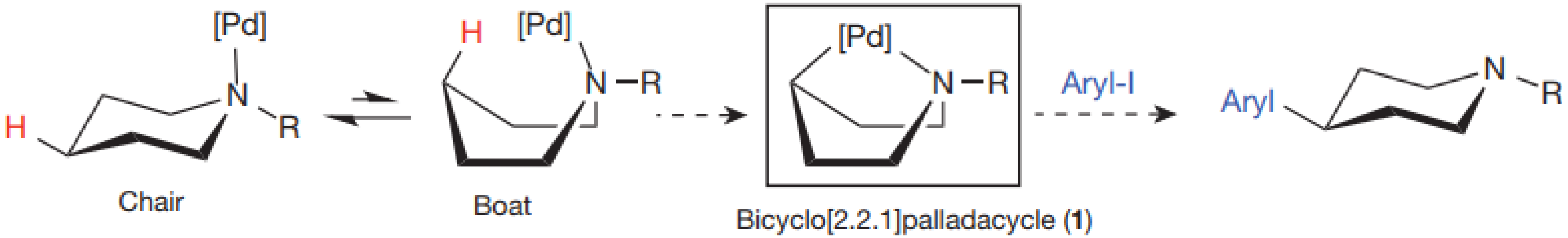


c



d





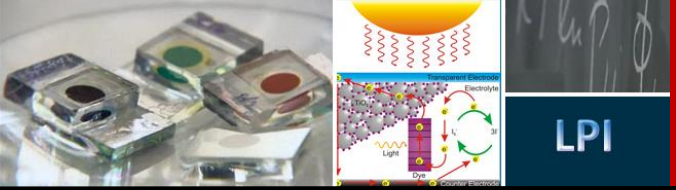
Sanford et al, *Nature* **2016**, *531*, 220

EDCH Course – CH 707

Wednesday, May 31, 2017

C-H Activation as an Alternative Tool for the Synthesis of Organic Electronic and Photonic Materials

Marko Stojanovic
Laboratory of Photonics and Interfaces (LPI)



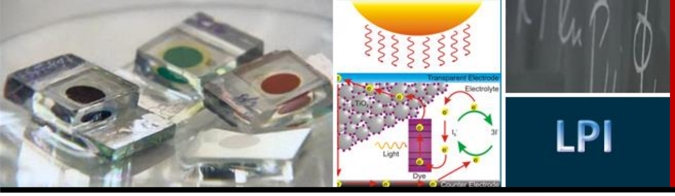
Outline

1. **Introduction:**
    1. Organic materials for optoelectronic applications: examples
    2. Classical routes for the synthesis of Organic materials for optoelectronic applications.
        1. Carbon-carbon bond formation
        2. Carbon-heteroatom bond formation

2. **Alternatives routes to state of the art protocols applied to small molecules**
    1. Pd-catalyzed direct Arylation
    2. Pd-catalyzed oxidative Arylation
    3. Metal-free Arylation
    4. Metal free amination

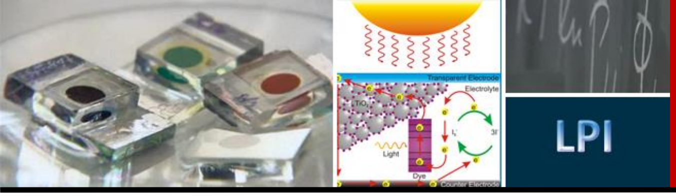
3. **Alternatives routes to state of the art protocols applied to polymers**

4. **Conclusion**



Introduction to optoelectronic materials:

Structure/performance correlation



Introduction

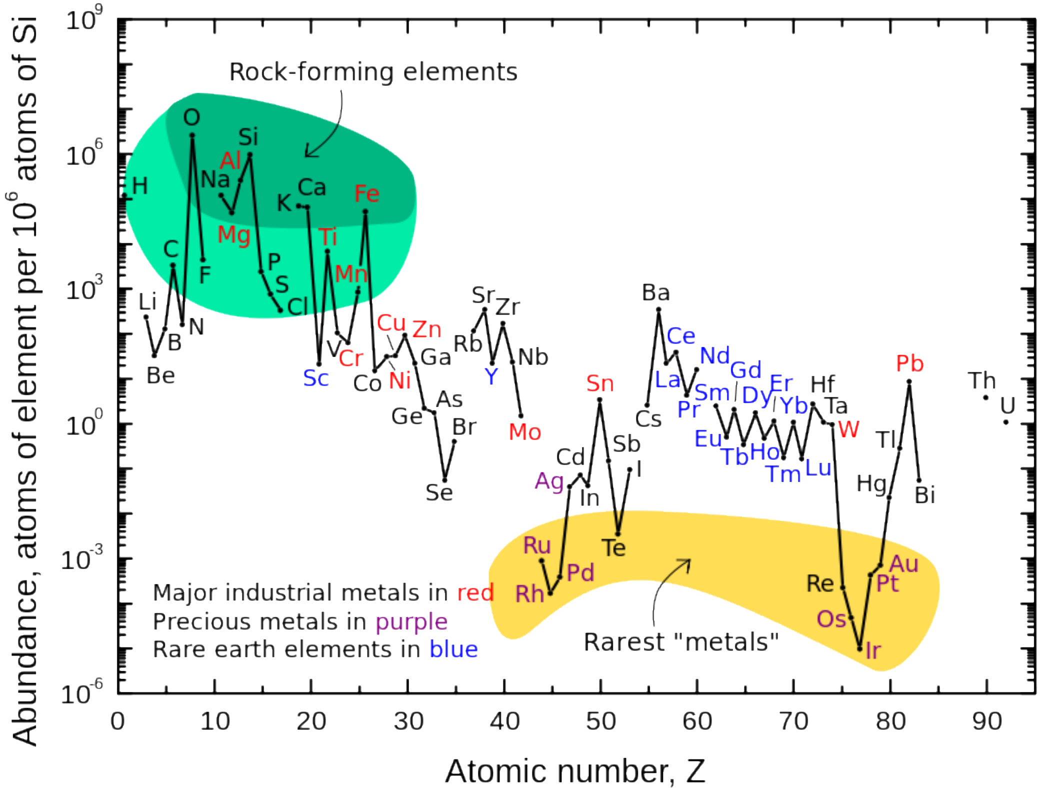
What is an optoelectronic material?

Optoelectronics: *“study of electronic devices able to control, detect or source light”*

Wikipedia

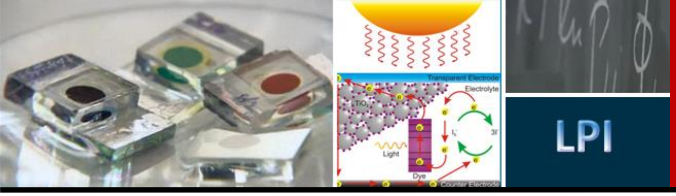
Organics offer a huge advantages over materials made from non earth abundant elements

Ex: Ruthenium based sensitizers, Osmium and Iridium based emitting layers, precious metal semi-conductors…



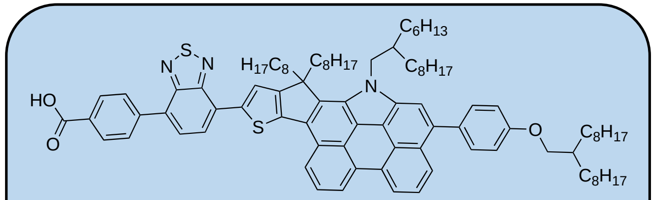
Source: Wikipedia

Review on organic optoelectronic materials: Ostroverkhova, O. *Chem. Rev.* **2016**, *116* (22), 13279–13412.



Introduction

Dye for High performance Dye Sensitized Solar Cells



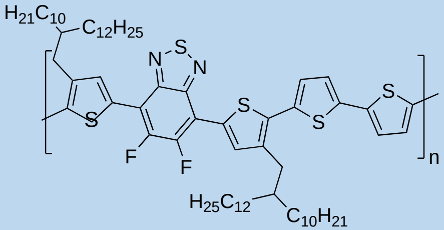
Sensitizer for dye sensitized solar cells, PCE = 12.0%

Yao, Z. et al.*Angew. Chemie - Int. Ed.* 2015, *54* (20), 5994–5998.

SwissTech - EPFL

Credits: EPFL/ A. Herzog

Semi conductor for high efficency PCBM C_{60} free organic Solar Cell



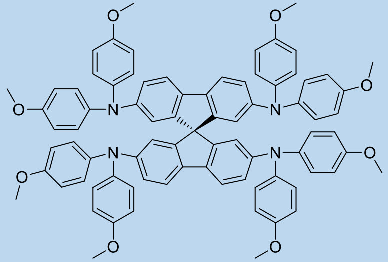
Semi conductor for Organic Solar cells PCE = 6.2 %

Zhao, J. et al. *Energy Environ. Sci.* 2015, *8* (2), 520–525.

Flexible solar celll

Taken from:
Root, S. E. et al. *Chem. Rev.* **2017**, acs.chemrev.7b00003.

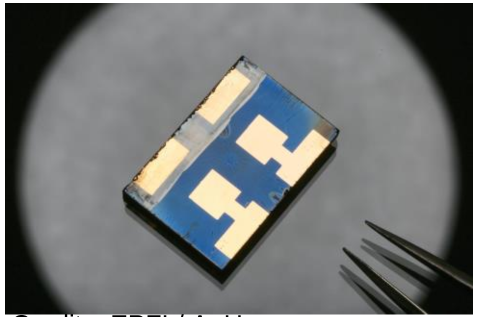
Hole transporting material for High efficency Organo lead halides Pervoskite Solar cell



Organic Semi conductor for Perovskite Solar cells
PCE = 20.2 %

Saliba, M. et al. *Science (80).* 2016, *354* (6309).

Laboratory of Photonics and Interfaces - EPFL



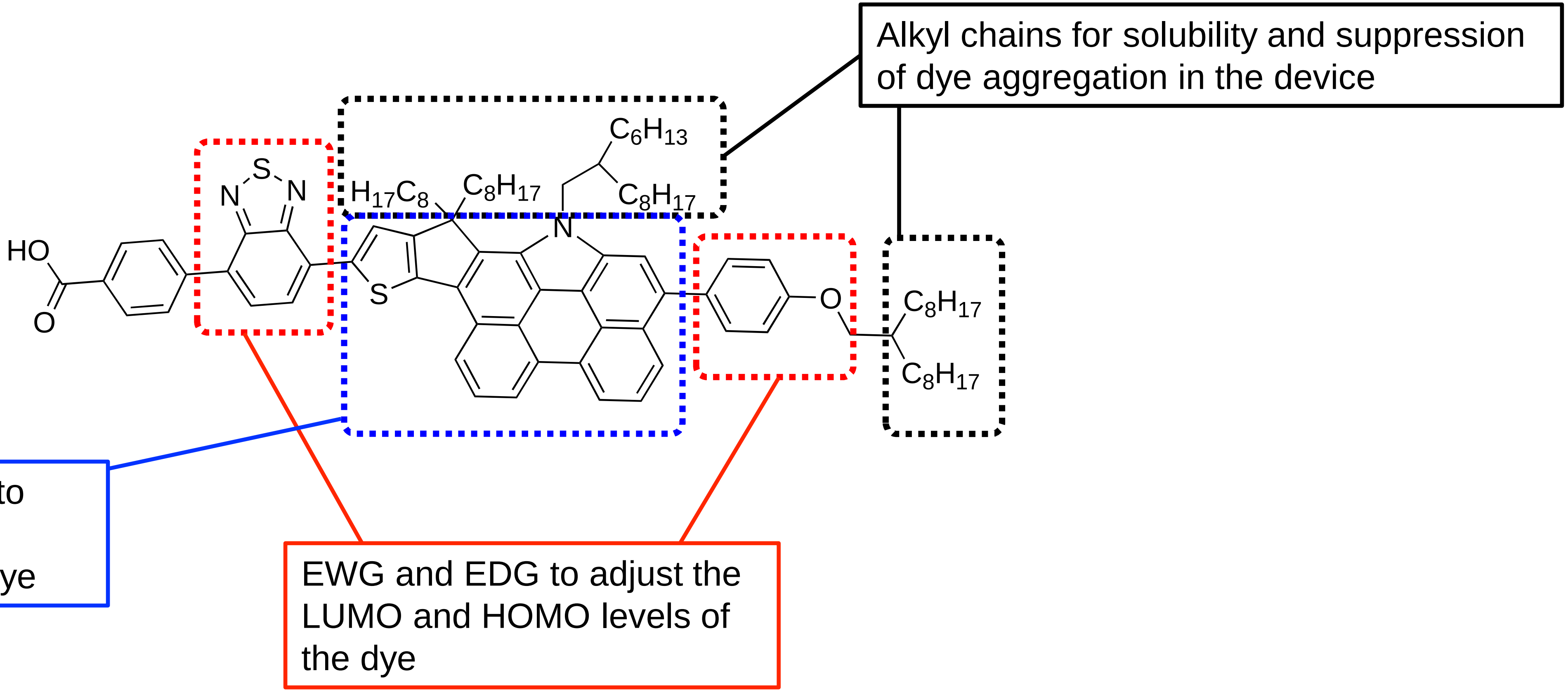
Credits: EPFL/ A. Herzog

Review on organic optoelectronic materials: Ostroverkhova, O. *Chem. Rev.* **2016**, *116* (22), 13279–13412.

Introduction

Why a need for such complicated structure ?

The molecular structure of the material has a huge impact on the device performance and stability

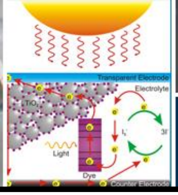


Alkyl chains for solubility and suppression of dye aggregation in the device

Conjugated core to improve spectral response of the dye

EWG and EDG to adjust the LUMO and HOMO levels of the dye

Yao, Z. et al.*Angew. Chemie - Int. Ed.* 2015, *54* (20), 5994–5998
Gao, P. et al. *Advanced Concepts in Photovoltaics*; 2014,



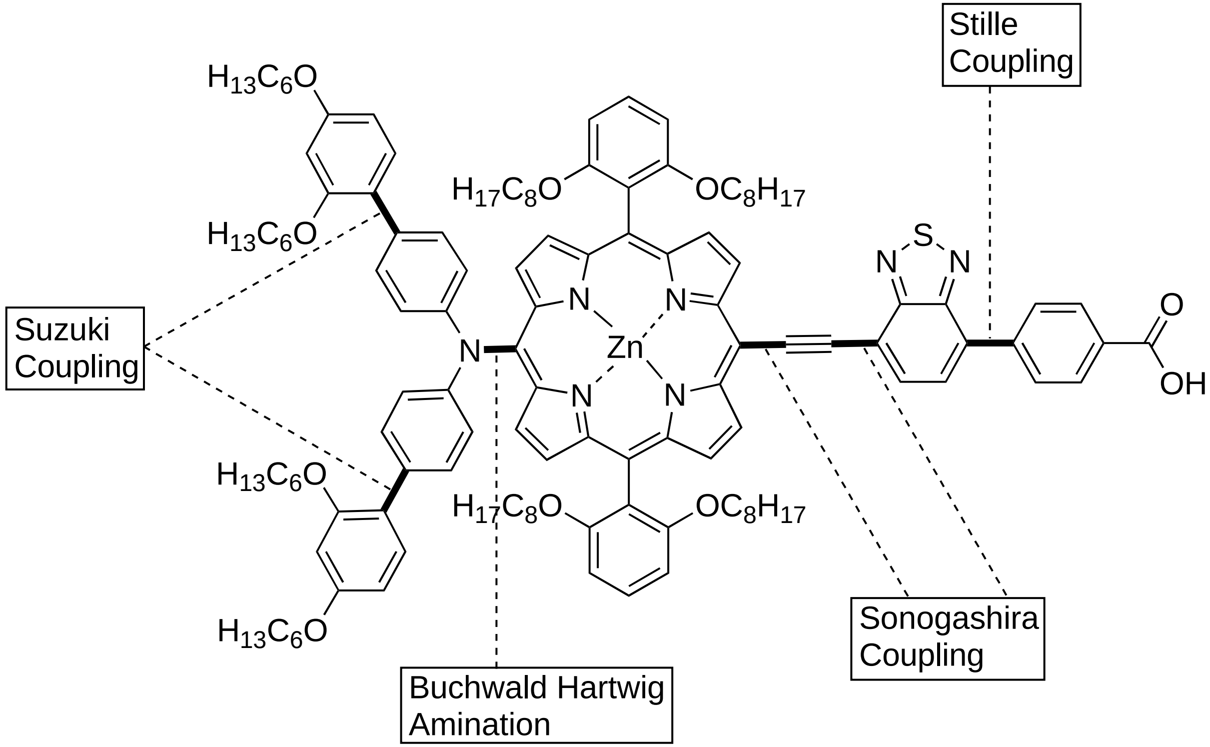
Classical routes for building organic optoelectronic materials

Cross coupling chemistry

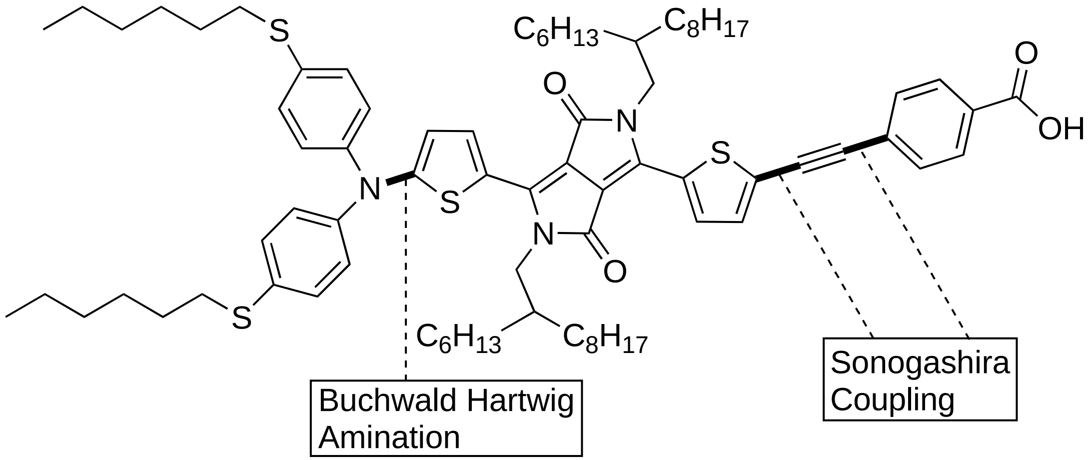
Introduction

What is the price to pay for such high performance devices ?

With great power conversion efficiency comes great molecular complexity



Unknown



Mathew, S. et al. *Nat. Chem.* **2014**, *6* (3), 242–247, Yella, A. et al. *Science (80-.).* **2011**, *334* (6056), 629–634.

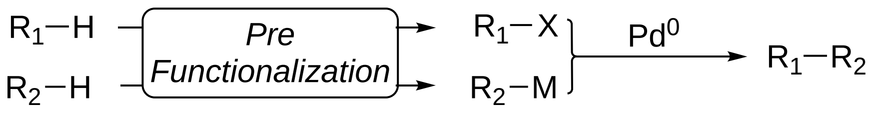
Classical routes for building organic optoelectronic materials

Carbon-carbon bond formation

Introduction

Palladium catalyzed cross coupling reactions:

Step 1:



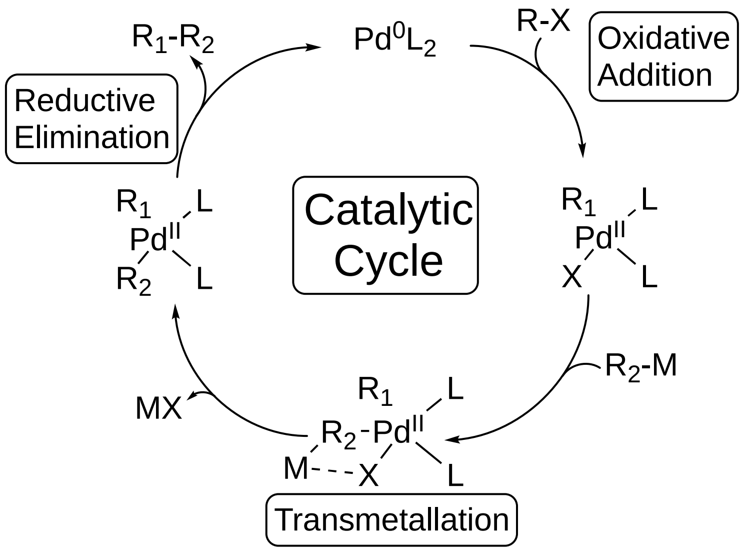
- Use of air and moisture sensitive reagent, highly toxic precursors:

Ex: Organo-lithium, organo-magnesium, organo-tin compounds,

But…

- Wide scope of reactions : precise design of the synthetic route

Step 2:



- Use of air and moisture sensitive reagent, highly toxic coupling partners, additives:

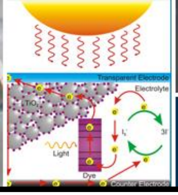
Ex: Organo-lithium, organo-magnesium, organo-tin compounds,

- Generation of highly toxic and enviromentally un-friendly wastes causing troublesome work ups

But…

- Some very simple system with high yield and functional group tolerance

Historical perspective: *Angew. Chemie - Int. Ed.* **2012**, *51* (21), 5062–5085.



Introduction

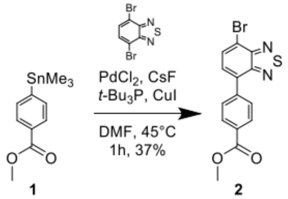
First issue:
chemical friendliness of the reaction

Example with Porphyrin Dye SM371

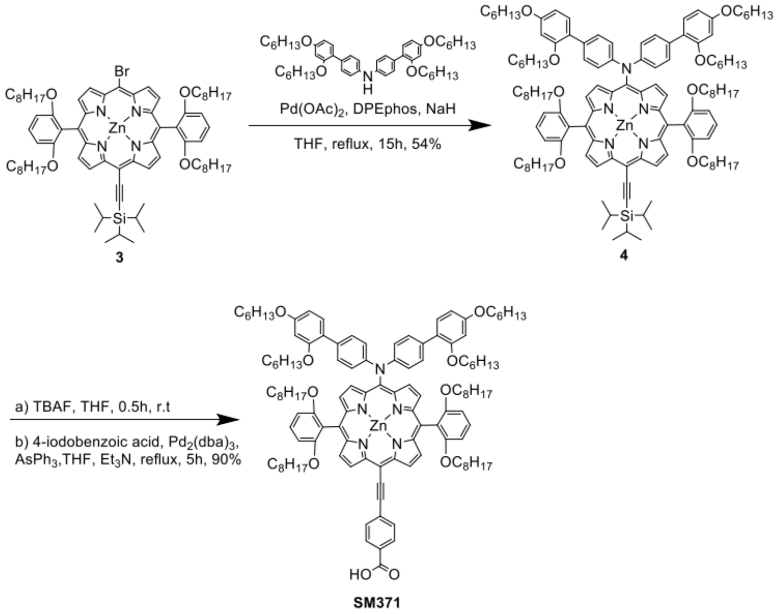
List of Hazardous chemicals :

CsF
$RSnMe_3$
DMF
THF
NaH
TBAF
$AsPh_3$
$P(tBu)_3$

DOI: 10.1038/NCHEM.1861 **SUPPLEMENTARY INFORMATION**



Scheme S1. *Synthesis of benzothiadiazole functionalized acceptor unit.*



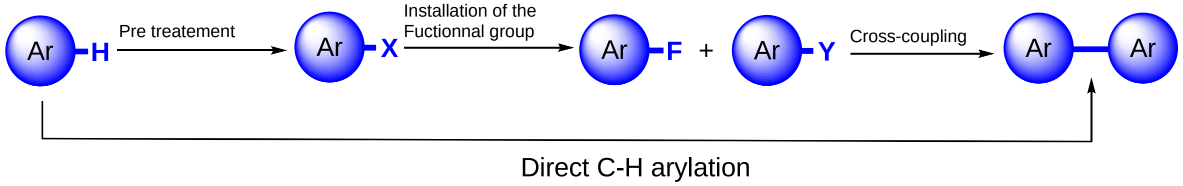
Mathew, S. et al. *Nat. Chem.* **2014**, *6* (3), 242–247.

Introduction

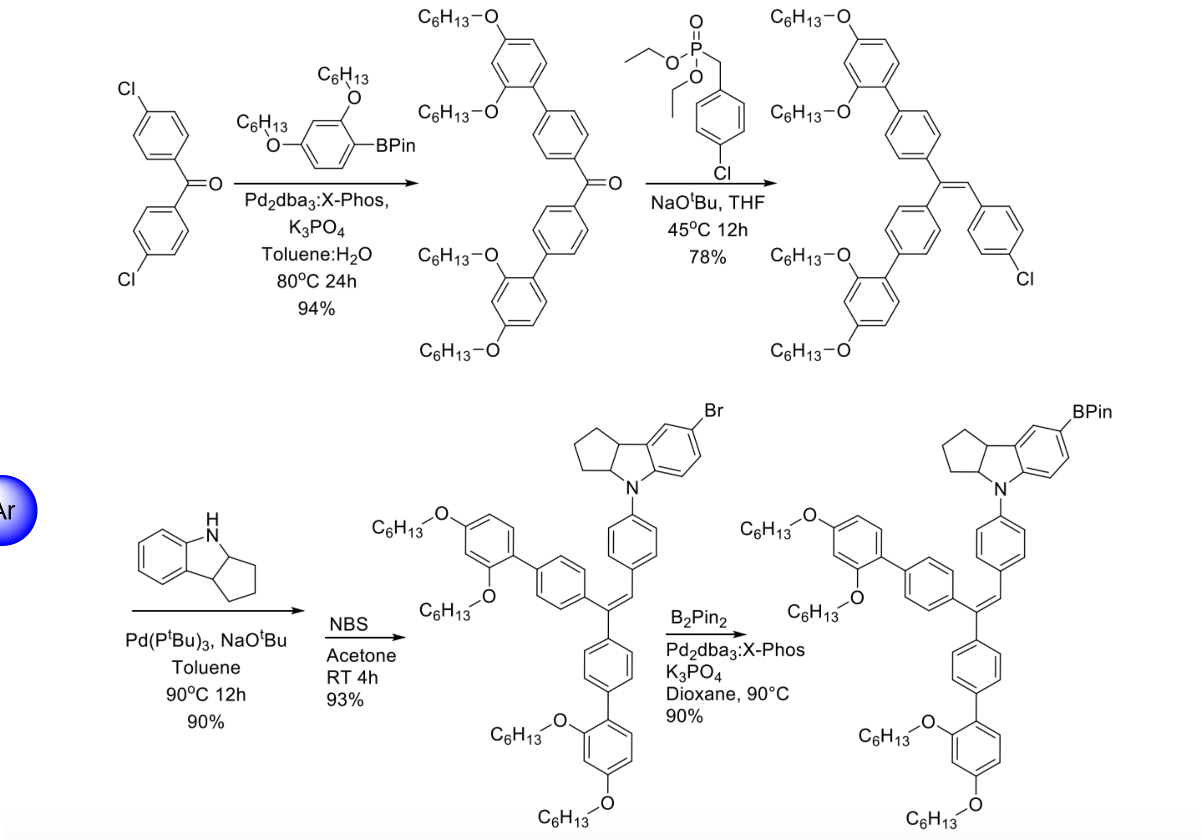
Second issue:
Long and tedious pre-functionalization of the Cross coupling partners

Pd-cross coupling requires pre-functionnalization of one of the two partners, which is step consumming.

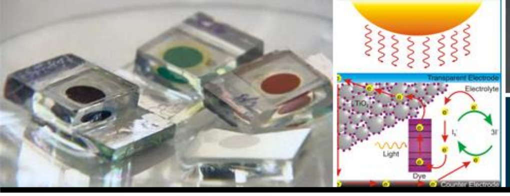
Examples:



X=halogen, Li
F=MgR, ZnR, SnR_3, BR_3

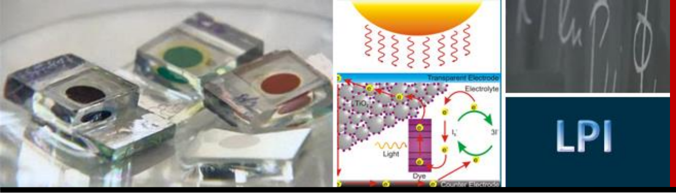


Yum, J. et al., *Sci. Rep.* **2013**, *3*, 2446.



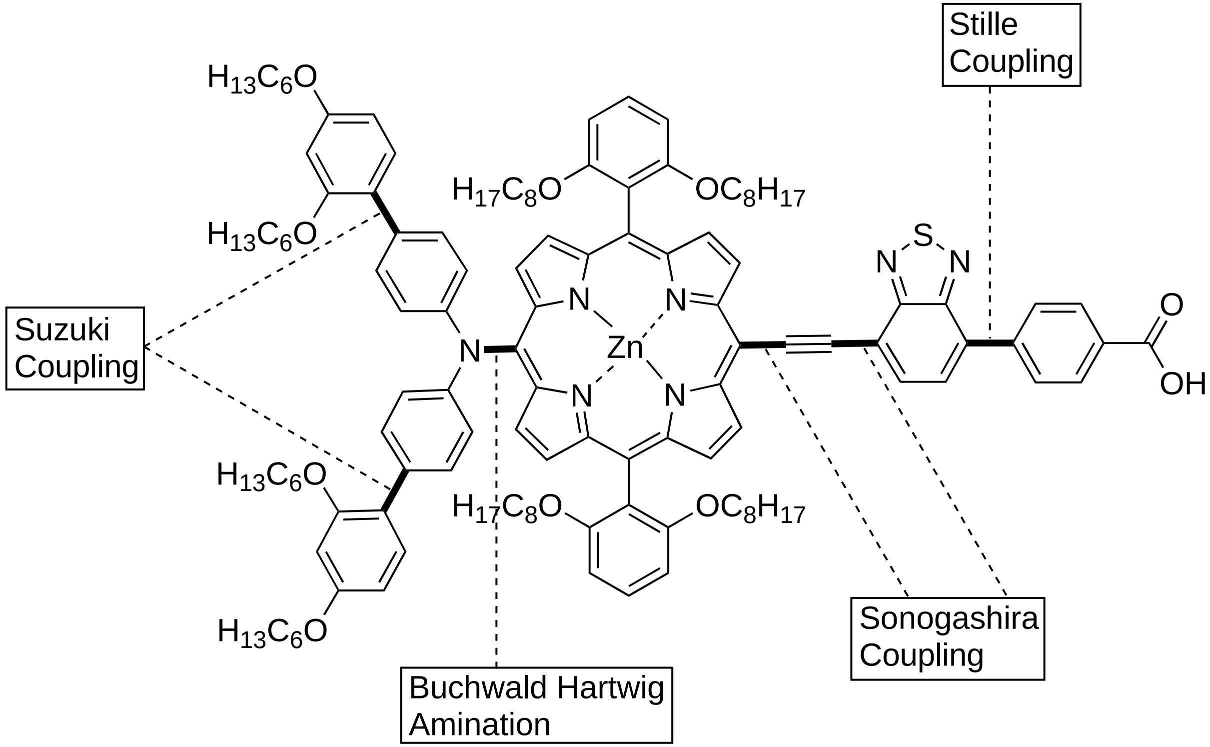
Classical routes for building organic optoelectronic materials

Carbon-heteroatom bond formation



Introduction

Heteroatom-Carbon bonds are often present to install electron rich moieties to optoelectronic materials.

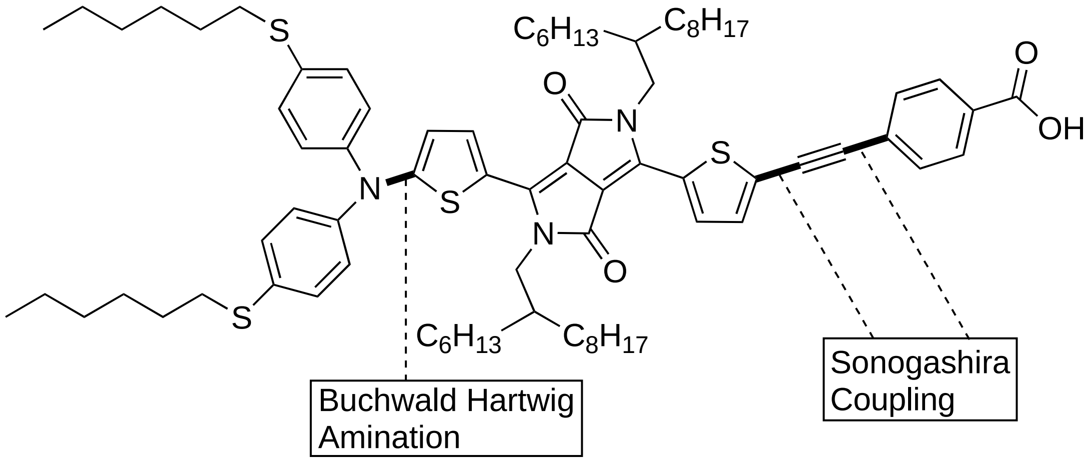


Stille Coupling

Suzuki Coupling

Buchwald Hartwig Amination

Sonogashira Coupling



Buchwald Hartwig Amination

Sonogashira Coupling

Mathew, S. et al. *Nat. Chem.* **2014**, *6* (3), 242–247, Yella, A. et al. *Science (80-.).* **2011**, *334* (6056), 629–634.

Introduction

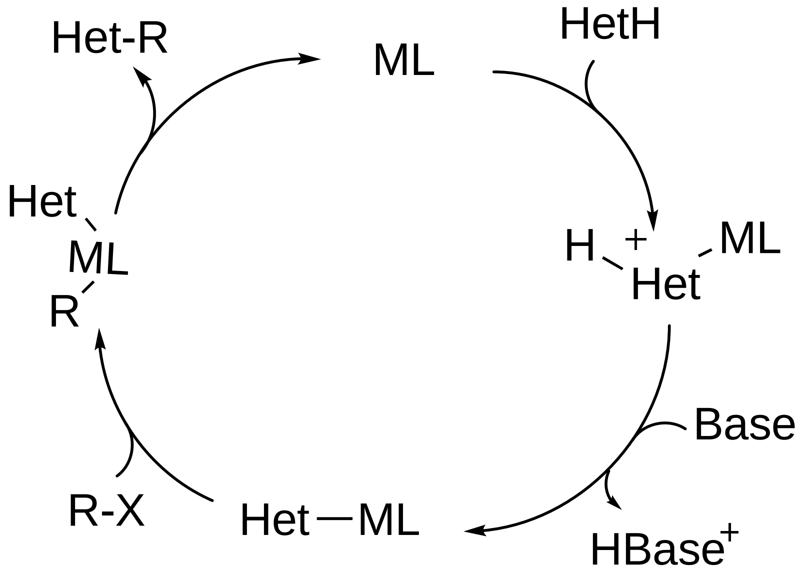
Heteroatom-Carbon bonds are often present to install electron rich moieties to optoelectronic materials.

Buchwald Hartwig cross coupling:
M=Palladium and L=phosphines

Ulmann C-N coupling:
M=Copper
L=Bipyridines, Phenanthrolines, chelating amines

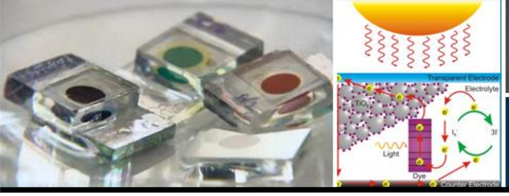
Ulmann C-O coupling:

M=Copper
L=diketo-esters, chelating diacetate



- Use of air and moisture sensitive reagent, very corrosive bases
- Generation of highly toxic and enviromentally un-friendly wastes causing troublesome work ups
- Need of high temperatures
- Low functional group tolerance

Historical perspective: *Angew. Chemie - Int. Ed.* **2012**, *51* (21), 5062–5085.



Alternatives routes to state of the art protocols

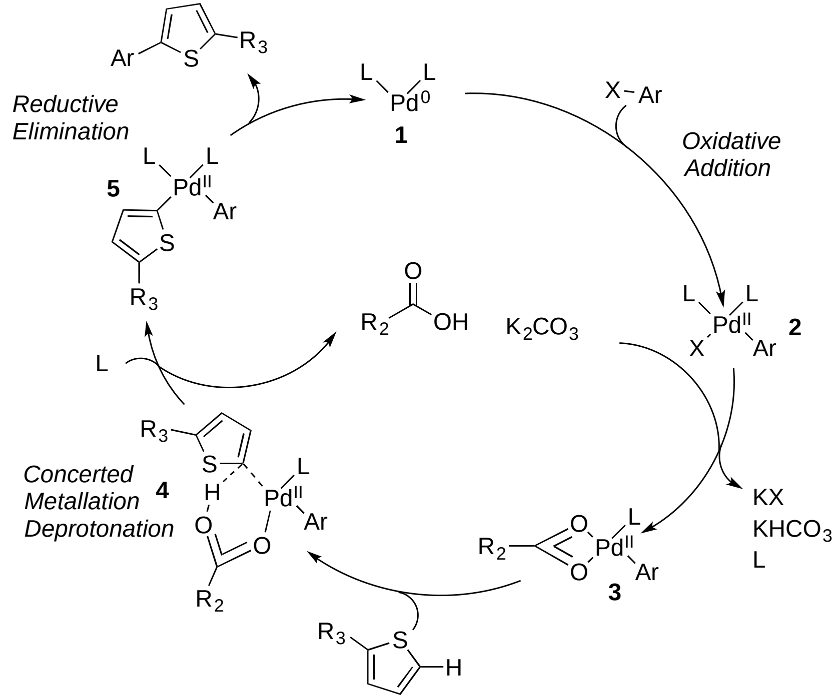
Direct arylation
Small molecules

Direct Arylation

Direct Arylation to build thiophenes based materials

Why Thiophenes?

- Very useful and popular building bloc
- Low RSE
- Helps improving spectra response
- Very versatile building bloc



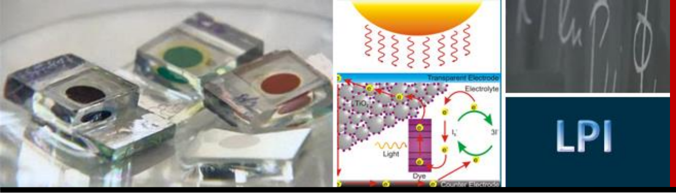
Improvements of cross-coupling:

- No hazardous chemical
- Harmless wastes
- No corrosive base

But…

- High catalyst loadings
- High temperatures >100°C
- Carcinogenic solvents (NMP, DMF, Toluene)

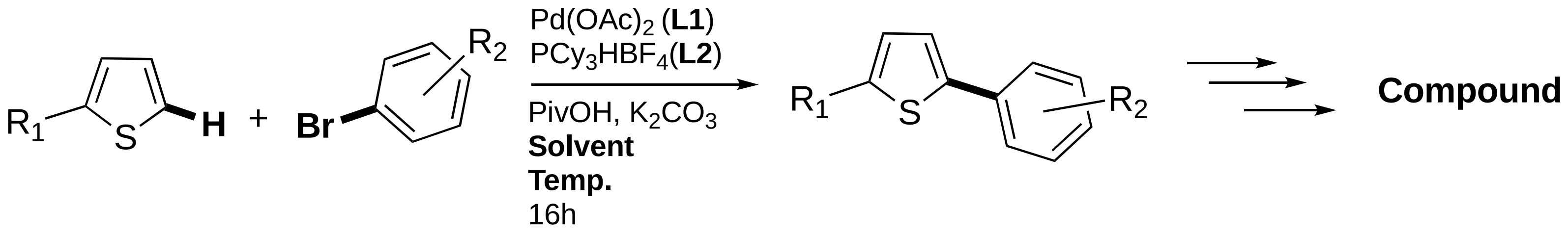
Okamoto, K. et al. *Macromolecules* **2013**, *46* (20), 8059–8078.



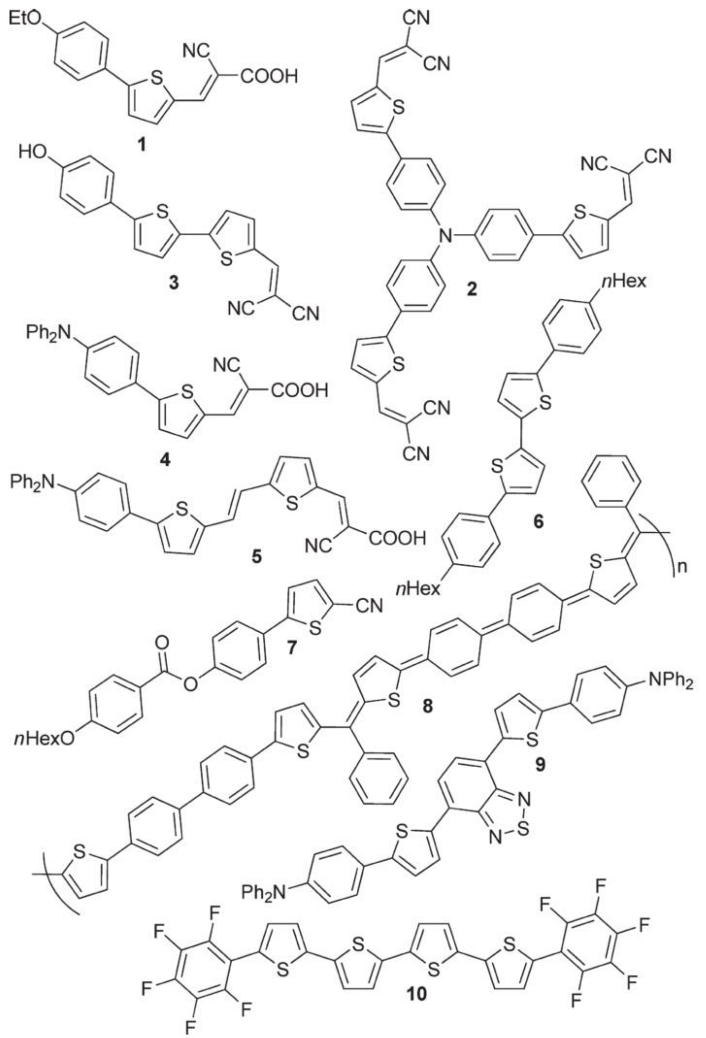
Direct arylation

Sucessful example Fagnou et al.

Proof of concept: synthesis of diverse materials with thiophene direct arylation chemistry



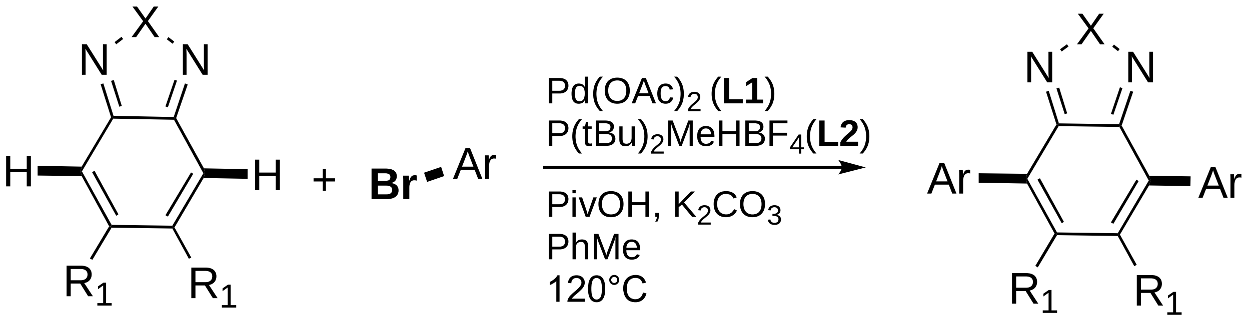
R_1	R_2	L1(mol%)	L2(mol%)	Solvent	Temp.(°C)	Yield(%)	Compound
RCHO	4-OEt	2	4	PhMe	110	91	**1**
H	4-TBSO	2	4	PhMe	100	52	**3**
RCHO	4-NPh_2	2	4	PhMe	100	91	**9,4,5**
CN	4-MeO	2	4	PhMe	100	97	**7**
H	4-(4-Br-Ph)	6	12	PhMe	110	66	**8**



Schipper, D. J.; Fagnou, K. *Chem. Mater.* **2011**, *23* (6), 1594–1600.

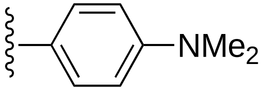
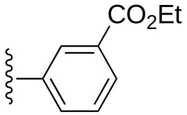
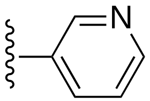
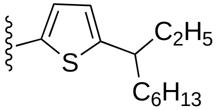
Direct arylation

Direct symmetric Arylation of electron deficient building blocks by Marder and Coworkers

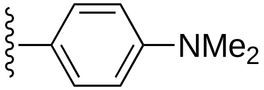
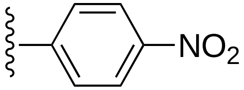
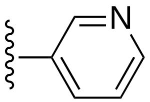
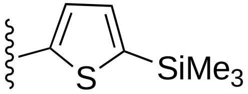


Pd(OAc)$_2$ (**L1**)
P(tBu)$_2$MeHBF$_4$(**L2**)
PivOH, K$_2$CO$_3$
PhMe
120°C

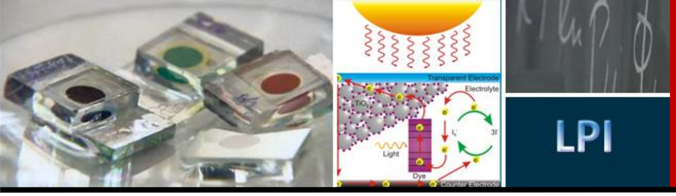
X=S, L1= 5 mol%, L2= 10 mol%

R_1	Ar	Yield(%)
F		96
CN		96
F		85
CN		93
F		70
CN		99
F		34
CN		72

X=NC$_8$H$_{17}$, L1= 10 mol%, L2= 20 mol%

R_1	Ar	Yield(%)
CN		74
CN		65
CN		68
CN		62

Zhang, J.; Parker, T. C.; Chen, W.; Williams, L.; Khrustalev, V. N.; Jucov, E. V.; Barlow, S.; Timofeeva, T. V.; Marder, S. R. *J. Org. Chem.* **2016**, *81* (2), 360–370.



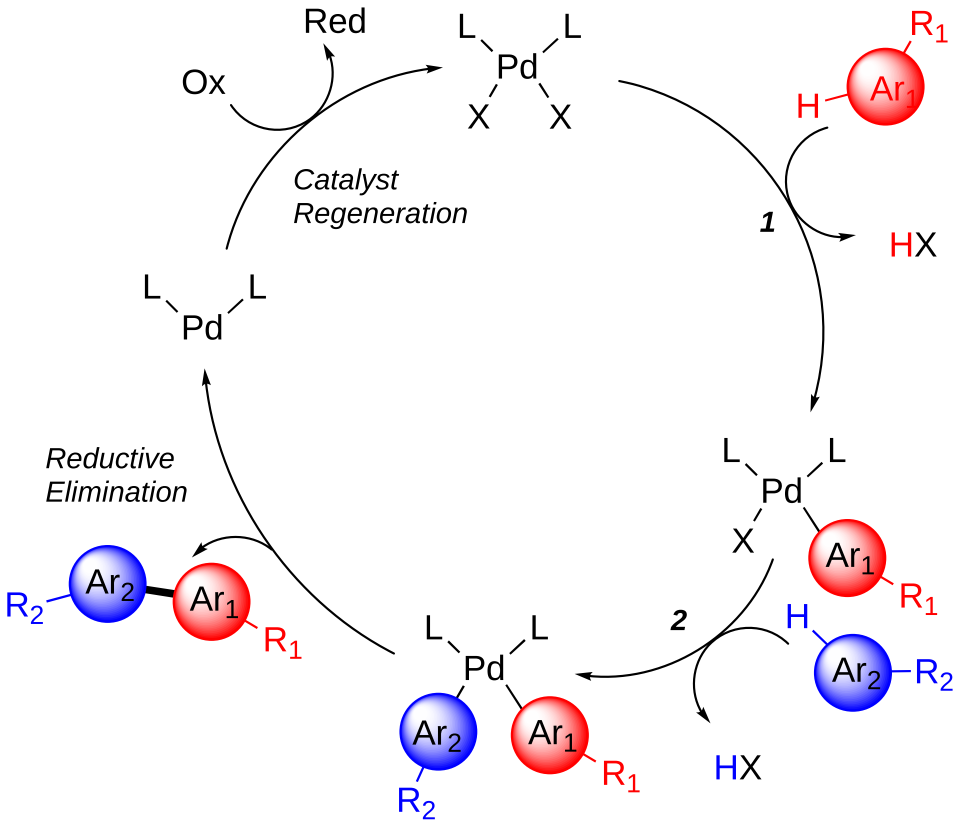
Alternatives routes to state of the art protocols

Oxidative coupling
Small molecules

C-H oxidative coupling

Oxidative coupling:

One step more efficient than direct Arylation chemistry



Improvements of cross-coupling:

- No hazardous chemical
- Harmless wastes
- Low temperatures
- Low catalytic loadings

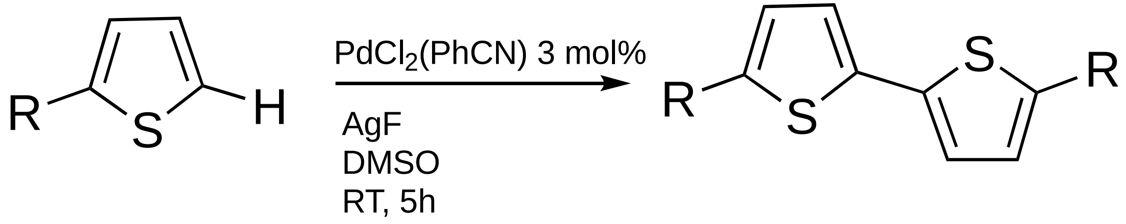
But…

- Use of stoichiometric amount of oxidant, often silver salts.
- Selectivity issues
- Carcinogenic solvents (NMP, DMF, DMSO)

Yu, S.; Liu, F.; Yu, J.; Zhang, S.; Cabanetos, C.; Gao, Y.; Huang, W. *J. Mater. Chem. C* **2017**, *5* (1), 29–40.

C-H oxidative coupling

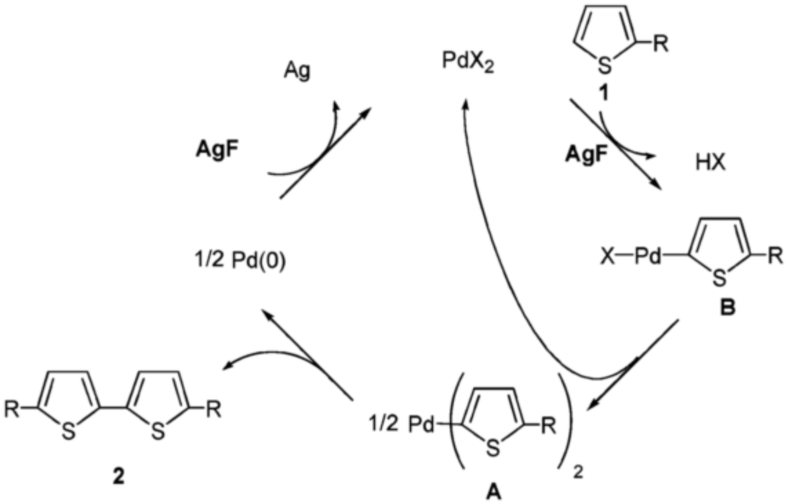
Early example of oxidative homocoupling of thiophenes by Mori



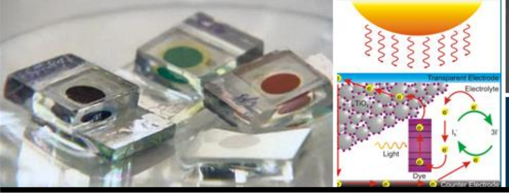
- Moderate ot good yields
- Low temperature and loading

R	Yield(%)
COOEt	85
COMe	69
Me	43
4-MePh	58
Br	77

Proposed Mechanism

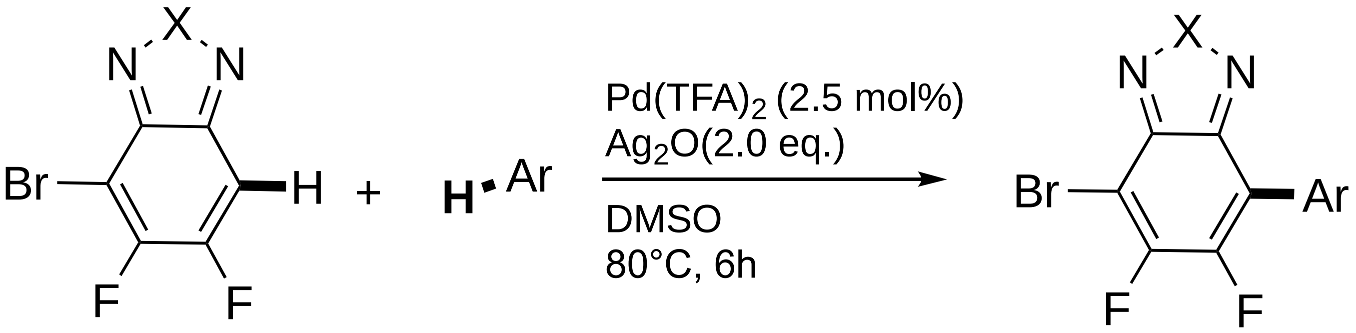


Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126* (16), 5074–5075.

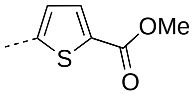
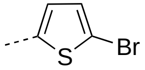
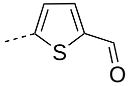
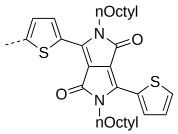
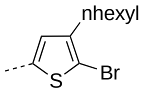


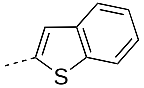
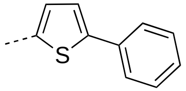
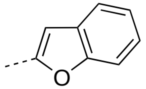
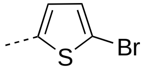
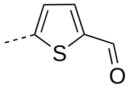

C-H oxidative coupling

Oxidative thienylation of benzothiadiazoles and benzotriazoles by Zhang

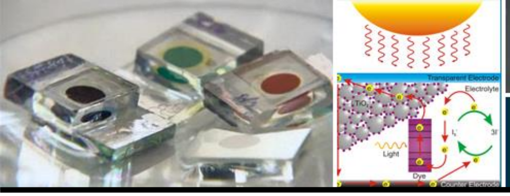


$Pd(TFA)_2$ (2.5 mol%)
Ag_2O(2.0 eq.)
DMSO
80°C, 6h

X	Ar	Yield(%)
S		81
S		73
S		74
S		68
S		84

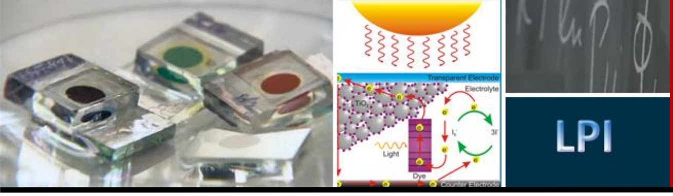
X	Ar	Yield(%)
S		86
S		84
S		53
N-nC_8H_{17}		52
N-nC_8H_{17}		62

He, C.-Y.; Wu, C.-Z.; Zhu, Y.-L.; Zhang, X. *Chem. Sci.* **2014**, *5* (4), 1317.



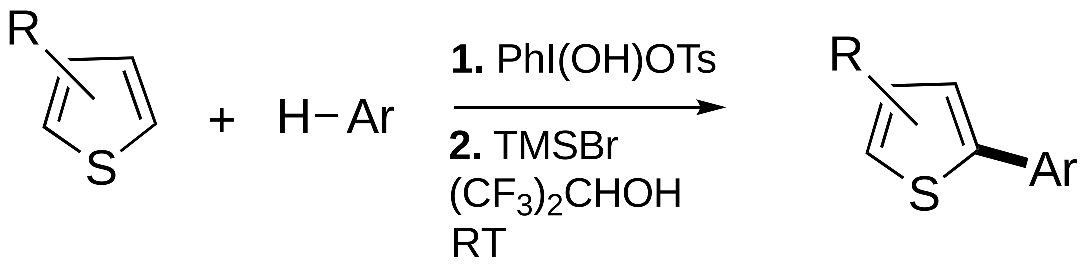
Alternatives routes to state of the art protocols

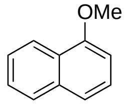
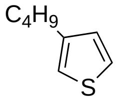
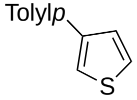
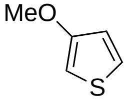
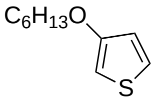
Metal free Arylation
Small molecules



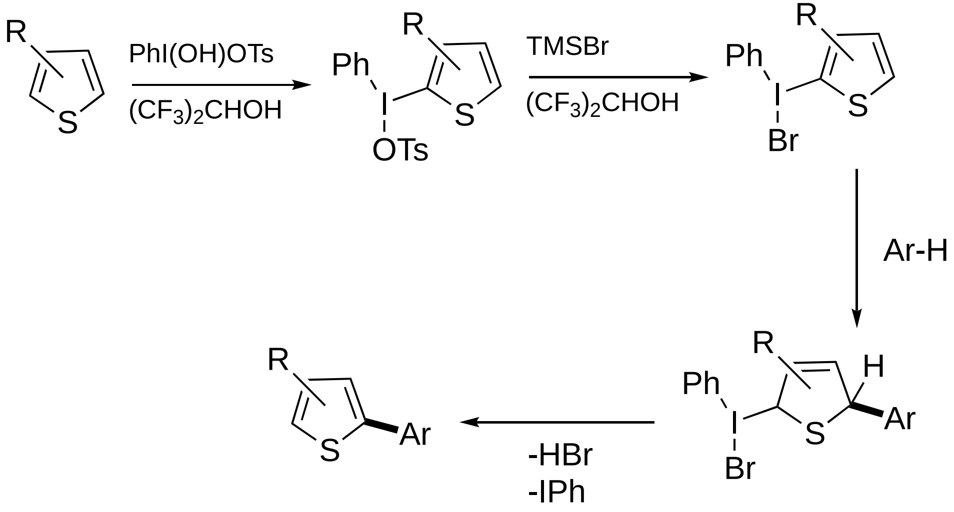
Metal Free Arylation

Metal free homocoupling with iodonium(III)/TMSBr activation by Kita and Dohi



R	Ar	Yield(%)
2-Me		98
2-butyl		88
2-hexyl		60
2-OMe		85
2-OHex		84

Proposed mechanism

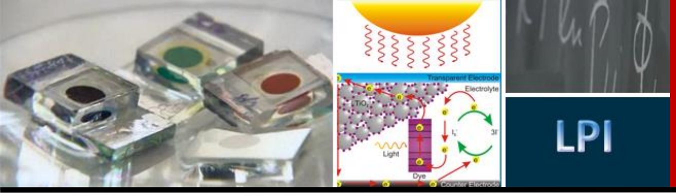


Morimoto, K.; Yamaoka, N.; Ogawa, C.; Nakae, T.; Fujioka, H.; Dohi, T.; Kita, Y. *Org. Lett.* **2010**, *12* (17), 3804–3807.
Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2009**, *131* (5), 1668–1669.

Alternatives routes to state of the art protocols

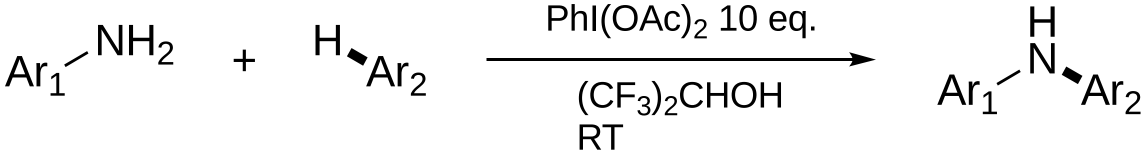
Metal free amination

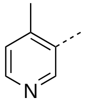
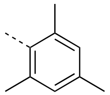
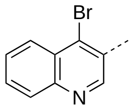
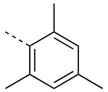
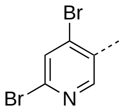
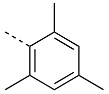
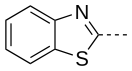
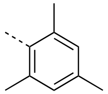
Small molecules



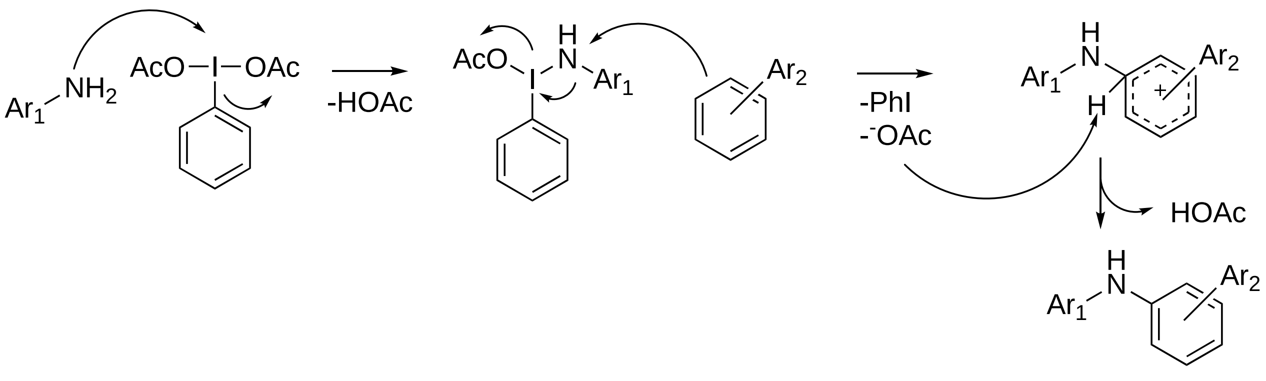
Metal Free Amination

Metal Free arylation of heterocycloanilines by Chupakhin

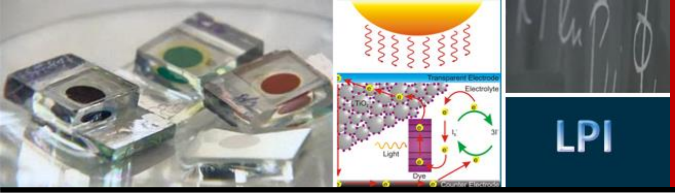


Ar$_1$	Ar$_2$	Yield(%)
		63
		85
		58
		43

Proposed mechanism:

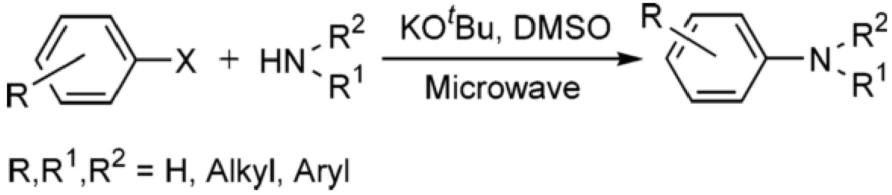


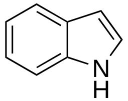
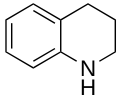
Manna, S.; Serebrennikova, P. O.; Utepova, I. A.; Antonchick, A. P.; Chupakhin, O. N. *Org. Lett.* **2015**, *17* (18), 4588–4591.



Metal Free Amination

Metal Free arylation of alphiatic and aryl amines by Tu



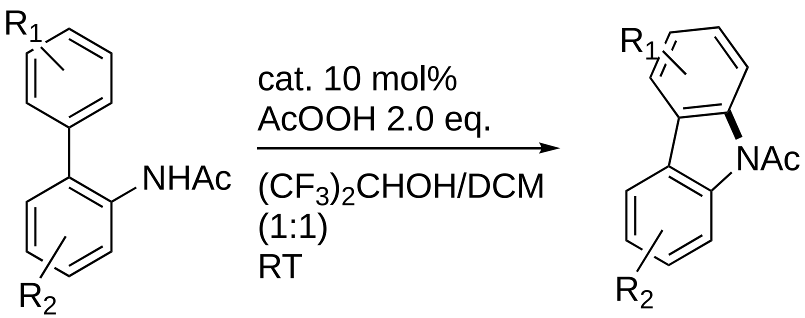
Ar-X	Amine	Yield(%)
PhBr	$PhNH_2$	61
PhBr	Ph_2NH	80
PhBr		58
PhBr		90

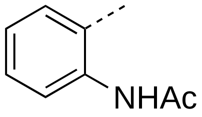
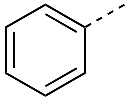
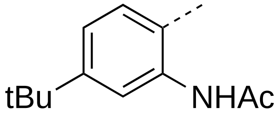
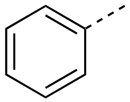
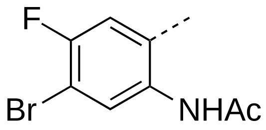
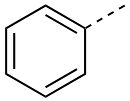
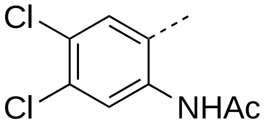
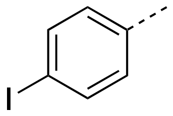
- Microwave assisted reaction
- No metal
- Good to moderate yields or aryl amines

Shi, L.; Wang, M.; Fan, C. A.; Zhang, F. M.; Tu, Y. Q. *Org. Lett.* **2003**, *5* (19), 3515–3517.

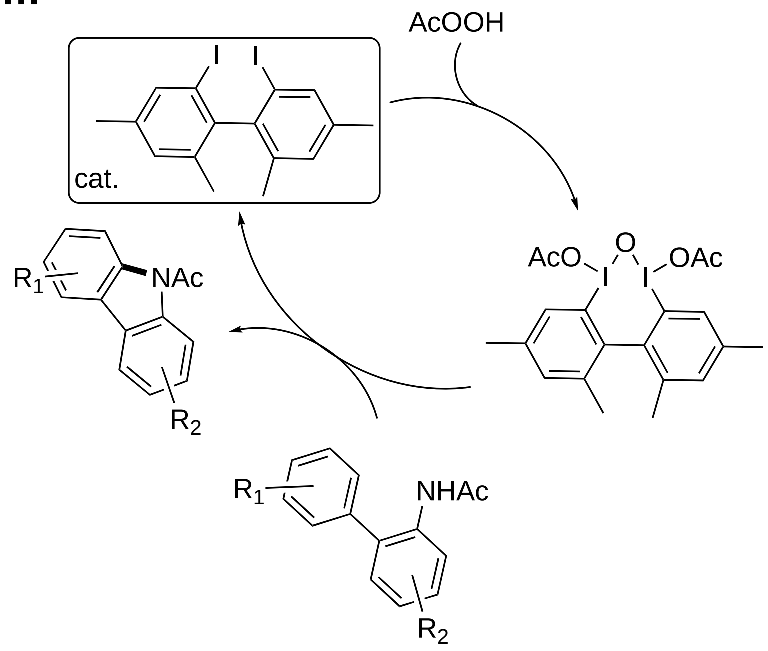
Metal Free Amination

Catalytic intramolecular Arylation with hyper valent Iodine catalyst



R_1	R_2	Yield(%)
		77
		65
		70
		56

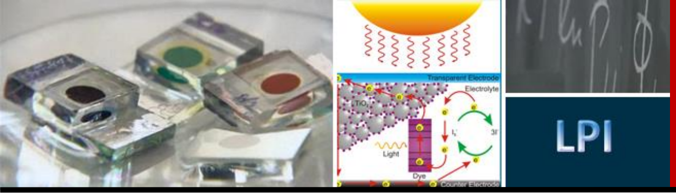
Proposed mechanism:



Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chemie - Int. Ed.* **2011**, *50* (37), 8605–8608.

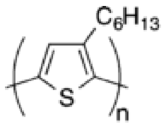
Alternatives routes to state of the art protocols applied

Direct arylation
Polymers

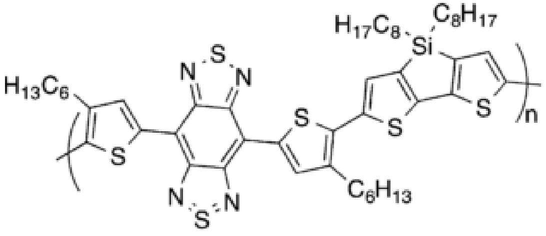


Thiophene direct arylation

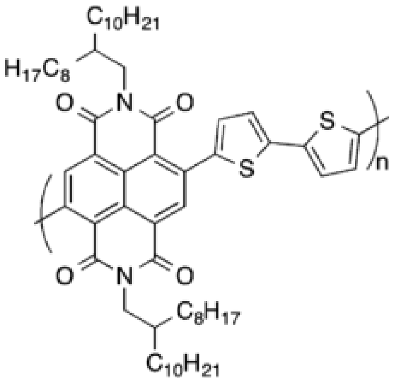
Synthesis of π-conjugated polymers:



P3HT



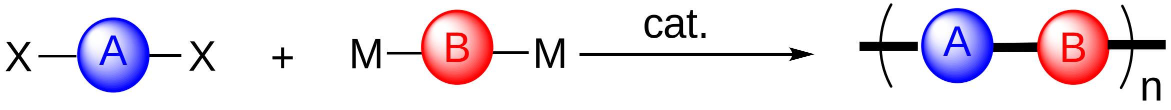
PBBTSiD



PNDIT2

Uses in OPV, OLED, OFETs and flexible electronics/printable semi-conductors

Classical cross-coupling route:



Catalysts: $Pd(PPh_3)_4$; $Ni(dppp)Cl_2$; Hermann Beller
M: organo-magnesium, organo tin,…

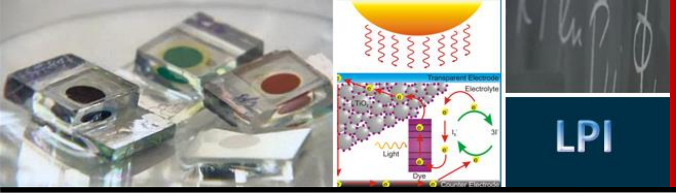
Advantages:

- Low dispersities
- High yields

Drawbacks:

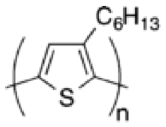
- Highly reactive
- Moisture sensitive
- toxic byproducts
- Stoichiometric amounts of organometallic reagents.

Root, S. E. et al. *Chem. Rev.* **2017**, acs.chemrev.7b00003.
Suraru, S.-L. et al. *ACS Macro Lett.* **2016**, *5* (6), 724–729.

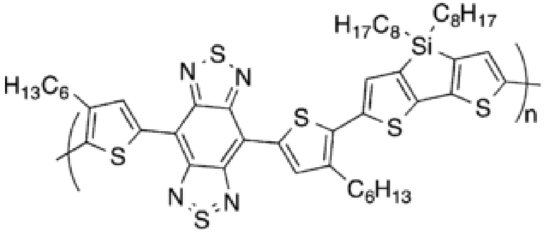


Thiophene direct arylation

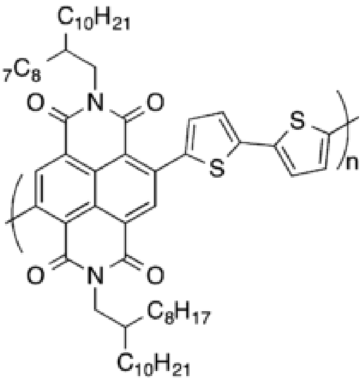
Synthesis of π-conjugated polymers:



P3HT



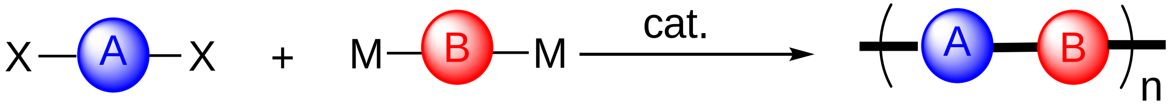
PBBTSiD



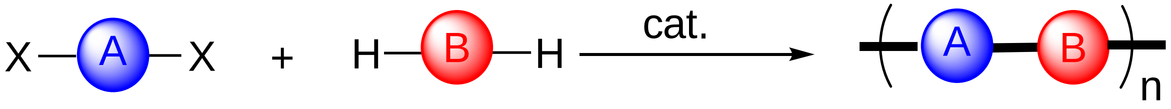
PNDIT2

Uses in OPV, OLED, OFETs and flexible electronics/printable semi-conductors

Classical crosscoupling route:



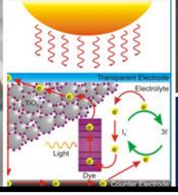
Direct arylation polymerization (DArP)



Challenges:

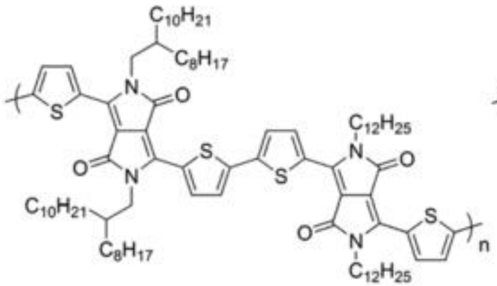
- **Control of the MW$_n$**
- **High reactivity**
- **Minimum downstream processing**

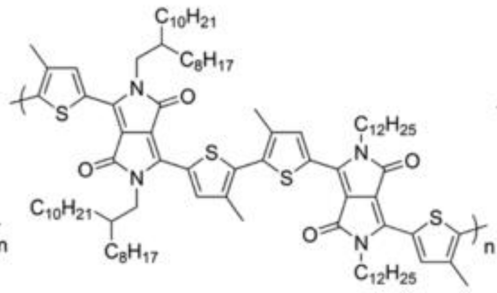
Root, S. E. et al. *Chem. Rev.* **2017**, acs.chemrev.7b00003.
Suraru, S.-L. et al. *ACS Macro Lett.* **2016**, *5* (6), 724–729.

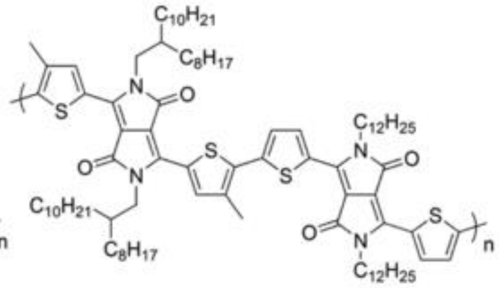



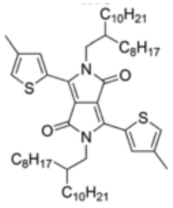
C-H oxidative coupling of thiophenes

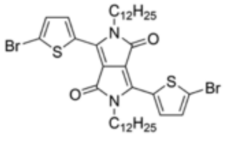
DArP of Diketopyrrolopyroles (DPP) by Leclerc

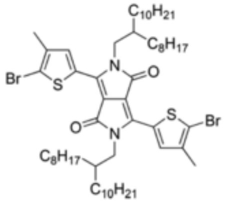

P1

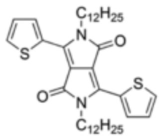

P2


P3 - P4

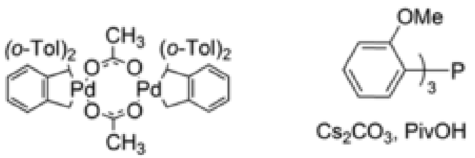

M5


M6


M3


M2

Catalytic system:

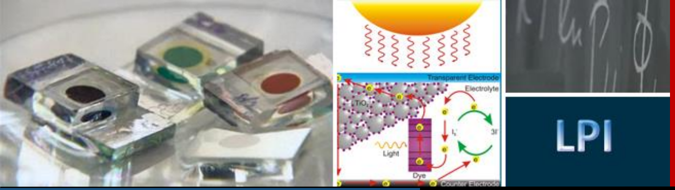

Pd(Herrmann-Beller)

Cs_2CO_3, PivOH
Toluene

Pd Loading: 2 mol%
Ligand Loading: 8 mol%
PivOH: 0.3 eq.

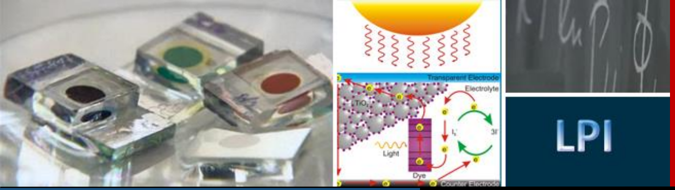
Polymer	Yield(%)	M_n(kDA)
P1	93	16
P2	61	6
P3(M5+M6)	83	15
P4(M3+M2)	84	46

Grzybowski, M.; Gryko, D. T. *Adv. Opt. Mater.* **2015**, *3* (3), 280–320
Pouliot, J.-R.; Sun, B.; Leduc, M.; Najari, A.; Li, Y.; Leclerc, M. *Polym. Chem.* **2015**, *6* (2), 278–282.



Conclusion

- State of the art cross coupling protocols are effective but not step economic or environmentally friendly.
- Direct Arylation protocols would help reducing the pre functionalization steps involving dangerous and hazardous chemicals.
- Improvements are needed regarding catalyst loadings and often high temperatures conditions.
- Improvements are needed towards selectivity and reactivity of the catalysts.
- Metal free protocols offer the most promising alternatives but are still limited to certain types of substrates.



Thank you!

Questions?

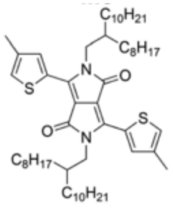
Problem 1

In 2015, Pouliot and co-workers reported the synthesis of high mobility DPP polymers via Direct Arylation polymerization.

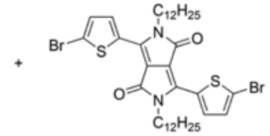
*They observed two drastically different yields for polymers **P2** and **P3**.*

Explain why based on the structure/reactivity of those monomers.

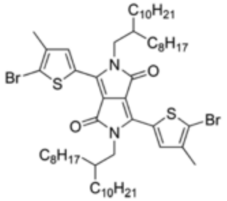
Polymer	Yield(%)	M_n(kDA)
P1	**93**	**16**
P2	**61**	**6**
P3(M5+M6)	**83**	**15**
P4(M3+M2)	**84**	**46**



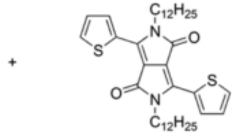
M5



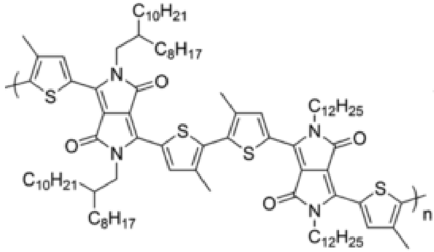
M6



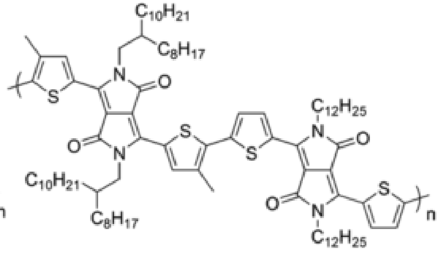
M3



M2

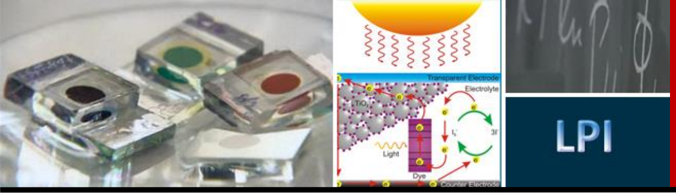


P2



P3 - P4

Grzybowski, M.; Gryko, D. T. *Adv. Opt. Mater.* **2015**, *3* (3), 280–320
Pouliot, J.-R.; Sun, B.; Leduc, M.; Najari, A.; Li, Y.; Leclerc, M. *Polym. Chem.* **2015**, *6* (2), 278–282.



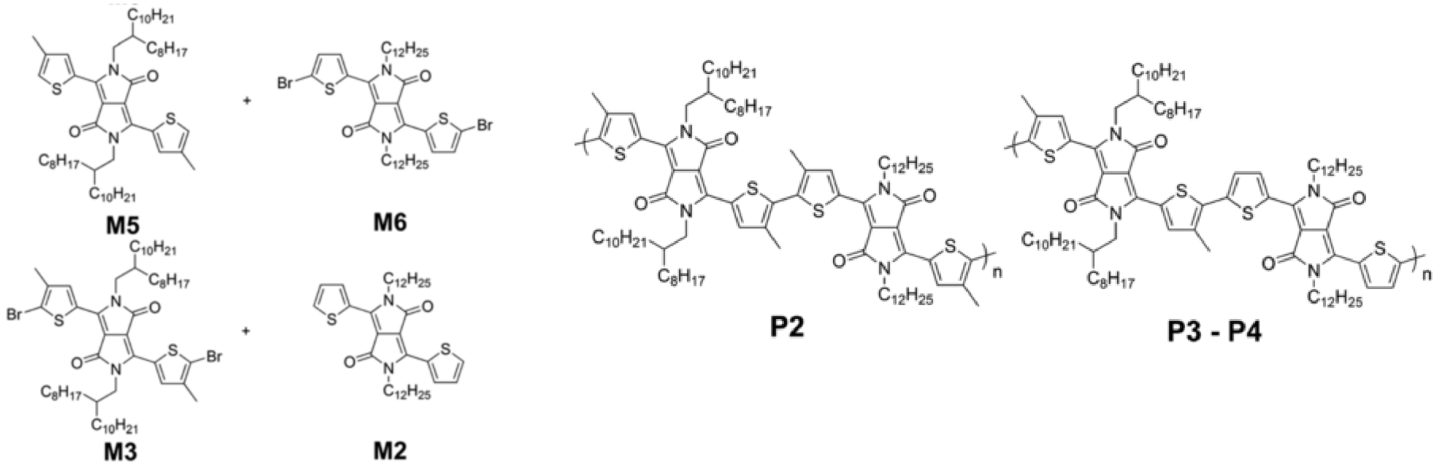
Problem 1

Answer:

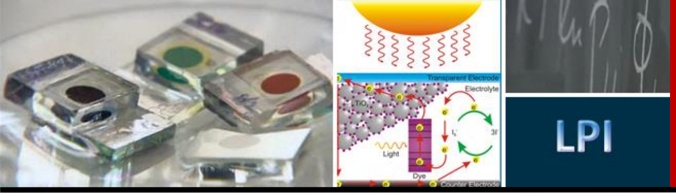
The methyl groups alpha to the activated bond in ***M5*** *decreases the acidity and thus the reactivity of the thiophenes towards CDM and hence the catalytic cycle. Additionally those methyl groups, increase the steric hindrance of these reactive sites.*

On the other hand, the other polymers have matching reactivity/structures.

Polymer	Yield(%)	M_n(kDA)
P1	**93**	**16**
P2	**61**	**6**
P3(M5+M6)	**83**	**15**
P4(M3+M2)	**84**	**46**



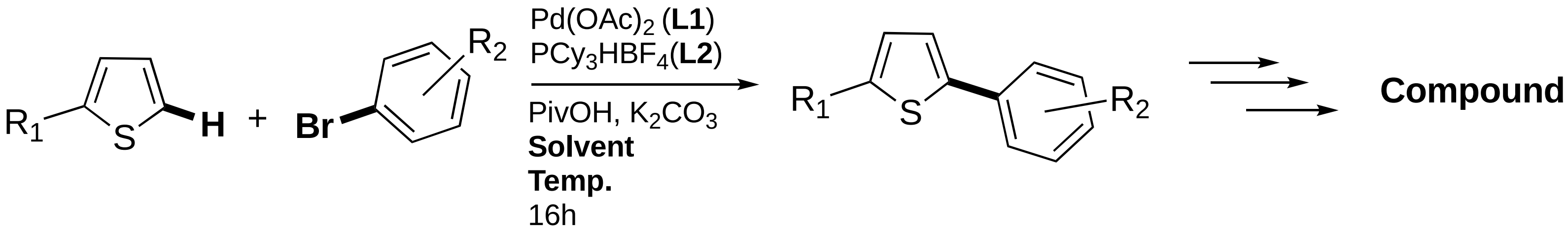
Grzybowski, M.; Gryko, D. T. *Adv. Opt. Mater.* **2015**, *3* (3), 280–320
Pouliot, J.-R.; Sun, B.; Leduc, M.; Najari, A.; Li, Y.; Leclerc, M. *Polym. Chem.* **2015**, *6* (2), 278–282.



Problem 2

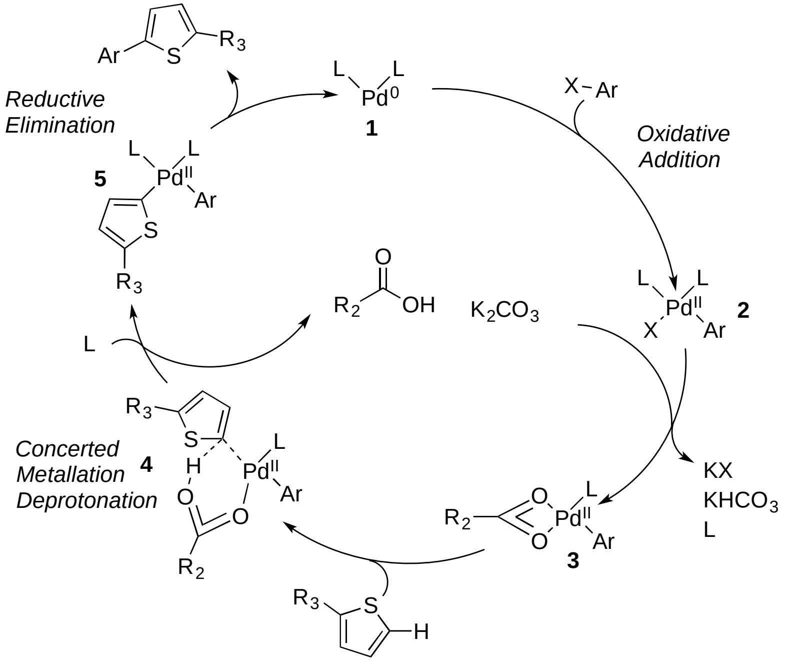
In 2011 Fagnou and co-workers developed an efficient protocol to synthesized a complete library of thiophenes based compounds for optoelectronic applications.

Explain why thiophenes are a very good candidate of CMD type of mechanism and hence C-H activation.



$Pd(OAc)_2$ (**L1**)
PCy_3HBF_4(**L2**)

PivOH, K_2CO_3
Solvent
Temp.
16h



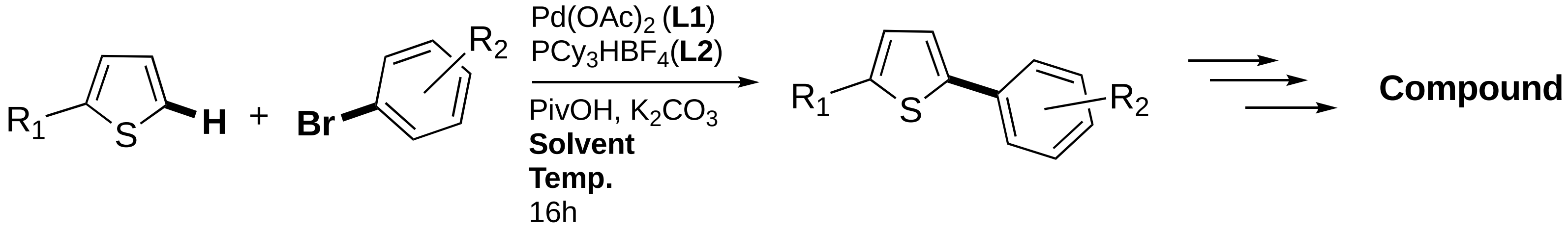
Schipper, D. J.; Fagnou, K. *Chem. Mater.* **2011**, *23* (6), 1594–1600.

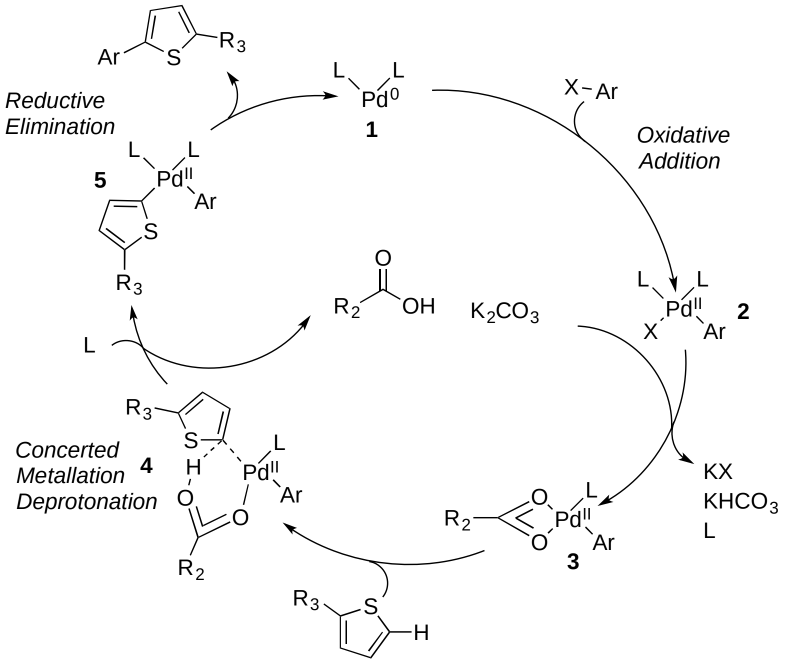
Problem 2

Answer:

The C-H bonds adjacent to the sulfur atom benefits of enhanced acidity due to the presence of this latter. This special feature is thus helping the selectivity towards this bond without the need of an pendant directing group or activating functionnality.

On the other hand, the efficiency of the cycle will depend on the electronics of the thiophene ring, thus limiting the scope of substrate for high efficiency catalysis





Schipper, D. J.; Fagnou, K. *Chem. Mater.* **2011**, *23* (6), 1594–1600.

Combination of photoredox catalysis with transition metal catalysis

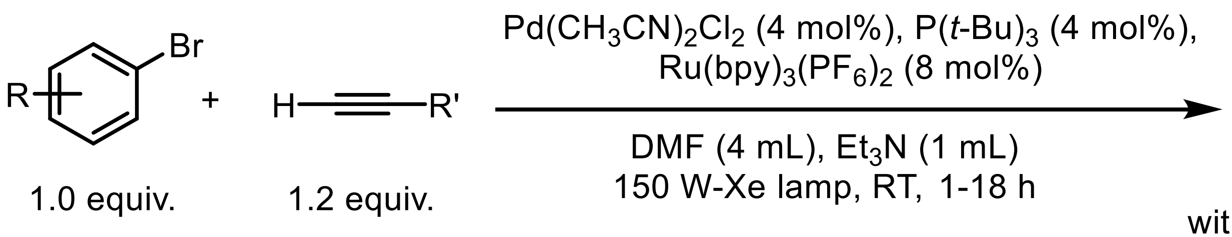
Frontiers in Chemical Synthesis
Runze Mao, EPFL
Advisor: Prof. Xile Hu
June 1st, 2017

1. INTRODUCTION

- Alliance with two giants

2. C-C bond formation

- Photoredox/Pd-catalyzed C-C bond formation-Sonogashira coupling



with photocatalyst, 80%-99% yield
without photocatalyst, 0-34% yield

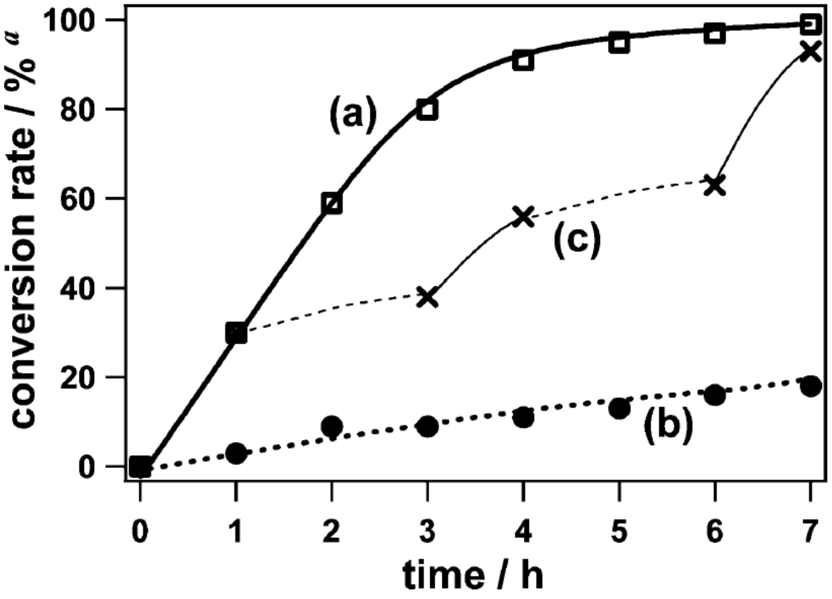
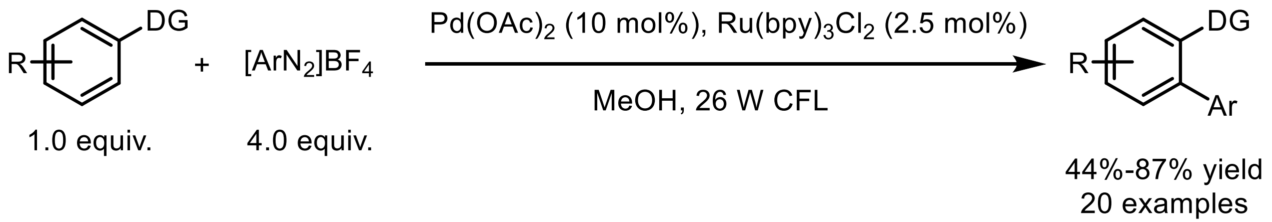


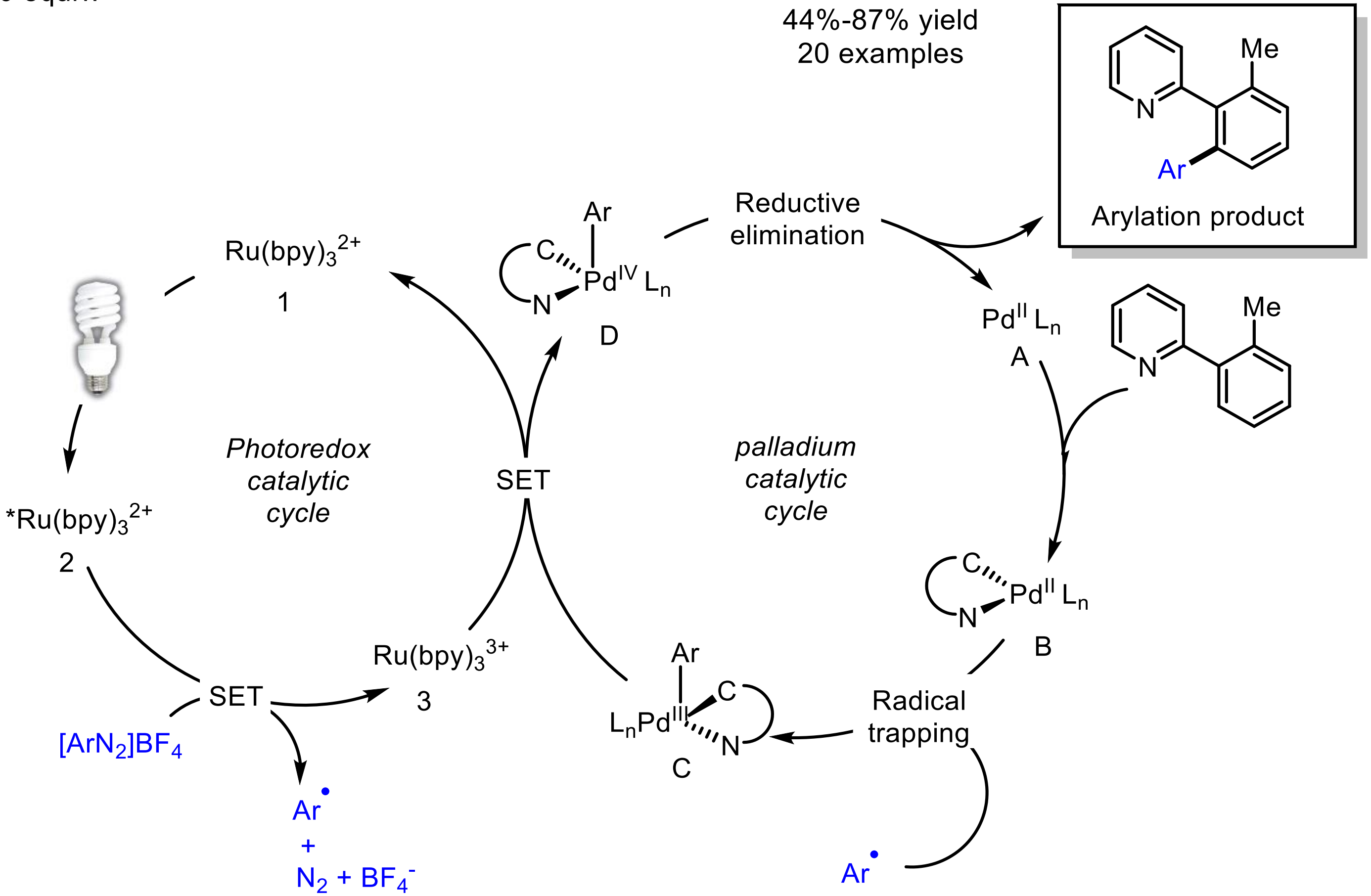
Fig. 1 Conversion rates for the Sonogashira coupling in the presence of Ru(bpy)$_3^{2+}$;
(a) with irradiation of 150 W-Xe lamp (420 < *k* < 800 nm),
(b) In the dark and
(c) irradiated on and off.
Solid and dotted curves are for the periods with irradiation or in the dark, respectively.

Osawa, M.; Nagai, H.; Akita, M. *Dalton Trans.* **2007**, *8,* 827−829.

2. C-C bond formation

➢ Photoredox/Pd-catalyzed directed C-H arylations

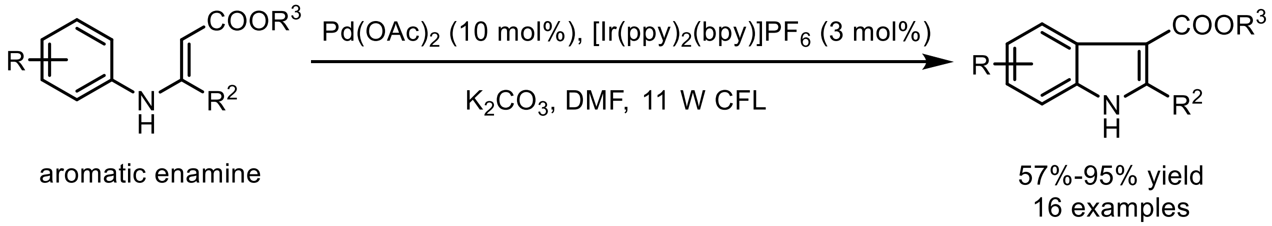


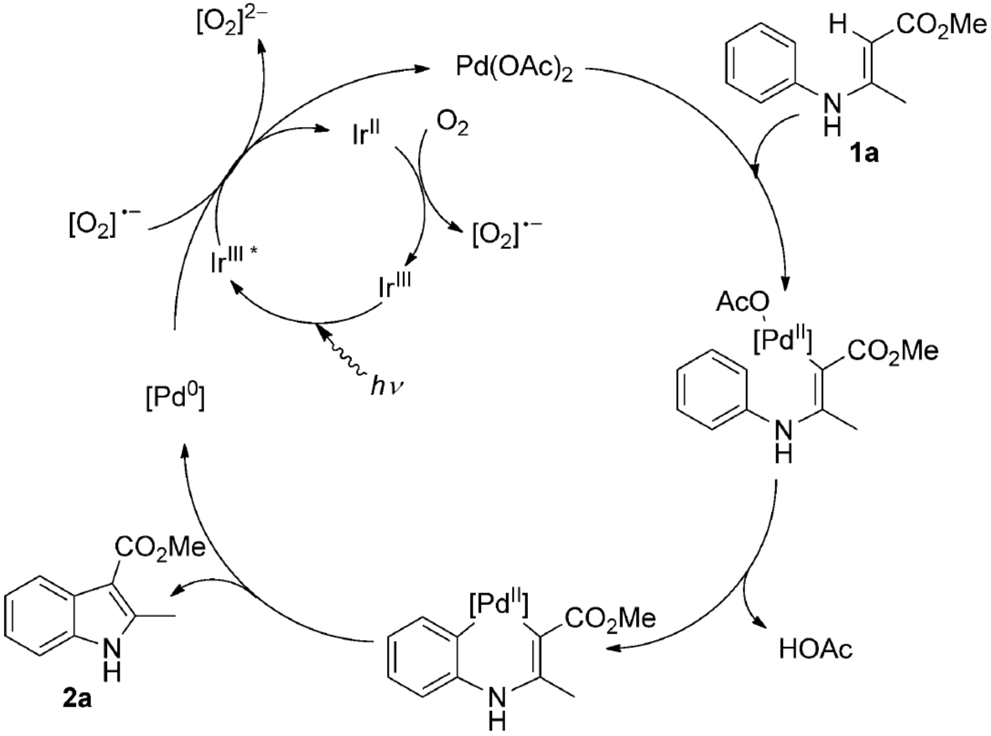


Kalyani, D.; McMurtrey, K. B.; Neufeldt, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18566−18569.

2. C-C bond formation

➢ Photoredox/Pd-catalyzed intramolecular C-H olefinations

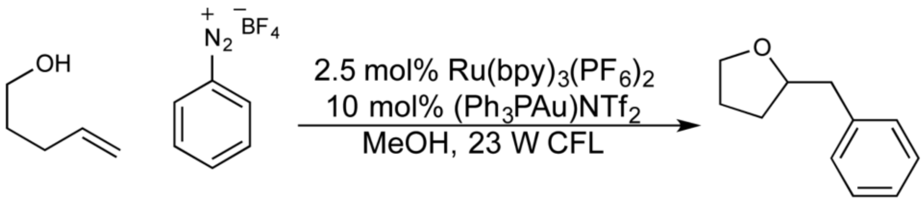




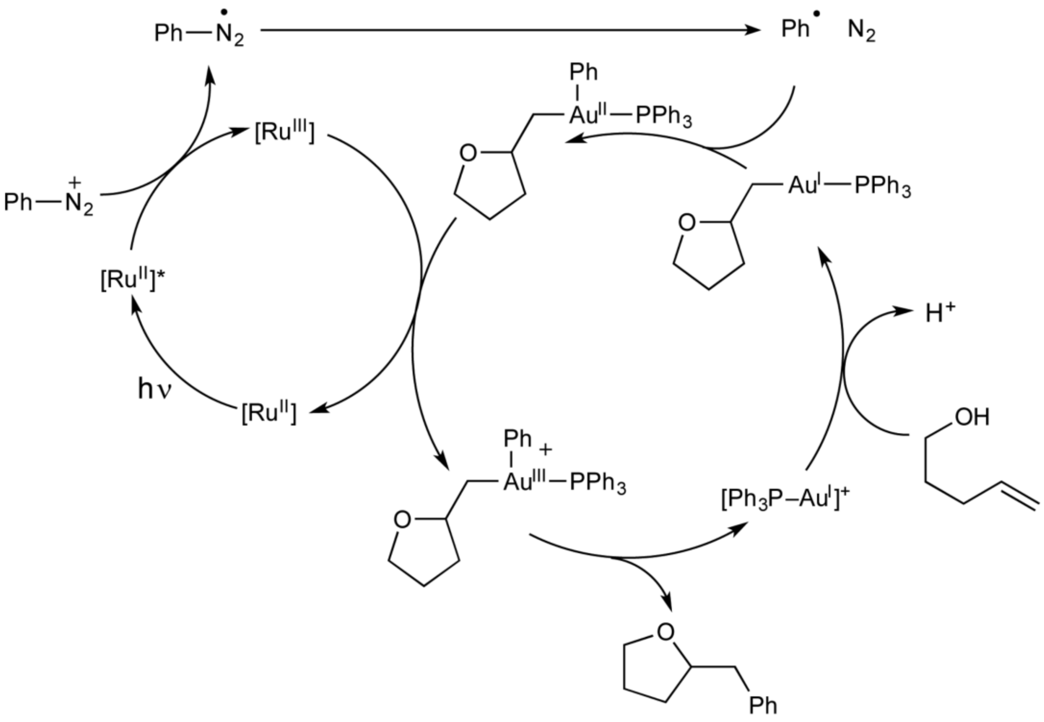
Zoller, J.; Fabry, D. C.; Ronge, M. A.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, *53,* 13264−13268.

2. C-C bond formation

➢ Photoredox/Au-catalyzed oxy/amino arylation



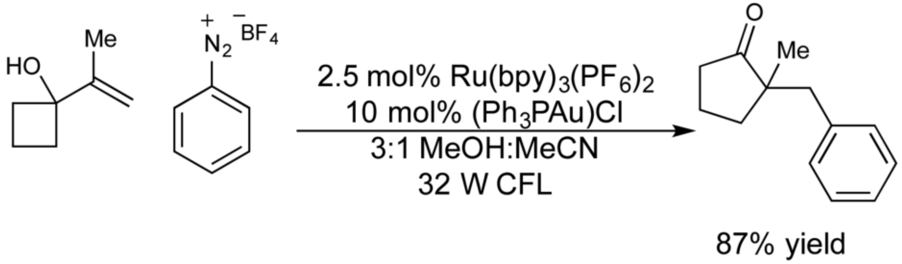
79% yield

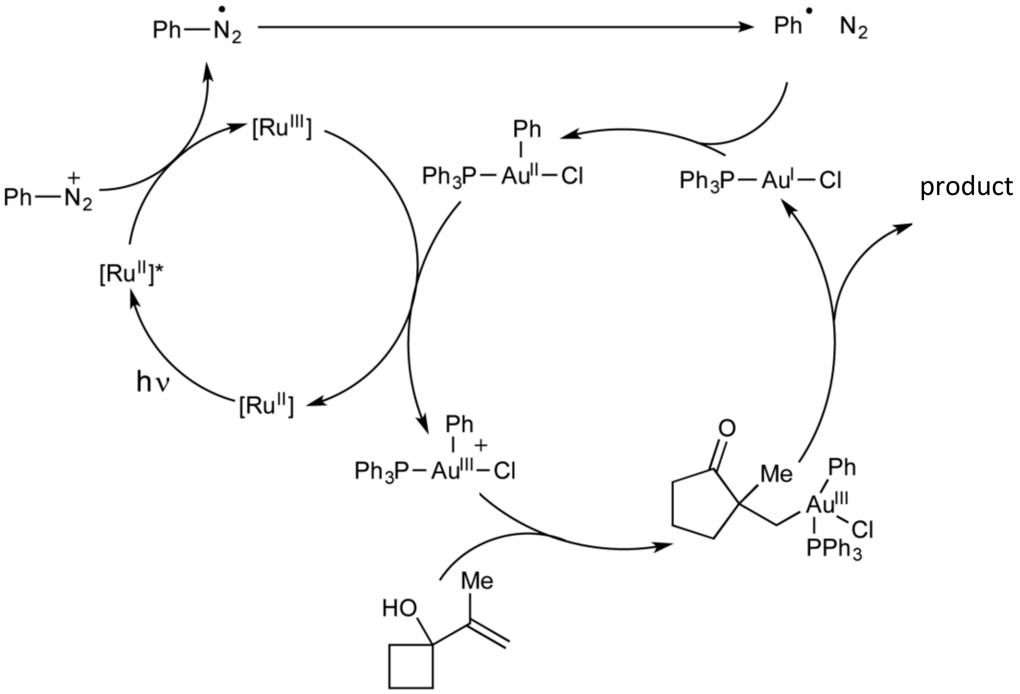


(a) Sahoo, B.; Hopkinson, M. N.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135,* 5505−5508.
(b) Hopkinson, M. N.; Sahoo, B.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356,* 2794−2800.

2. C-C bond formation

➢ Photoredox/Au-catalyzed ring expansion-arylation reactions





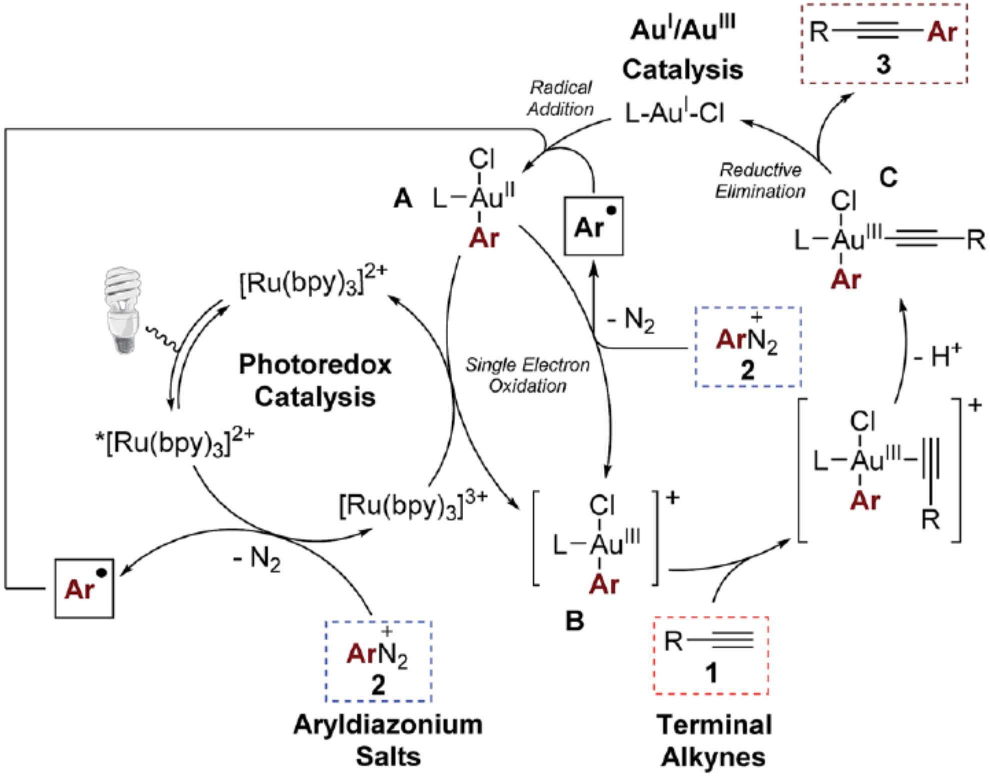
Shu, X.-Z.; Zhang, M.; He, Y.; Frei, H.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5844−5847.

2. C-C bond formation

➢ Photoredox/Au-catalyzed C(sp)-C(sp²) couplings

$$R{-}{\equiv} \; + \; [ArN_2]BF_4 \xrightarrow[\text{DMF, 23 W CFL}]{\text{10 mol\% L-Au-Cl, 0.5 mol\% }[Ru(bpy_3)](PF_6)_2} R{-}{\equiv}{-}Ar$$

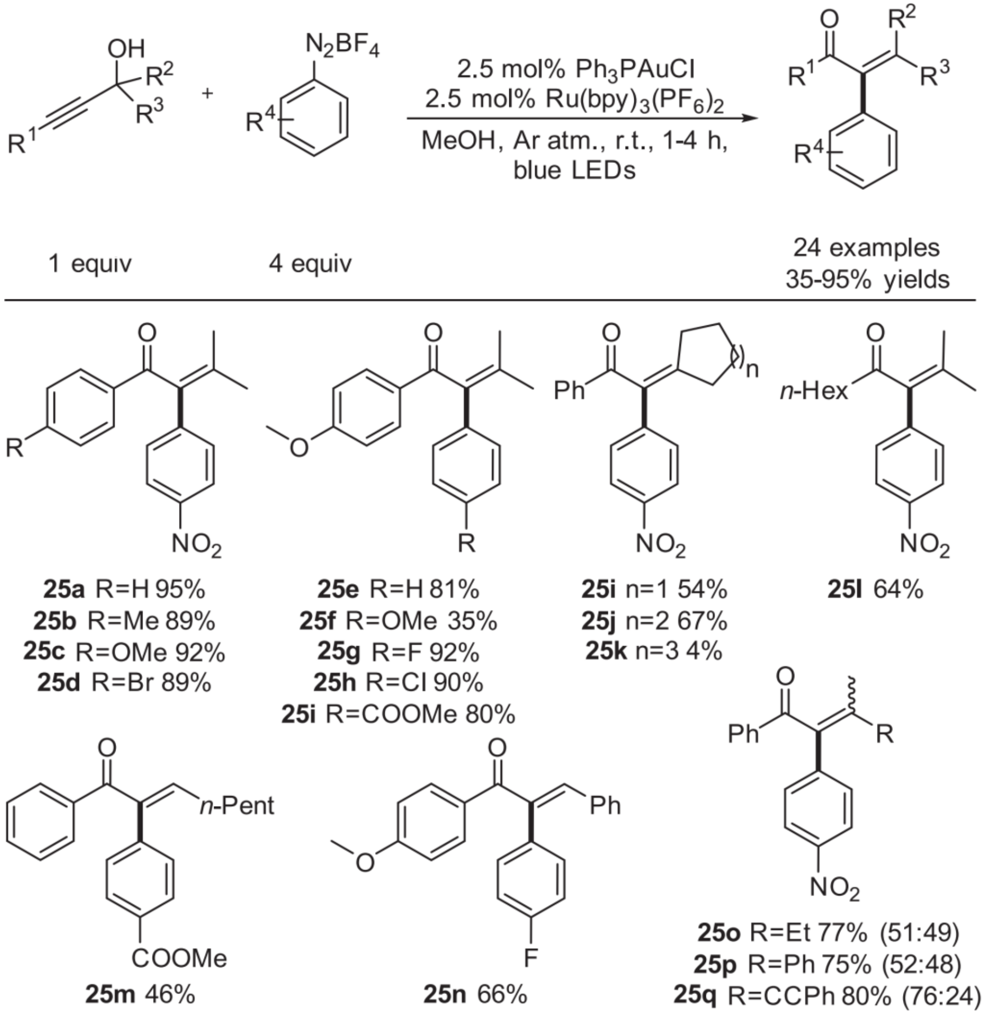
R= Aryl or Allkyl



Tlahuext-Aca, A.; Hopkinson, M. N.; Sahoo, B.; Glorius, F. *Chem. Sci.* **2016**, *7*, 89-93.

2. C-C bond formation

➢ Photoredox/Au-catalyzed Meyer-Schuster rearrangement



25a R=H 95%
25b R=Me 89%
25c R=OMe 92%
25d R=Br 89%

25e R=H 81%
25f R=OMe 35%
25g R=F 92%
25h R=Cl 90%
25i R=COOMe 80%

25i n=1 54%
25j n=2 67%
25k n=3 4%

25l 64%

25m 46%

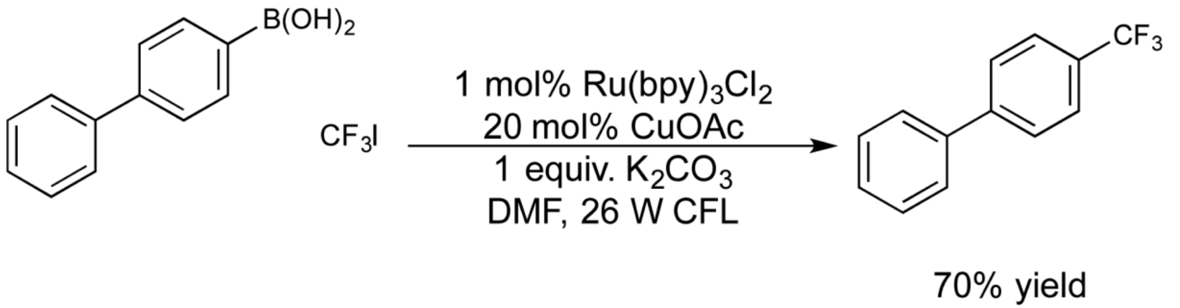
25n 66%

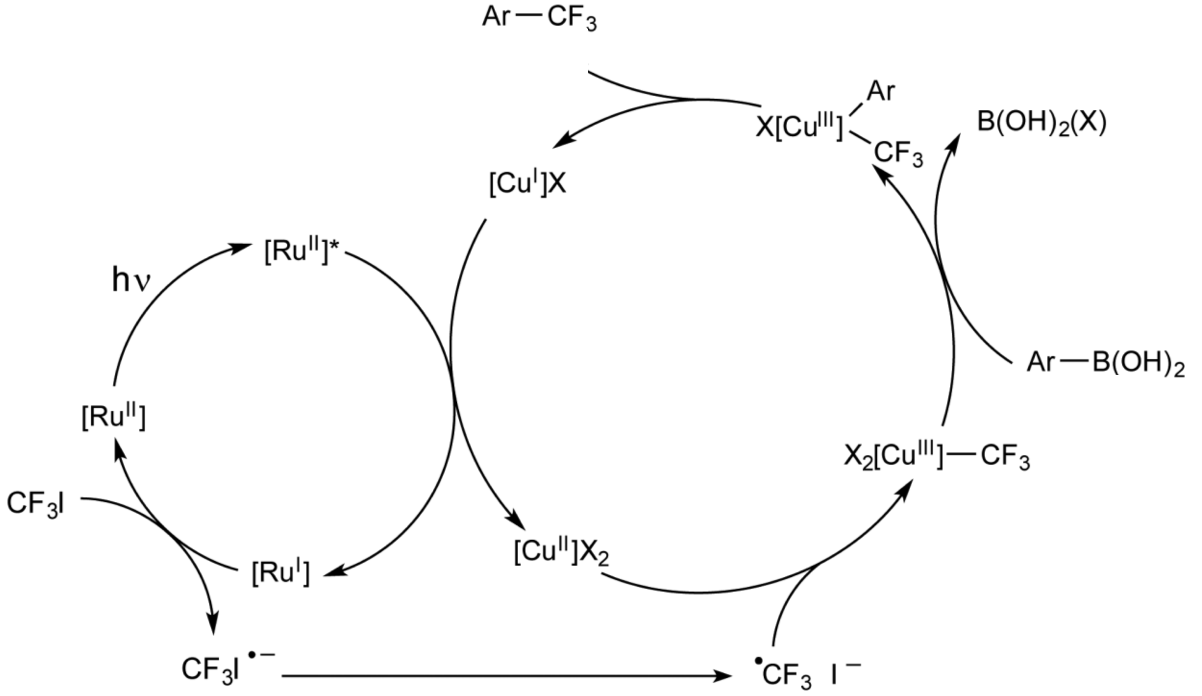
25o R=Et 77% (51:49)
25p R=Ph 75% (52:48)
25q R=CCPh 80% (76:24)

Tlahuext-Aca, A.; Hopkinson, M. N.; Garza-Sanchez, R. A.; Glorius, F. *Chem. - Eur. J.* **2016**, *22*, 5909–5913.

2. C-C bond formation

- **Photoredox/Cu catalyzed trifluoromethylation of boronic acid**

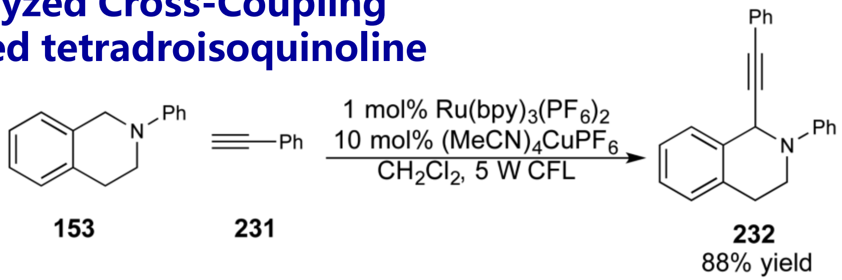


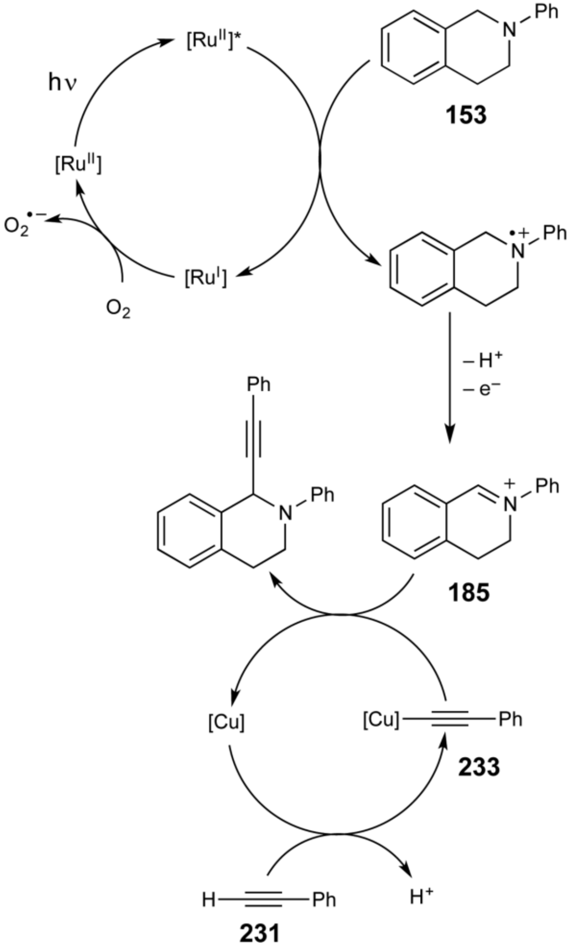


Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, *134,* 9034−9037.

2. C-C bond formation

- **Photoredox/Cu-Catalyzed Cross-Coupling**
  Synthesis of alkynlated tetradroisoquinoline

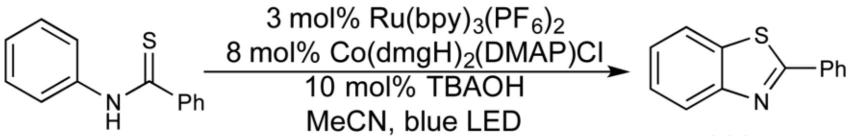




Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2012**, *14,* 94–97

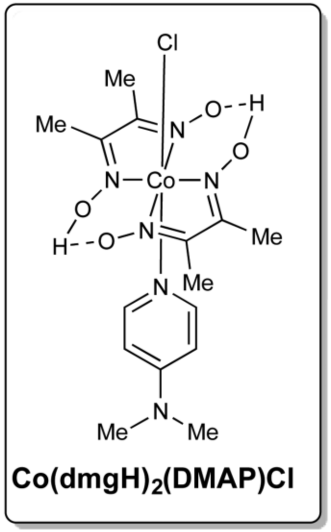
2. C-C bond formation

Photoredox/Co-Catalyzed Cross-Coupling

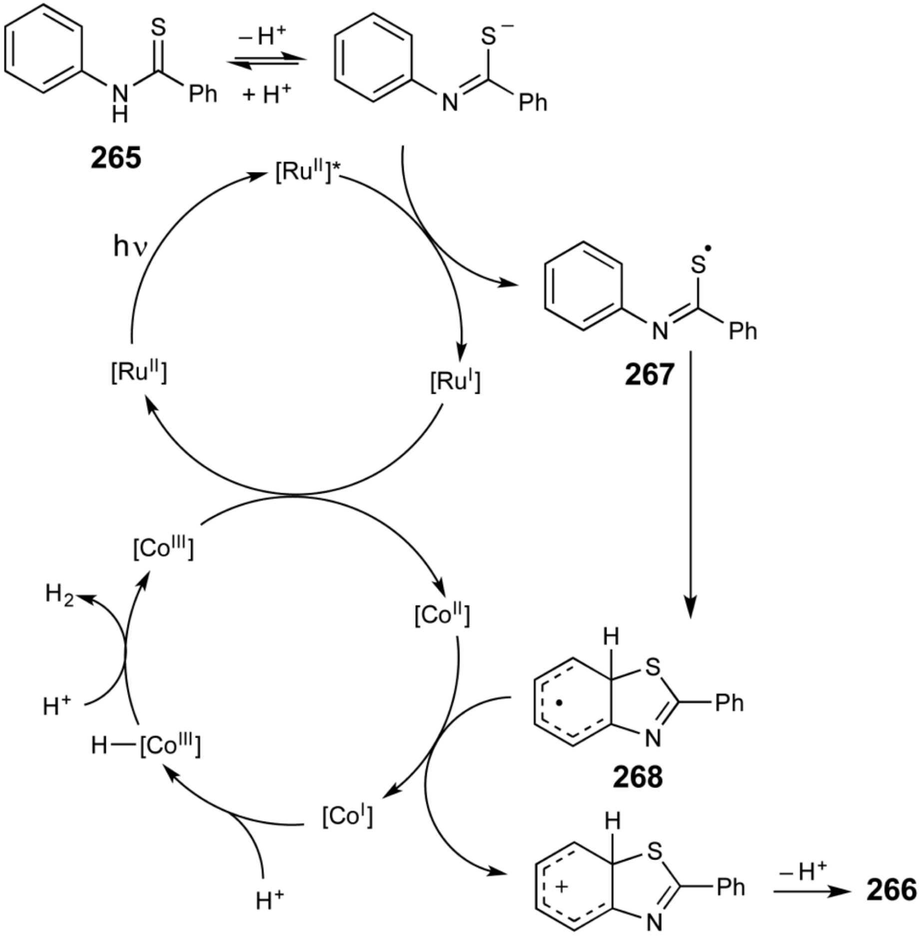


265

266
99% yield



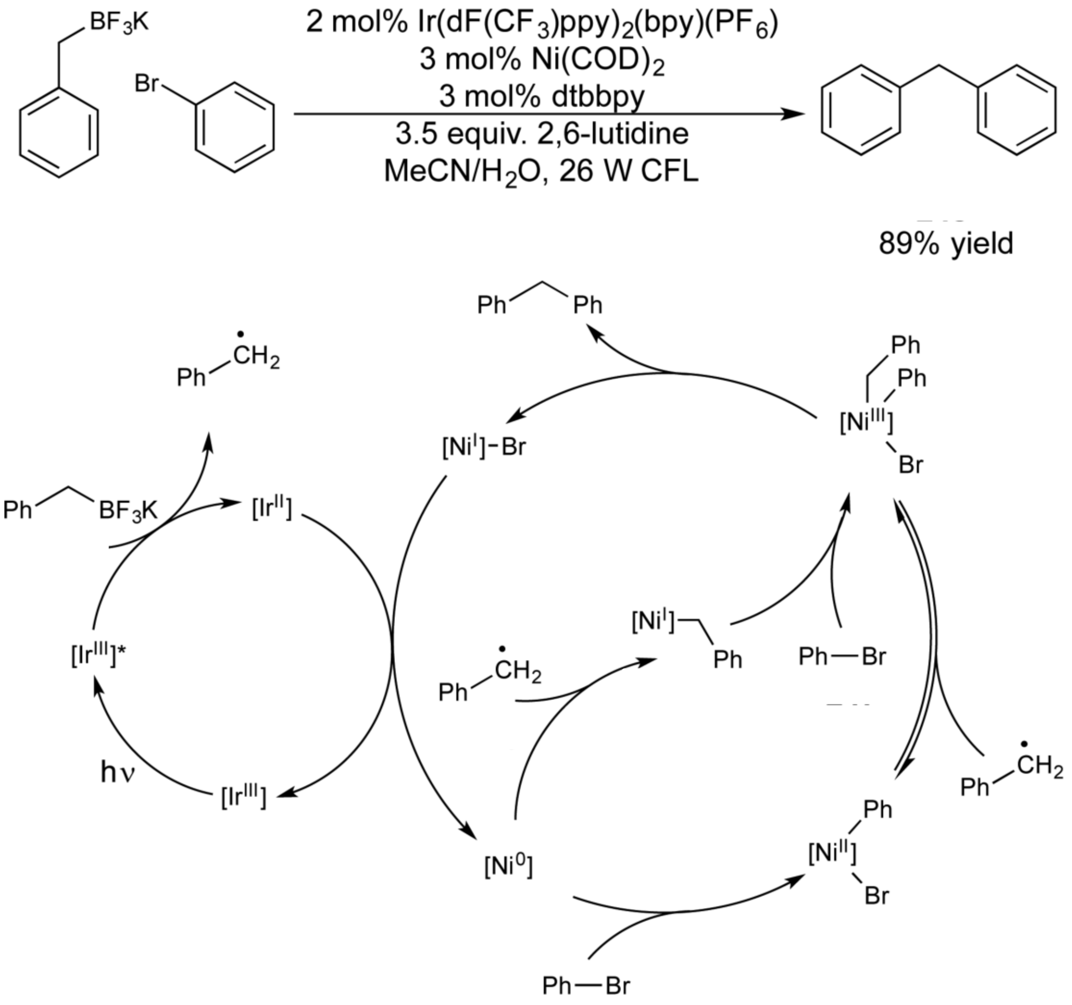
Co(dmgH)$_2$(DMAP)Cl



Zhang, G.; Liu, C.; Yi, H.; Meng, Q.; Bian, C.; Chen, H.; Jian, J.-X.; Wu, L.-Z.; Lei, A. *J. Am. Chem. Soc.* **2015**, *137*, 9273-9280.

2. C-C bond formation

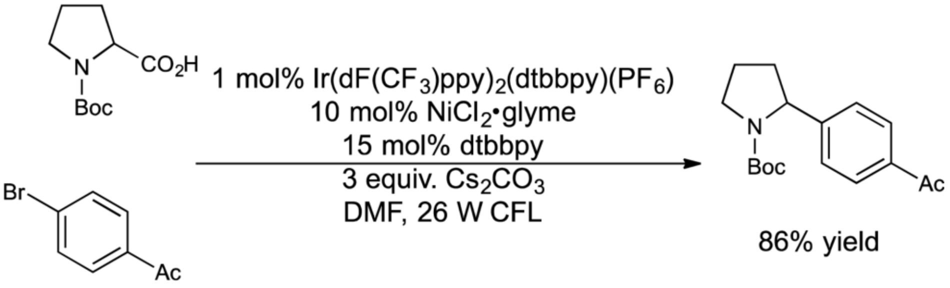
- **Ni-Catalyzed Cross-Coupling Employing Photocatalytically Generated Benzylic Radicals**



Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345,* 433–436.

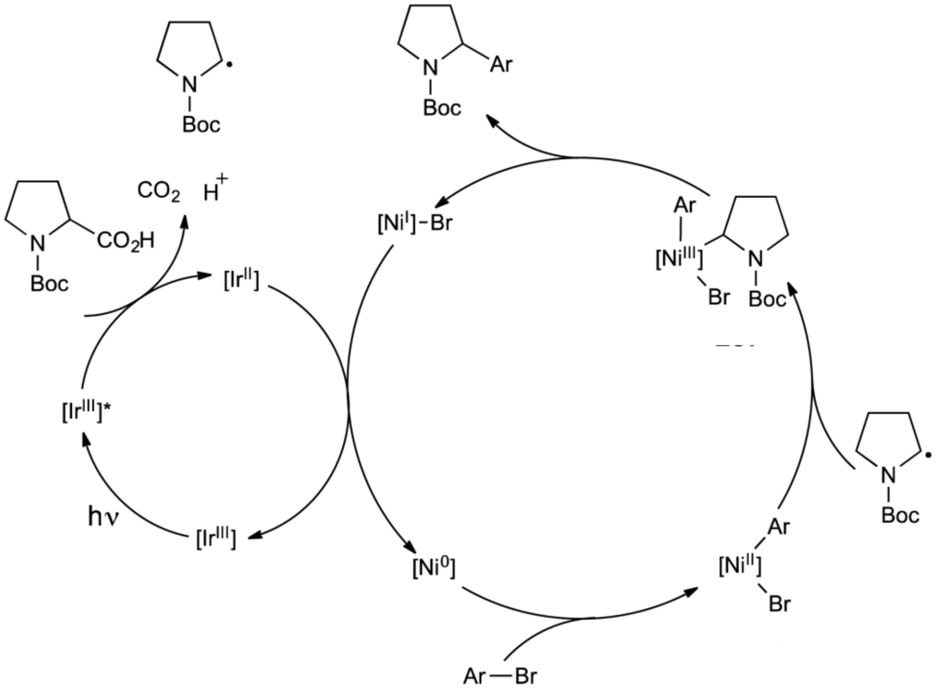
2. C-C bond formation

- **Nickel-Catalyzed Cross Coupling Using Photocatalytic Decarboxylation To Generate α-Amino Radicals**



1 mol% $Ir(dF(CF_3)ppy)_2(dtbbpy)(PF_6)$
10 mol% $NiCl_2$•glyme
15 mol% dtbbpy
3 equiv. Cs_2CO_3
DMF, 26 W CFL

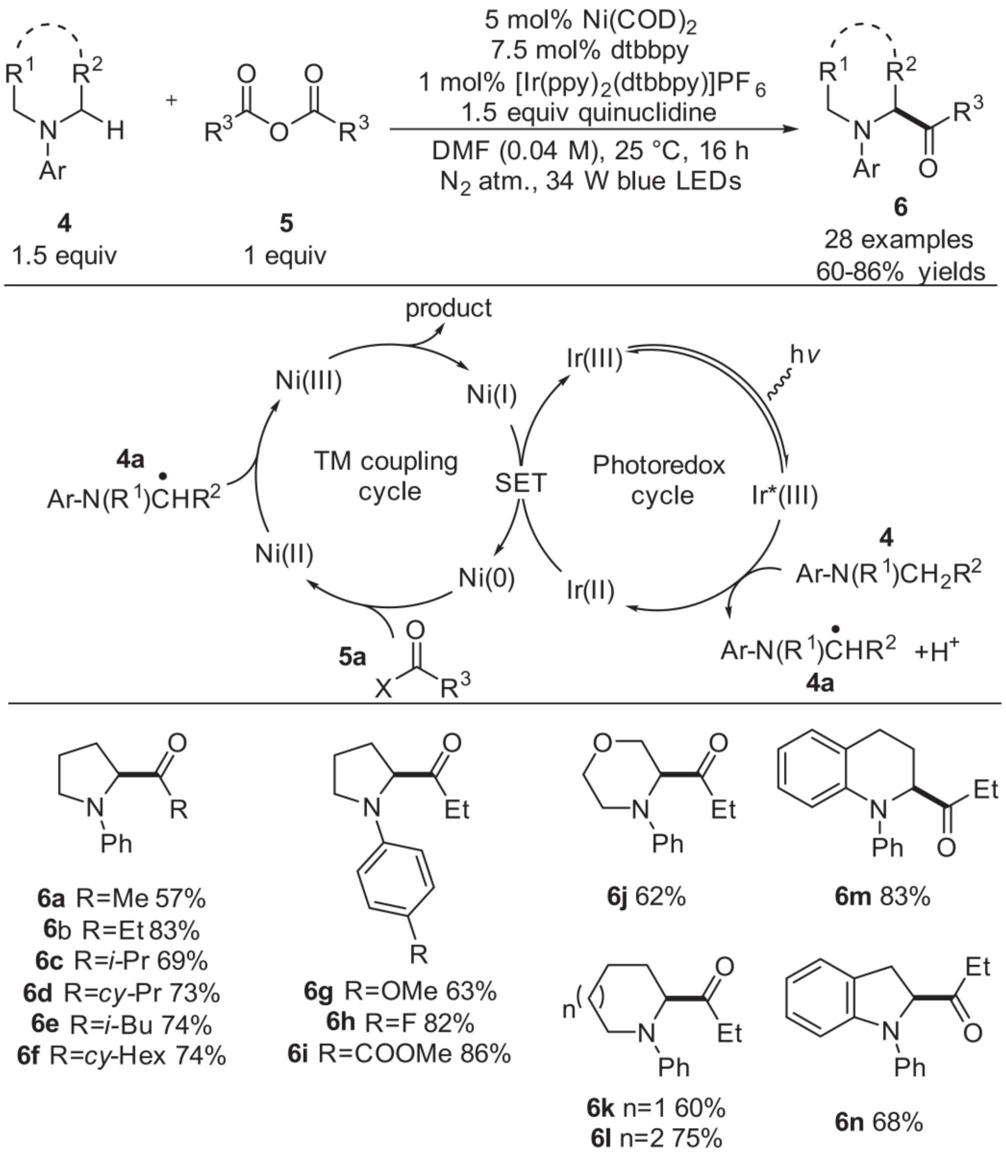
86% yield



Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345,* 437−440.

2. C-C bond formation

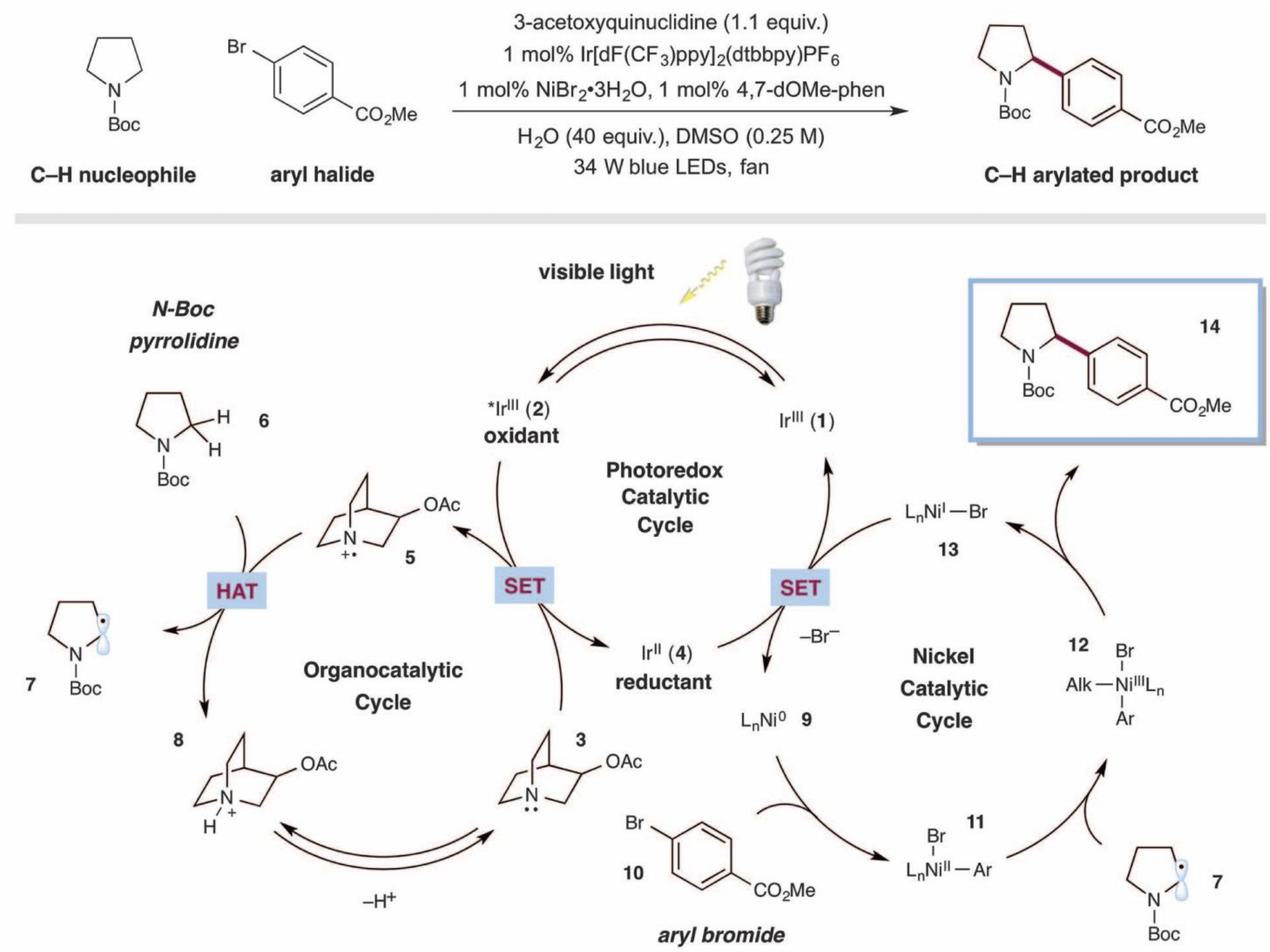
- **Photoredox/Ni-Catalyzed Cross-Coupling**



Joe, C. L.; Doyle, A. G. *Angew. Chem., Int. Ed.* **2016**, *55,* 4040–4043.

2. C-C bond formation

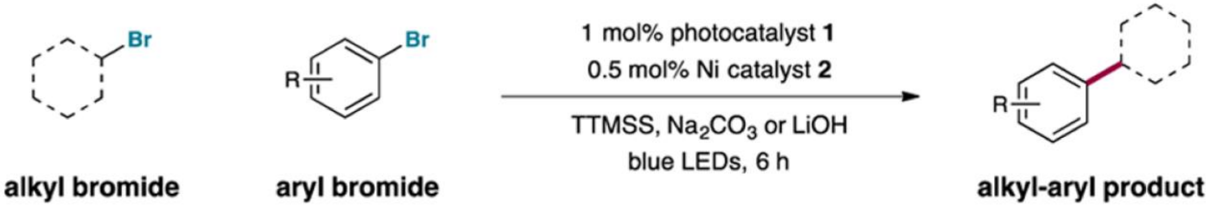
- **Photoredox/Ni-Catalyzed Cross-Coupling**

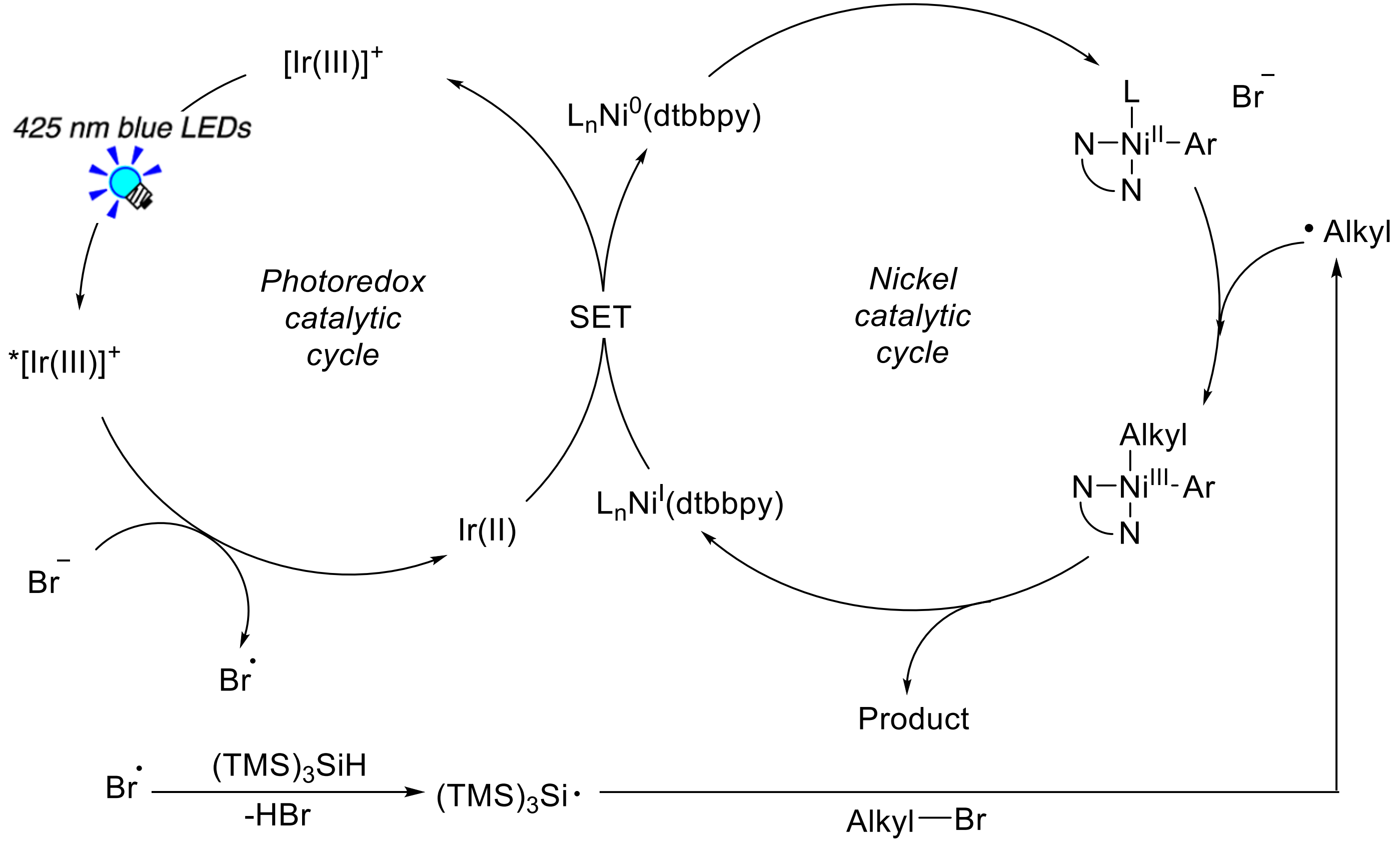


Shaw, M. H.; MacMillan, D. W. C. *et al. Science* **2016**, *352*, 1304-1308.

2. C-C bond formation

Photoredox/Ni-Catalyzed Cross-Coupling

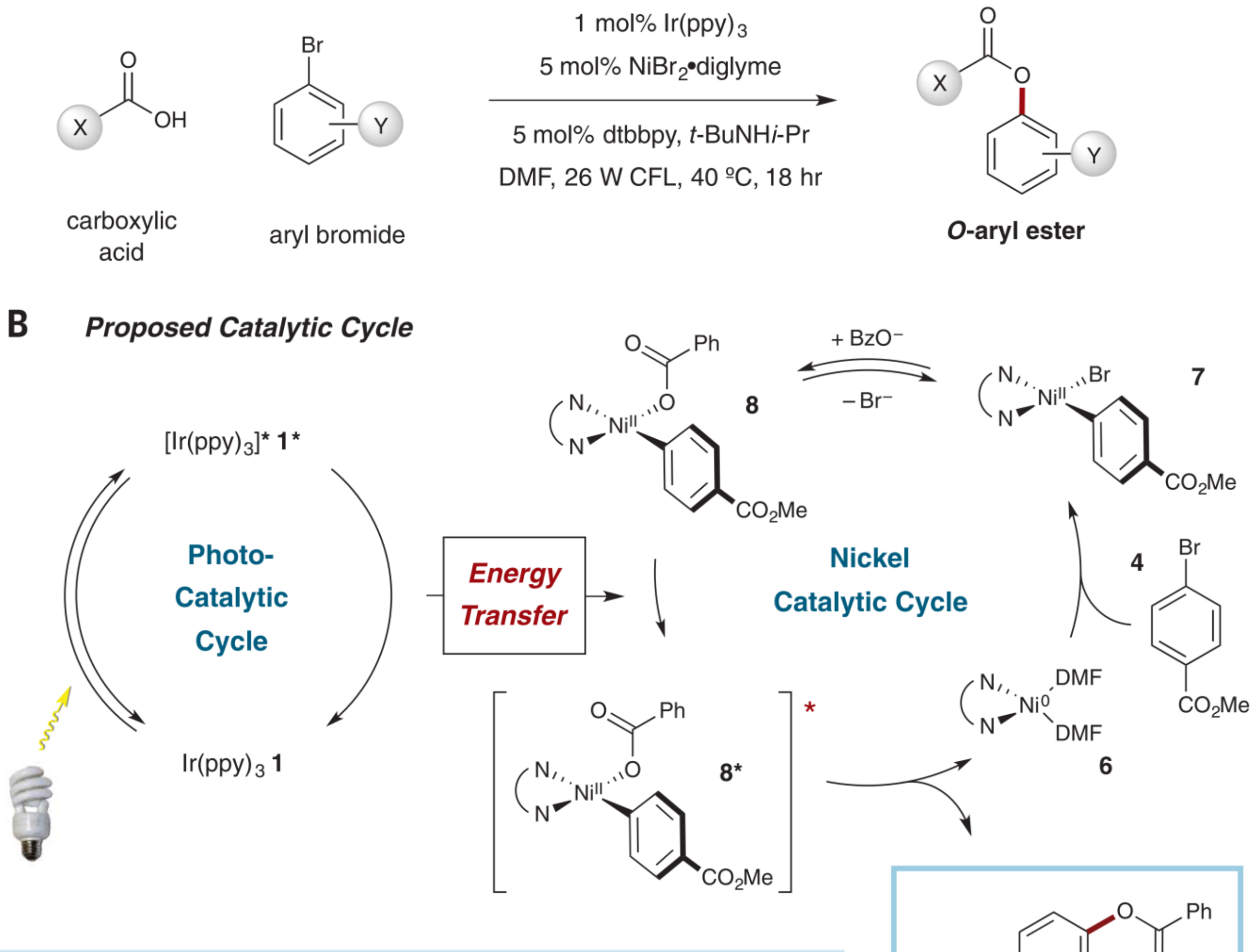




Shaw, M. H.; MacMillan, D. W. C. *et al. Science* **2016**, *352*, 1304-1308.

2. C-C bond formation

➢ Energy transfer

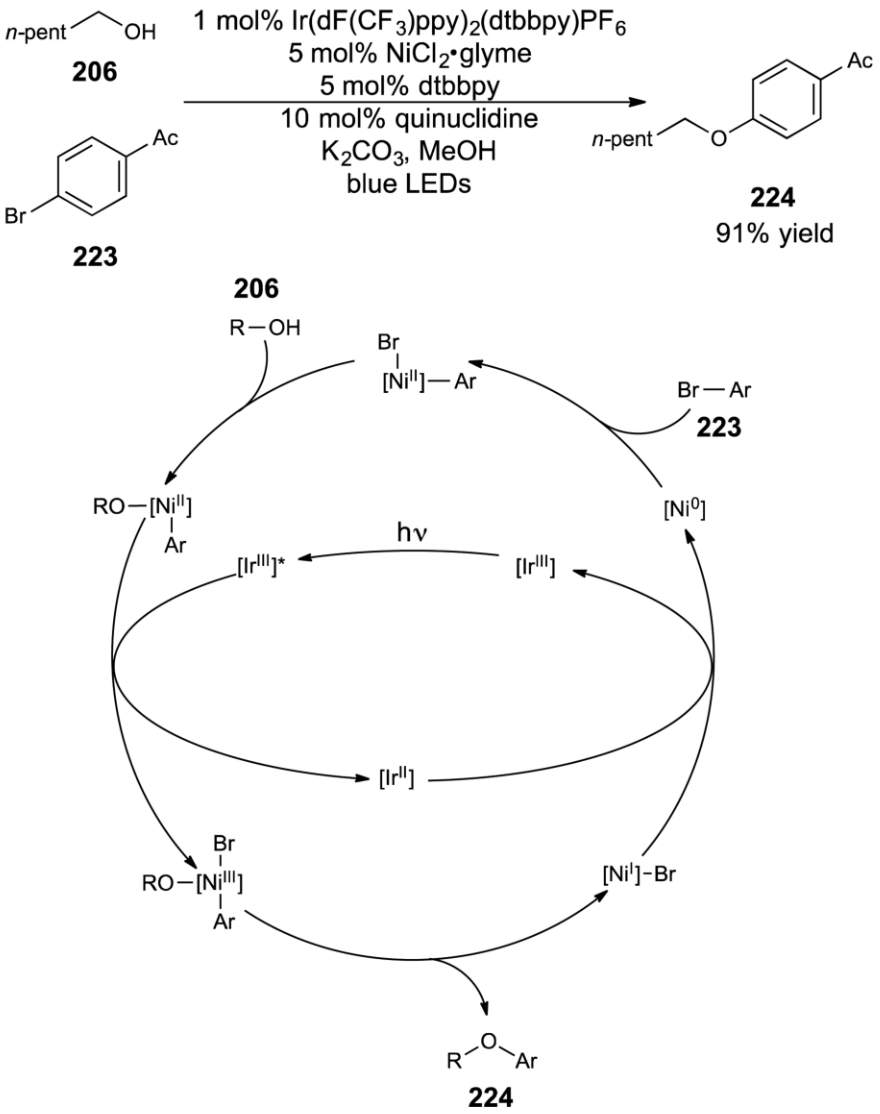


- *Ir-to-Ni energy transfer induces C–O reductive elimination*
- *underexploited mechanism of organometallic activation*

Welin et al., Science 355, 380–385 (2017)

3. C-(hetero) atom formation

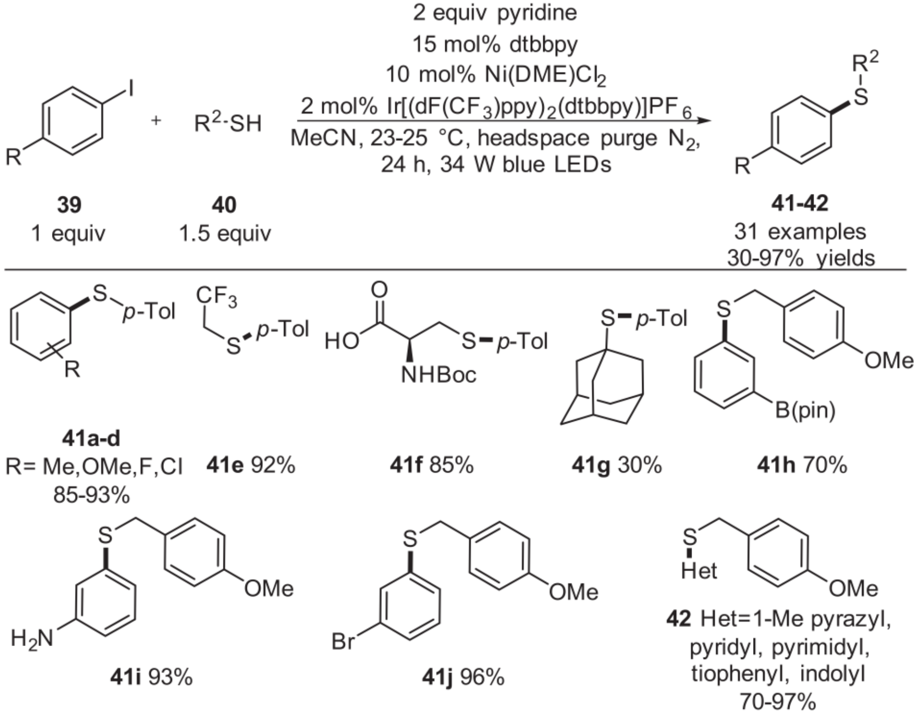
➢ C-O bond formation

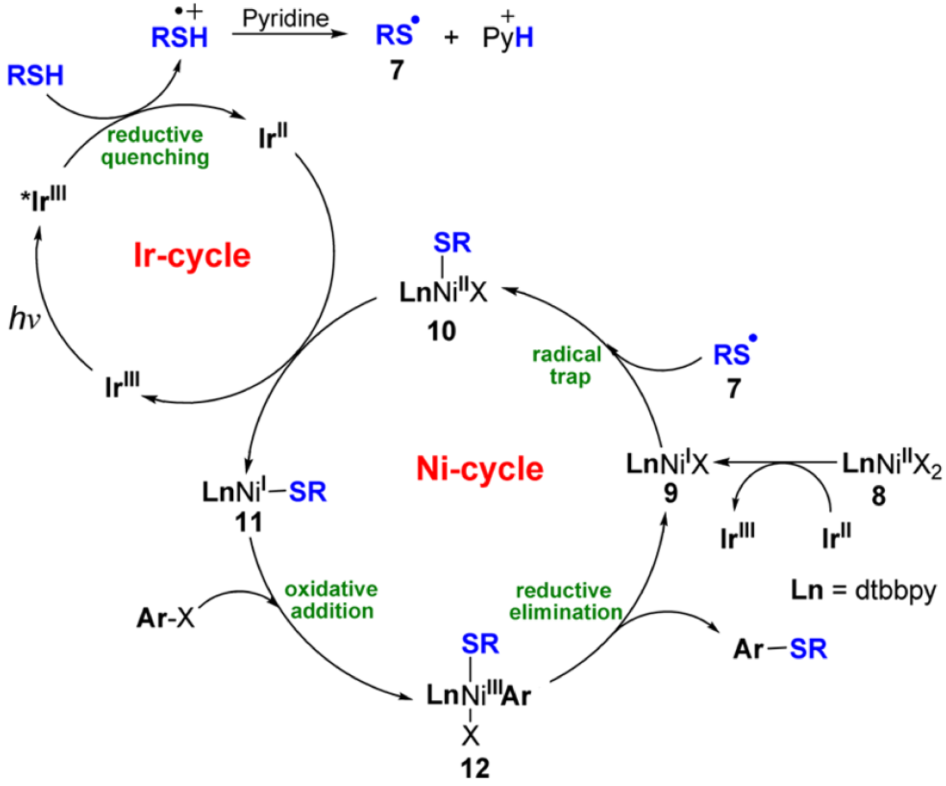


Terrett, J. A.; Cuthbertson, J.D.; Shurtleff, V.W.; MacMillan, D. W. C. *Nature* **2015**, *524,* 330–334.

3. C-(hetero) atom formation

➢ C-S bond formation

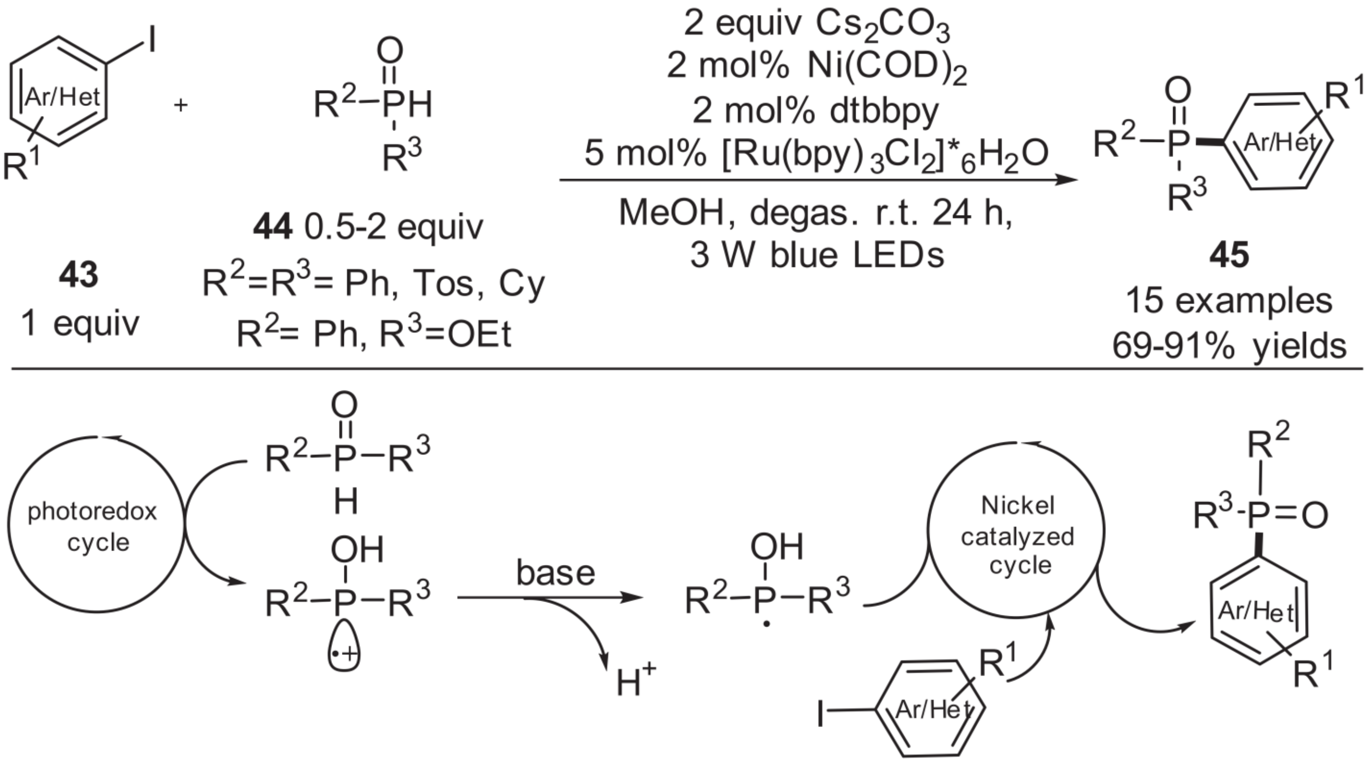




Oderinde, M. S.; Frenette, M.; Robbins, D. W.; Aquila, B.; Johannes, J. W. *J. Am. Chem. Soc.* **2016**, *138,* 1760–1763.

3. C-(hetero) atom formation

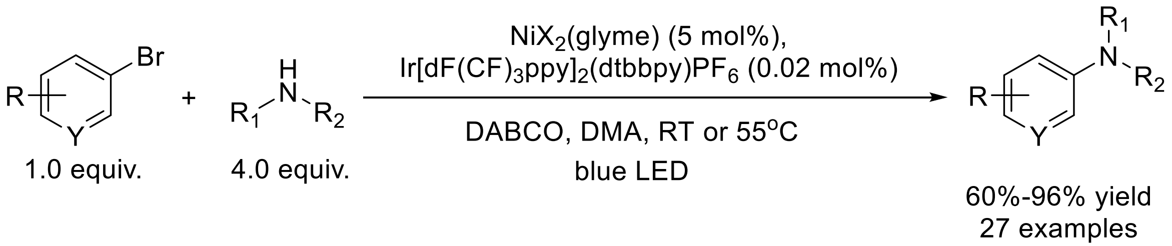
- **C-P bond formation**

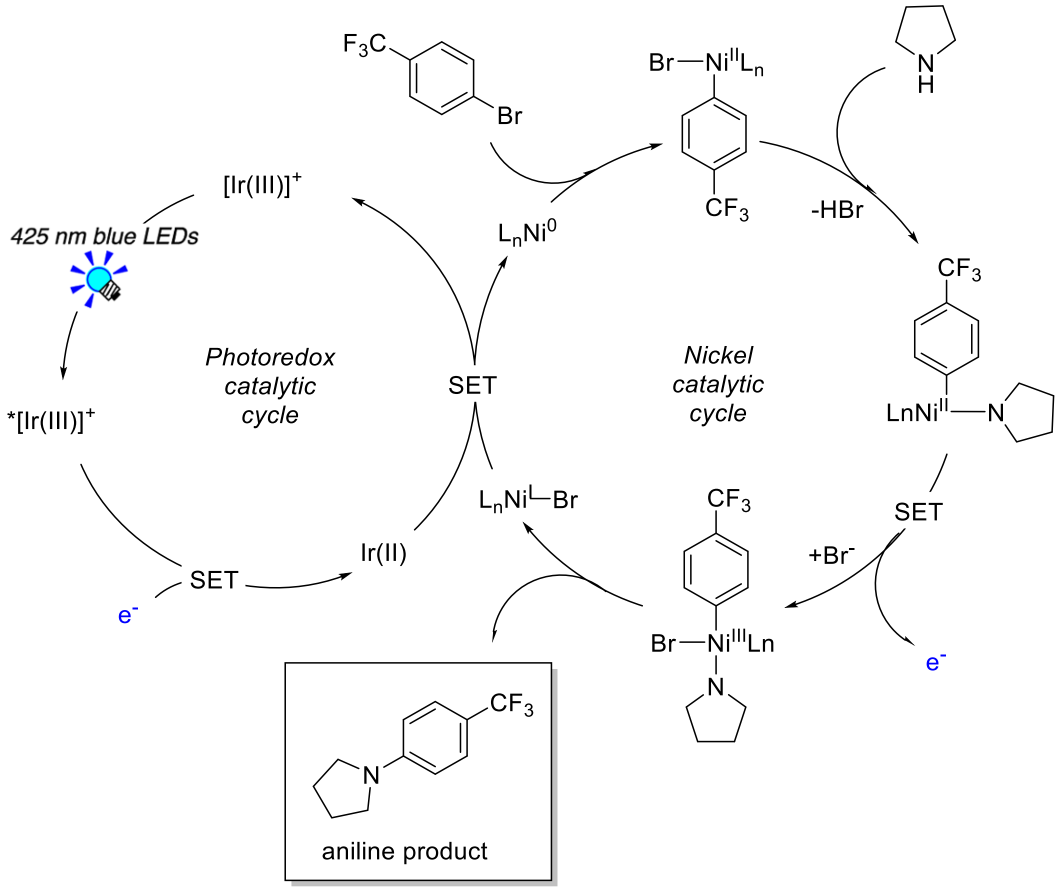


Xuan, J.; Zeng, T.-T.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. *Chem. Eur. J.* **2015**, *21*, 4962–4965.

3. C-(hetero) atom formation

➢ C-N bond foramtion

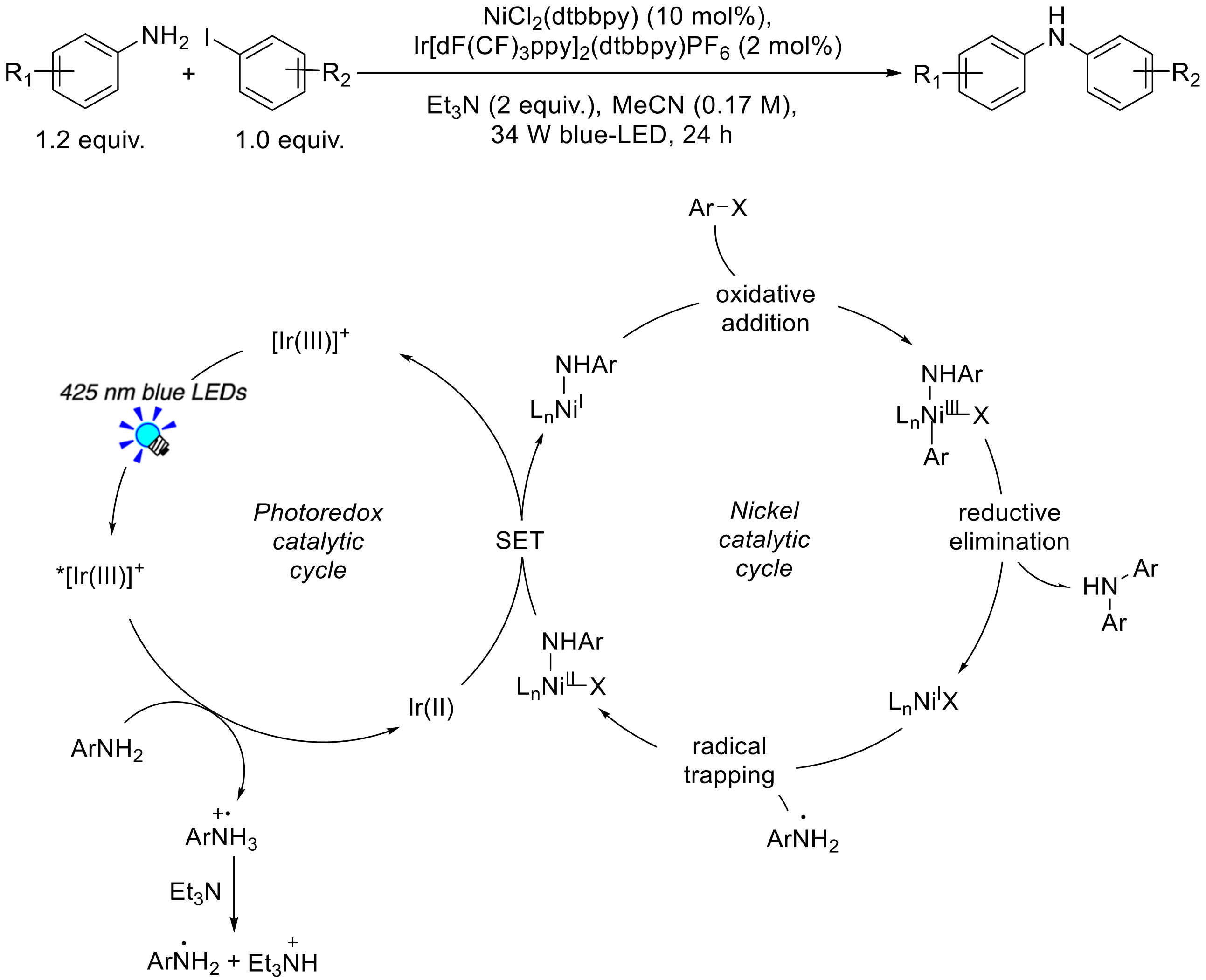




MacMillan, D. W. C. *et al. Science* **2016**, *353*, 279–283.

3. C-(hetero) atom formation

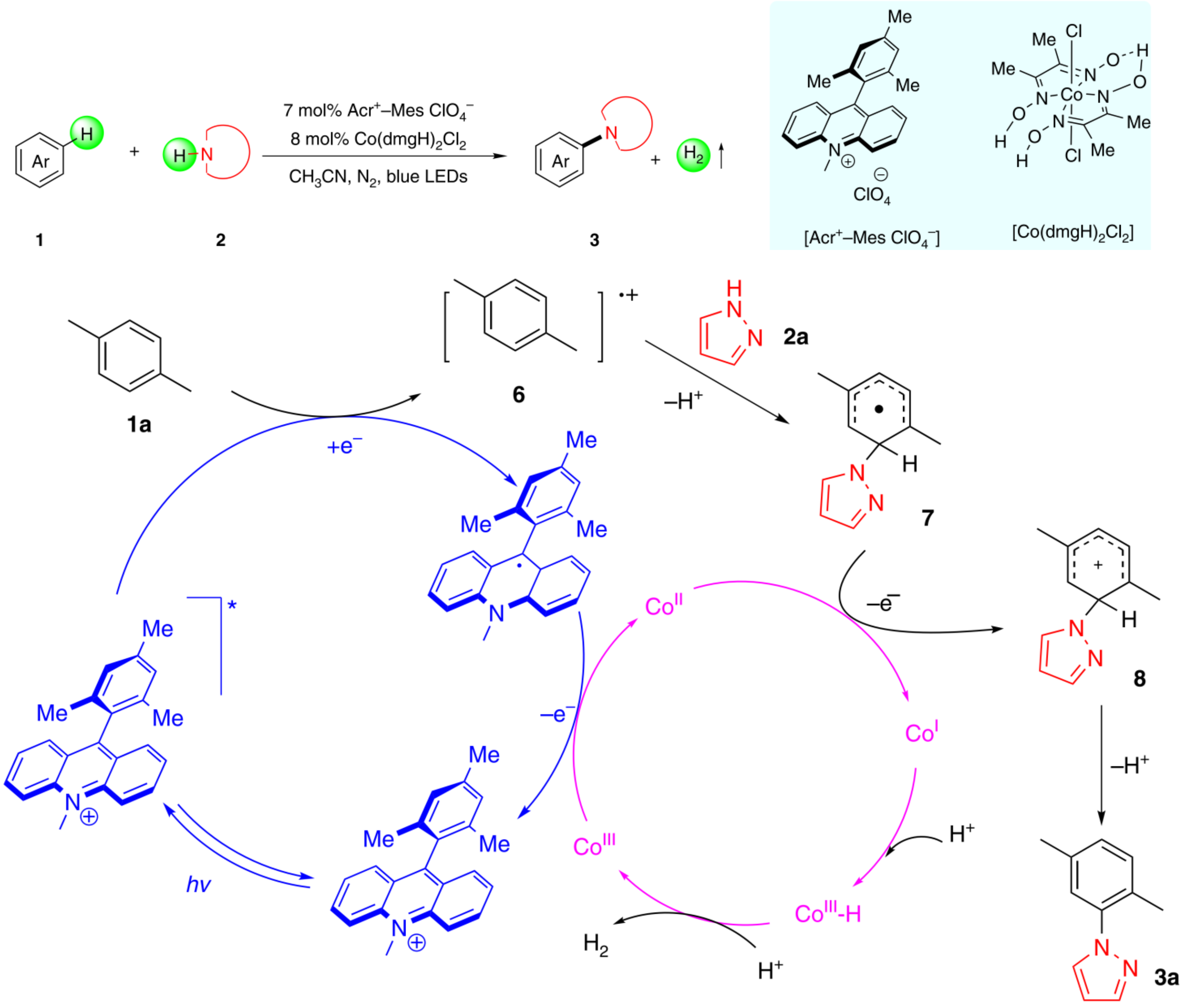
➢ C-N bond formaion



Martins S. Oderinde, Jeffrey W. Johannes *et al. Angew. Chem. Int. Ed.* **2016**, *55,* 1 – 6

3. C-(hetero) atom formation

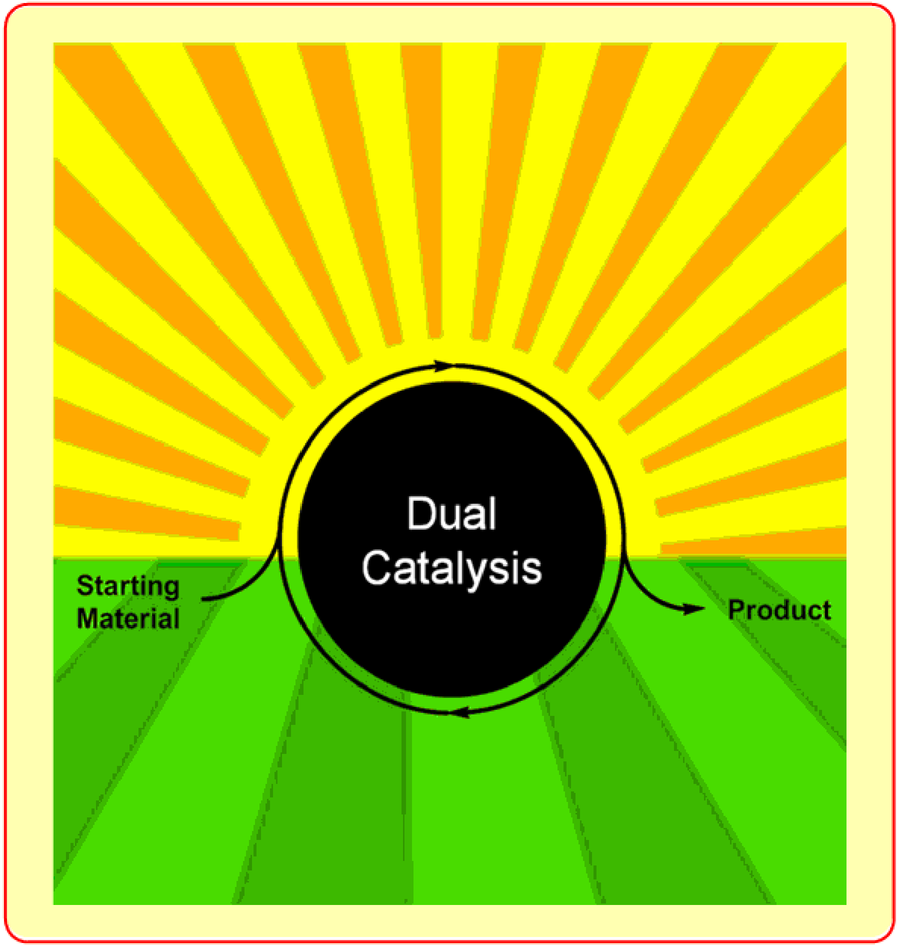
➢ C-N bond formaion



Linbin Niu, Hong Yi, Shengchun Wang, Tianyi Liu, Jiamei Liu and Aiwen Lei, *Nature Comm.*, **2017**, *8,* 14226-14232.

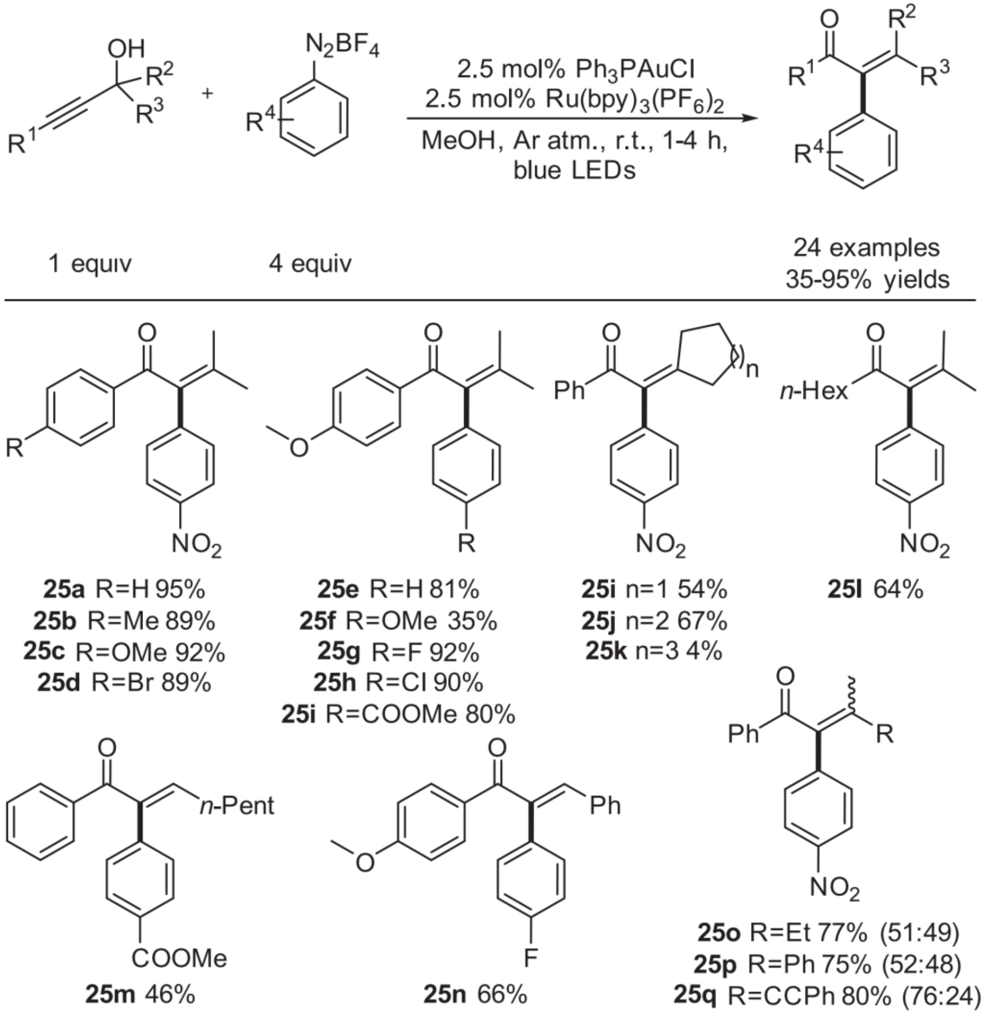
Question 1

- Why combine photoredox catalysis with transition metal catalysis?



Question 2

- **What is the mechanism of this reaction?**



Tlahuext-Aca, A.; Hopkinson, M. N.; Garza-Sanchez, R. A.; Glorius, F. *Chem. - Eur. J.* **2016**, *22*, 5909–5913.

THANKS!

Asymmetric Cooperative Catalysis of Transition Metals and Bronsted Acids

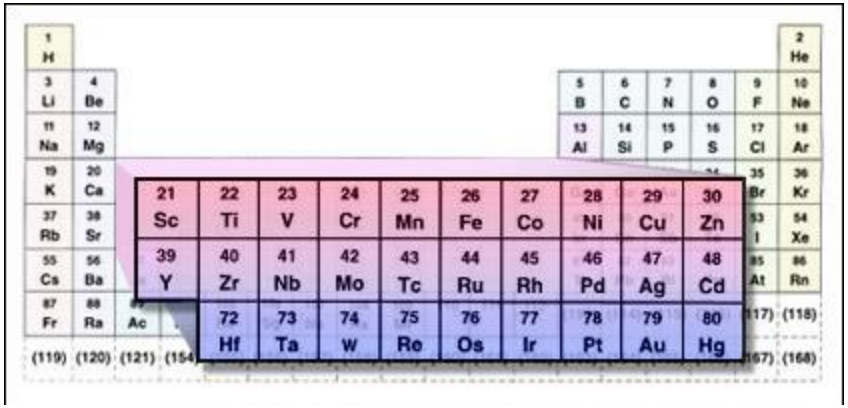
Yun-Suk Jang

Agenda

- Introduction
  - Overview
  - Concept
    - Examples Transition Metals with Aminocatalysts
  - Chiral Bronsted Acid Approaches
- Asymmetric Counter Anion Directed Catalysis (ACDC)
  - Examples
- Chiral Bronsted Acid Activation
  - Examples
- Summary
- Questions

Transition Metal Catalysis

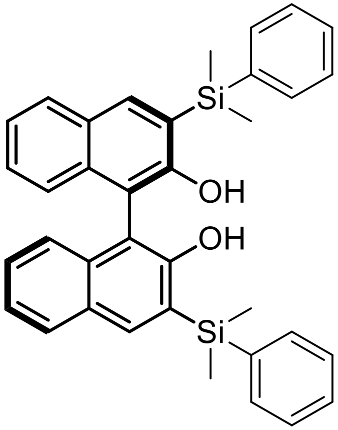
- **Advantages:**
  - Chemoselectivity
  - Regioselectivity
  - Stereoselectivity
  - High yield
  - Reproducibility
  - Low catalyst loading
- One of the most useful and powerful tool in organic chemistry.

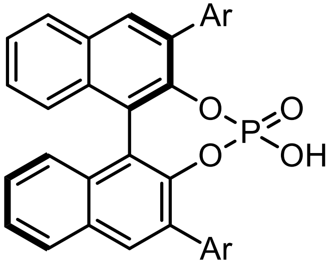


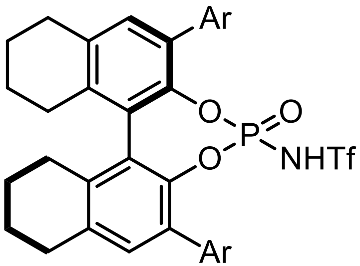
Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, 2nd ed., **2004**, vol. 1 and 2.

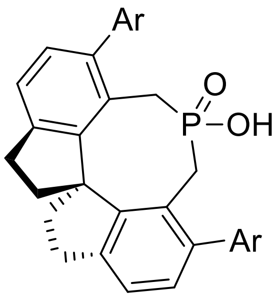
Chiral Bronsted Acids

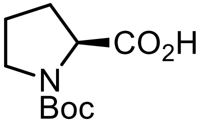
- Access to enantiomerically enriched molecules
- Belong to organocatalysts
- Main advantages:
  - Not expensive
  - Easily accessible
  - Stable to air and moisture
- One of the most useful and powerful tool in organic chemistry.







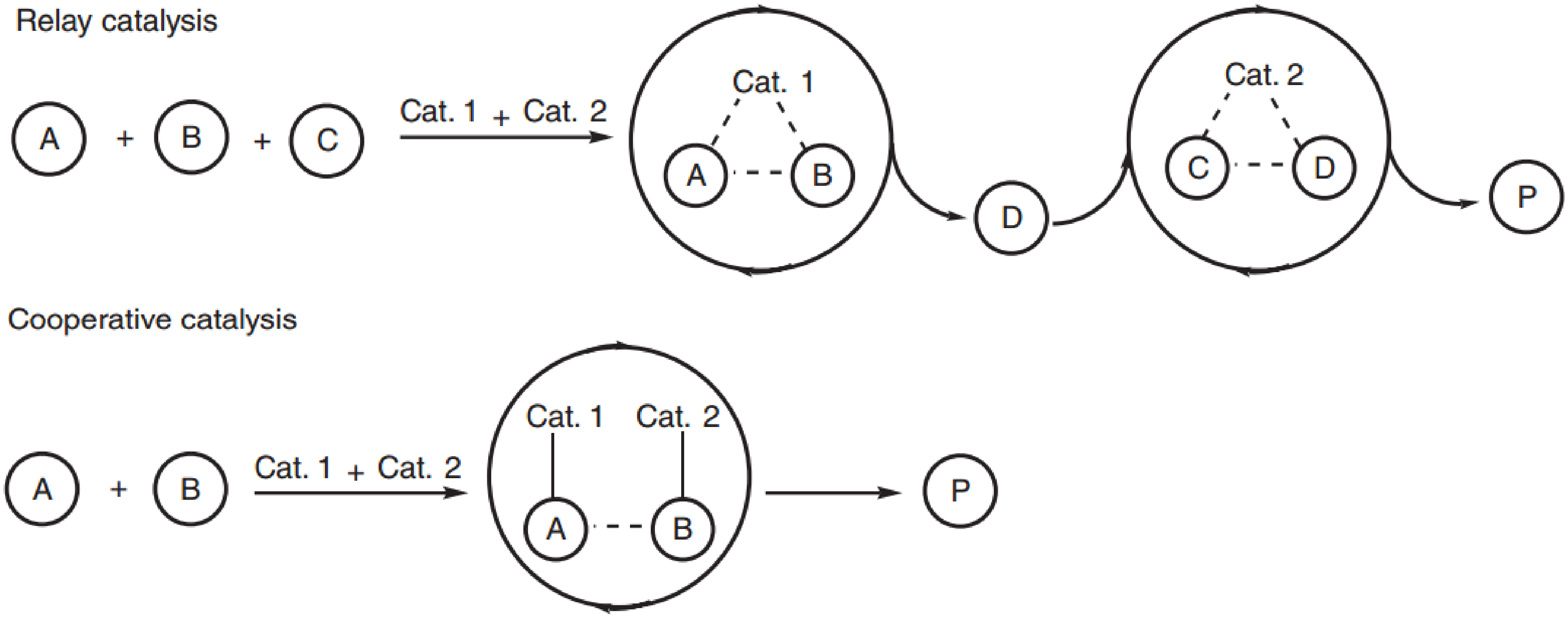




etc.

Cooperative Catalysis : Designing Efficient Catalysts for Synthesis (Ed,: R. Peters), Wiley-VCH, Weinheim, **2015**.

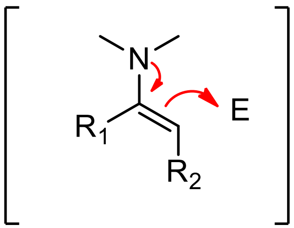
Concept: Sequential vs. Simultaneously Catalysis



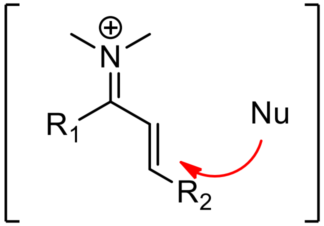
Cooperative Catalysis : Designing Efficient Catalysts for Synthesis (Ed,: R. Peters), Wiley-VCH, Weinheim, **2015**.

Overview of Other Related Cooperative Catalysis

Amine-Activated Carbonyl Compounds and Transition Metals



Enamine catalysis



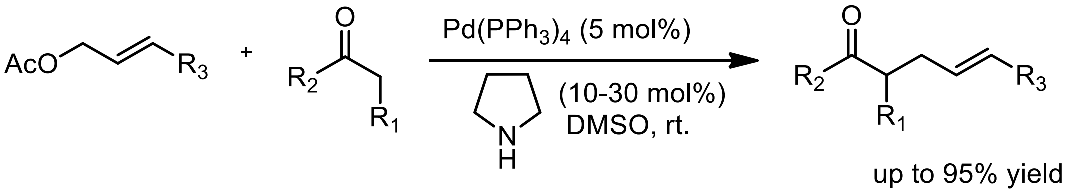
Iminium catalysis

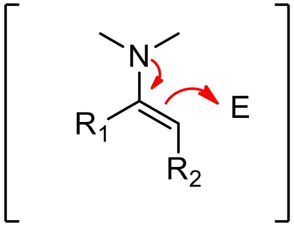
Amine activations are the most studied organocatalytic system

C. Zhong, X. Shi, *Eur. J. Org. Chem*. **2010**, *16*, 2999-3025

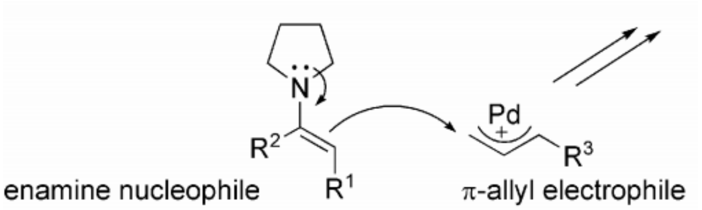
Intermolecular α-allylation

First example, Cordova et al. in 2006,





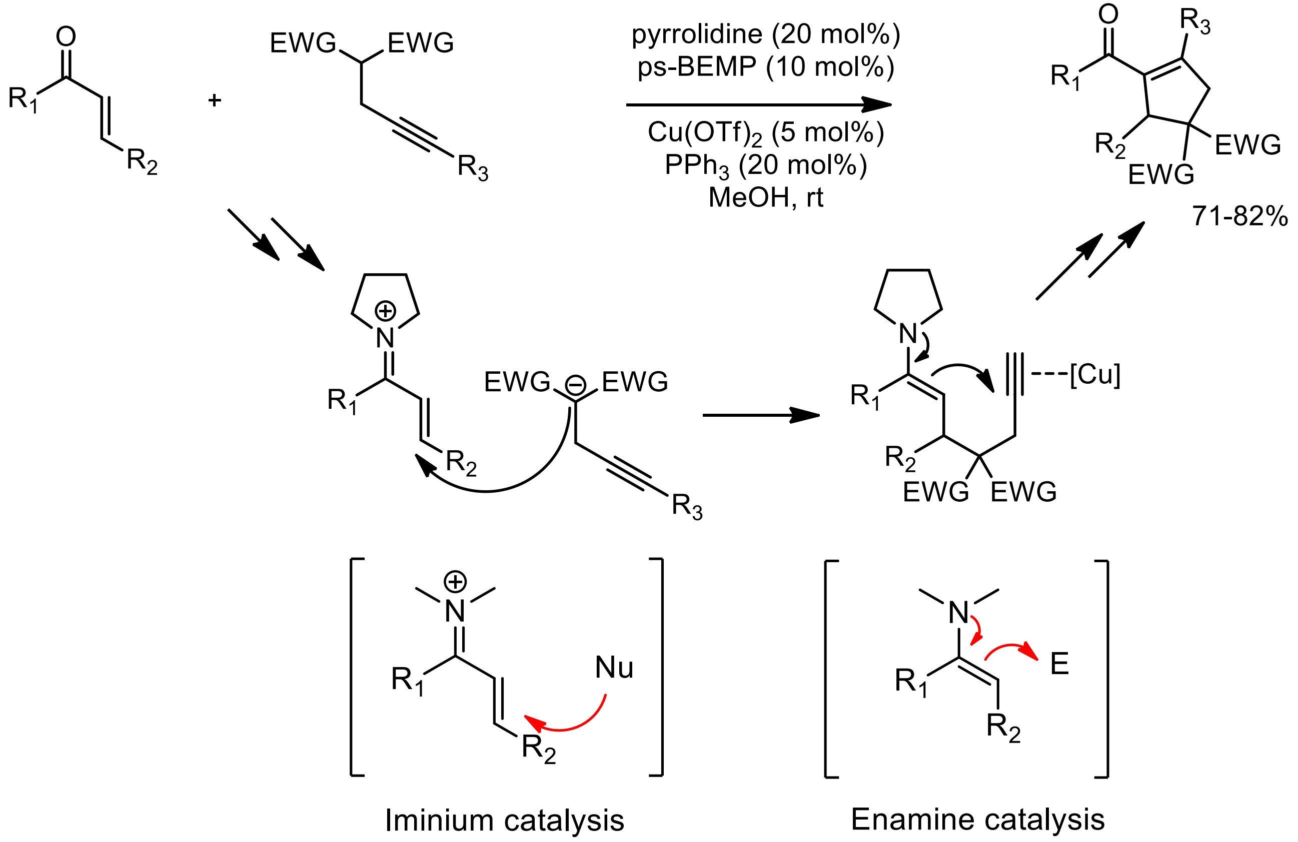
Enamine catalysis



I. Ibrahem, A. Cordova, *Angew. Chem. Int. Ed.* **2006**, *45*, 1952-1956

Iminium, enamine, Cu(I) cascade catalysis

Tandem reaction published by Dixon



pyrrolidine (20 mol%)
ps-BEMP (10 mol%)
$Cu(OTf)_2$ (5 mol%)
PPh_3 (20 mol%)
MeOH, rt

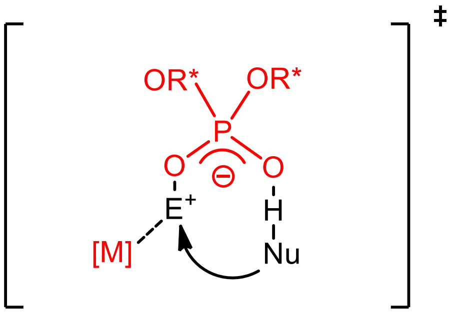
Iminium catalysis

Enamine catalysis

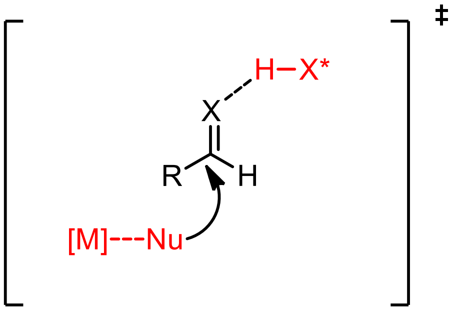
T. Yang, A. Ferrali, L. Campbell, D. J. Dixon, *Chem. Commun*. **2008**, 2923-2925.

Concept: Chiral Bronsted acid and Transition Metal

2 General Approaches:



Asymmetric Counter Anion Directed Catalysis (ACDC)

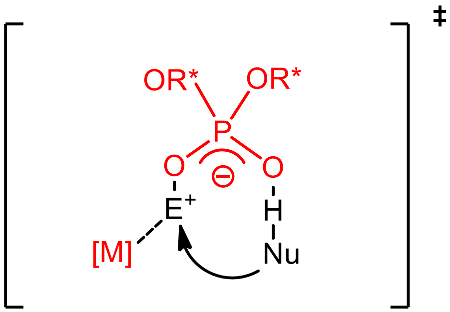


Chiral Brönsted Acid Activation

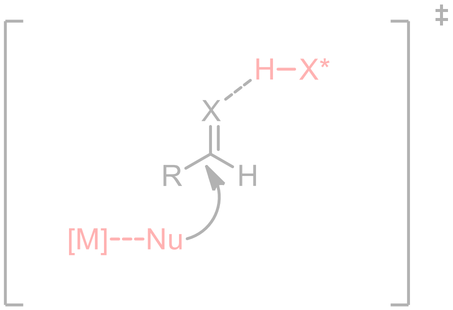
C. Zhong, X. Shi, *Eur. J. Org. Chem*. **2010**, *16*, 2999-3025

Chiral Bronsted acid and Transition Metal Concept

2 possible approaches:



Asymmetric Counter Anion Directed Catalysis (ACDC)

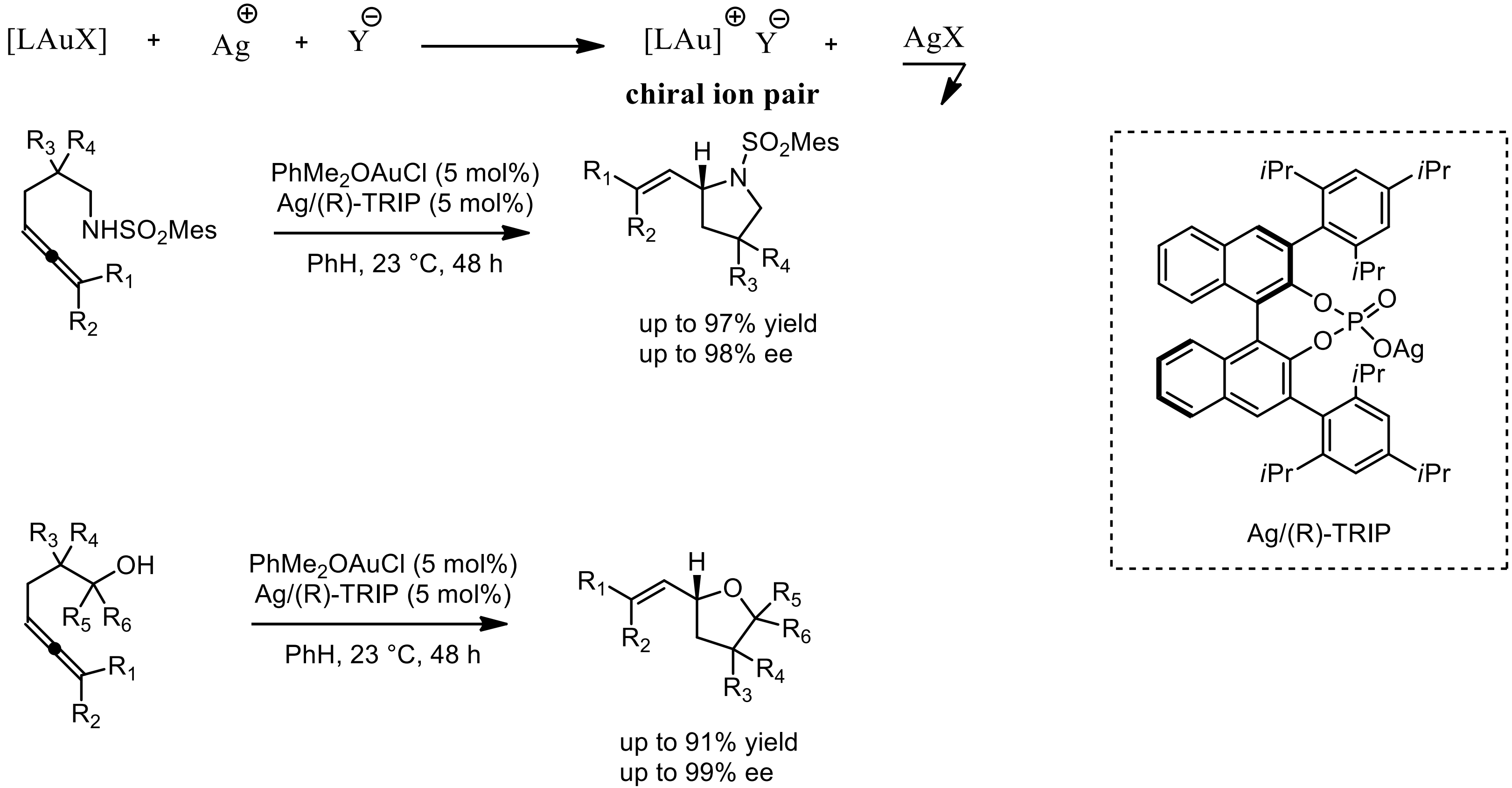


Chiral Brönsted Acid Activation

C. Zhong, X. Shi, *Eur. J. Org. Chem*. **2010**, *16*, 2999-3025

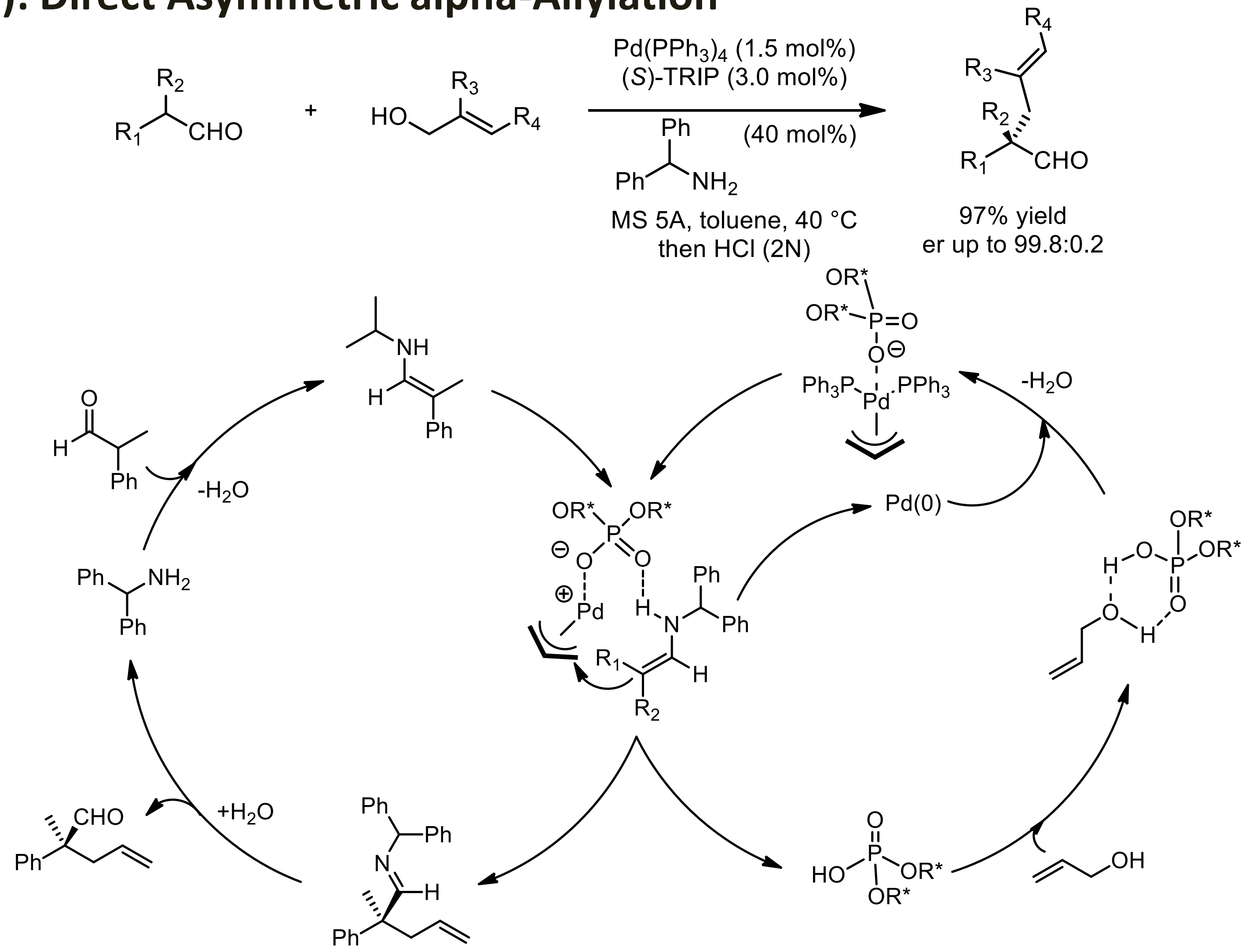
Asymmetric Counter-Anion-directed catalysis Strategy (ACDC)

Au(I): First example proposed by Toste et al,



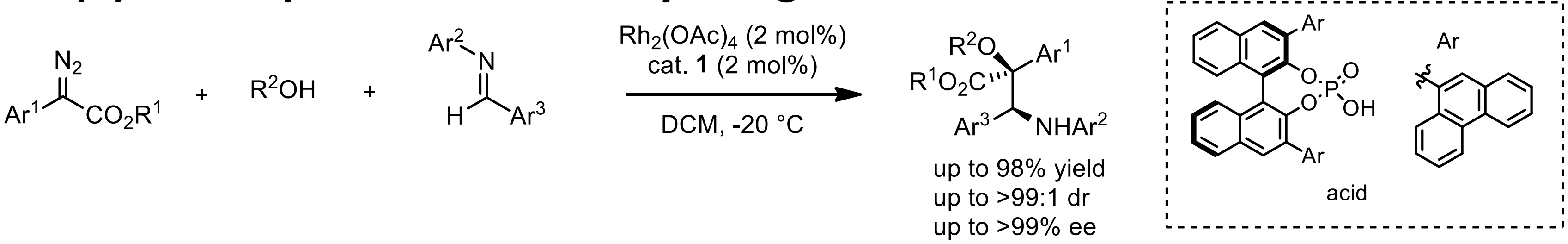
G. L. Hamiltion, E. J. Kang, M. Mba, F. D. Toste *Science* **2007**, *317*, 496-499.

Pd(0): Direct Asymmetric alpha-Allylation



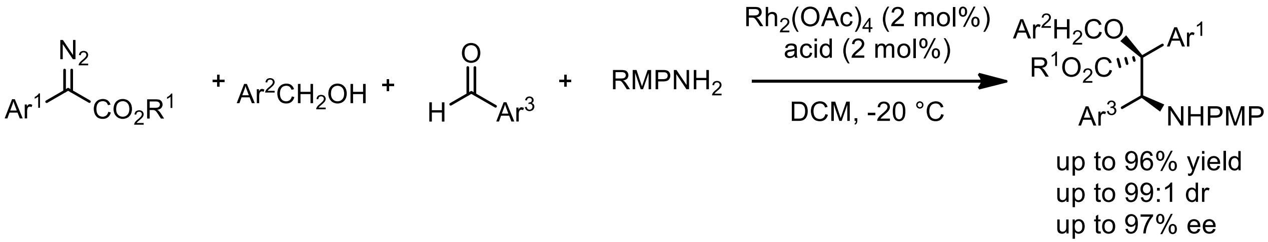
G. Jiang, B. List *Angew. Chem. Int. Ed*. **2011**, *50*, 9471-9474.

Rh(II): 3 Component Reaction by Gong:



up to 98% yield
up to >99:1 dr
up to >99% ee

Rh(II): 4 Component Reaction by Hu:

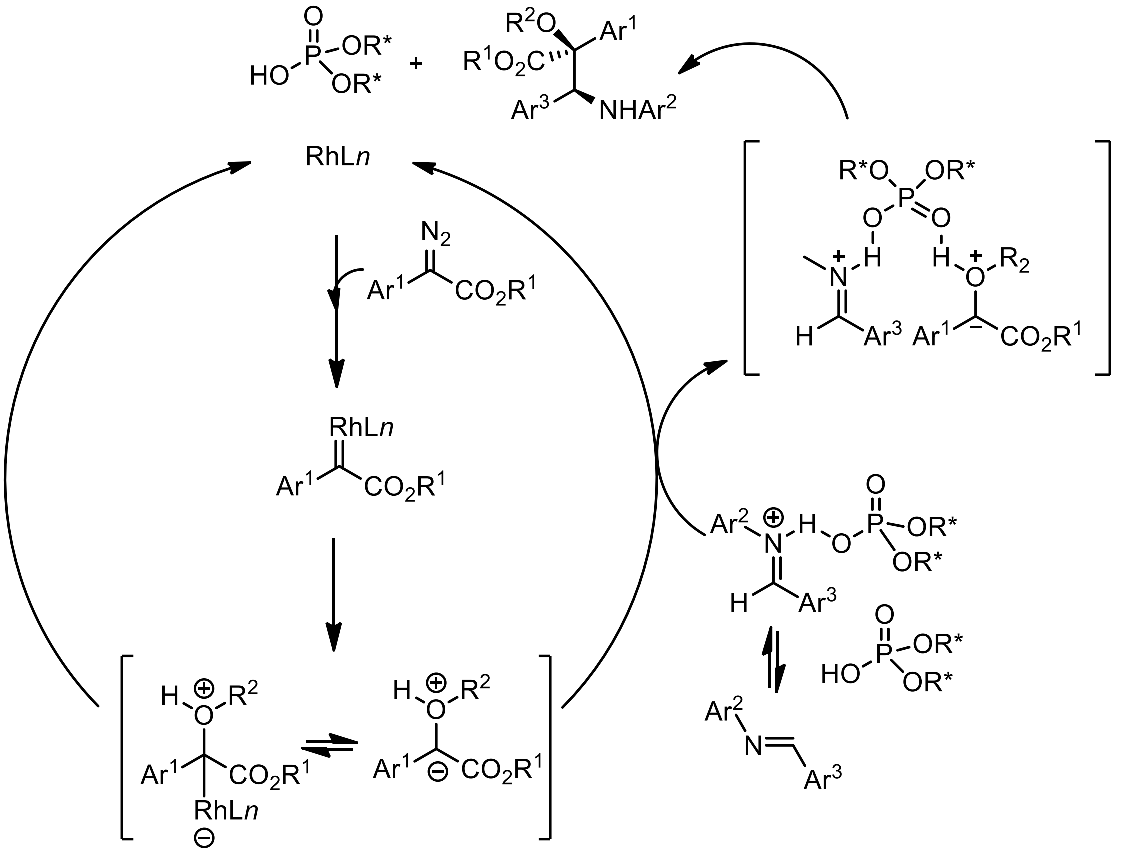


up to 96% yield
up to 99:1 dr
up to 97% ee

1) W.-H. Hu, X.-F. Xu, J. Zhou, W.-J. Liu, H.X. Huang, J. Hu, L. P. Yang, L.-Z. Gong, *J. Am. Chem. Soc*. **2008**, *130*, 7782-7783.

2) Xu, X., Zhou, J., Yang, L., and Hu, W. *Chem. Commun.* **2008**, 6564-6566.

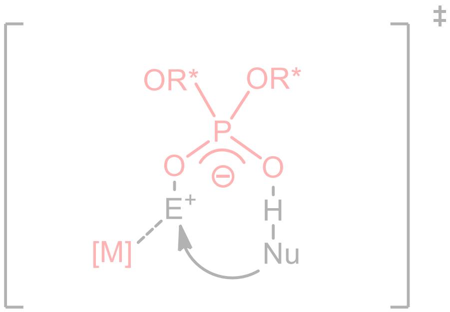
Proposed Catalytic Cycle for 3 Component Reaction



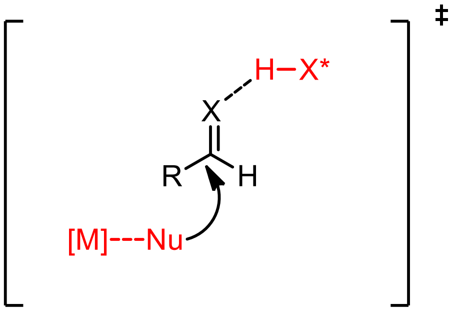
W.-H. Hu, X.-F. Xu, J. Zhou, W.-J. Liu, H.X. Huang, J. Hu, L. P. Yang, L.-Z. Gong, *J. Am. Chem. Soc*. **2008**, *130*, 7782-7783.

Chiral Bronsted acid and Transition Metal Concept

2 possible approaches:



Asymmetric Counter Anion Directed Catalysis (ACDC)

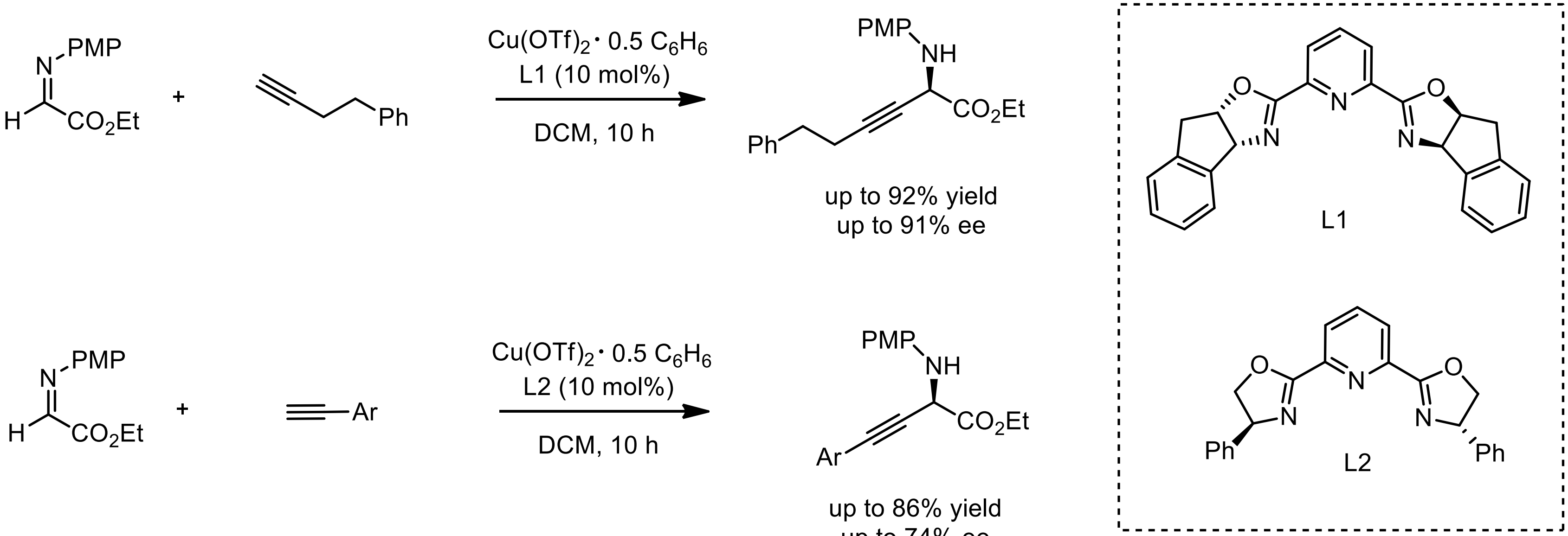


Chiral Brönsted Acid Activation

C. Zhong, X. Shi, *Eur. J. Org. Chem*. **2010**, *16*, 2999-3025

Chiral Bronsted Acid Activation

Asymmetric alkynylation of α-imino esters proposed by Chan *et al.* with limited scope:



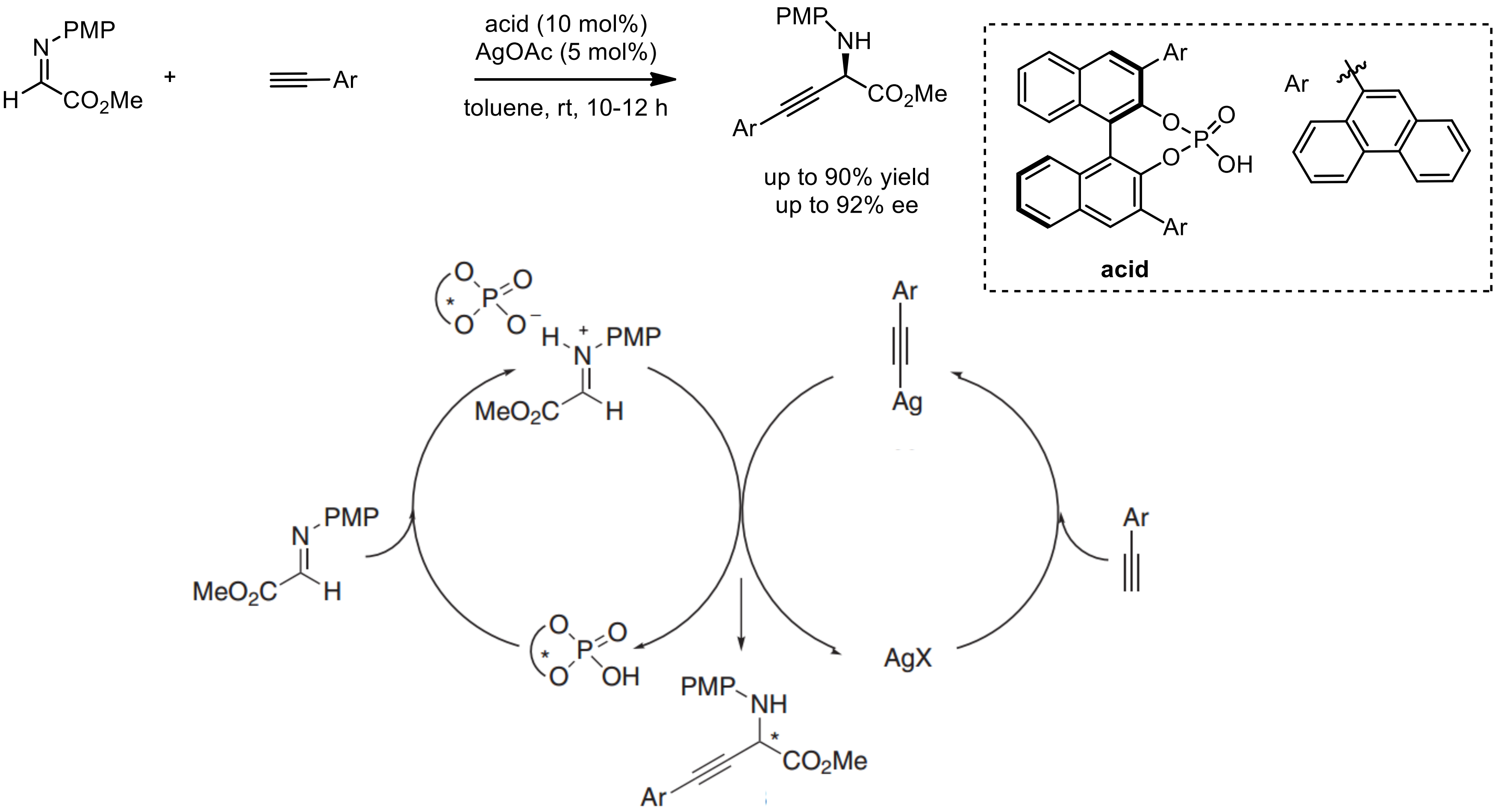
up to 92% yield
up to 91% ee

up to 86% yield
up to 74% ee

J.-X. Ji, J. Wu, A. S. C. Chan, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 11196-11200.

Chiral Bronsted acid activation: *sp* carbon nucleophile

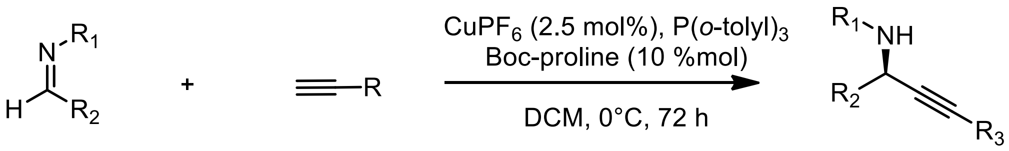
Silver Catalysed Enantioselective Alkyne Addition:



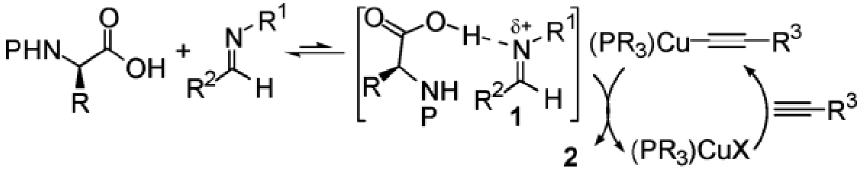
M. Rueping, A. P. Antonchick, C. Brinkmann, *Angew. Chem. Int. Ed*. **2007**, *46*, 6903-6906.

Chiral Bronsted acid activation: *sp* carbon nucleophile

Asymmetric Imine Alkynation:

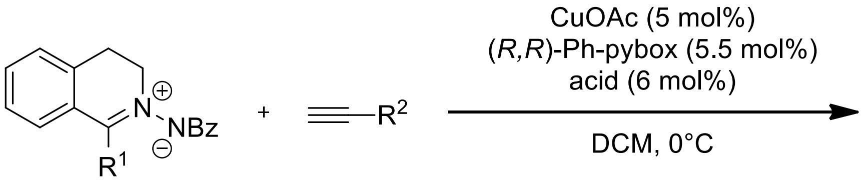


up to 92% yield
up to 99% ee



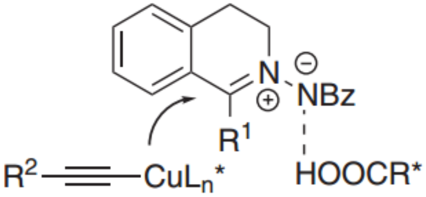
Y. Lu, T. C. Johnstone, B. A. Arndtsen, *J. Am. Chem. Soc*. **2009**, *131*, 11284-11285.

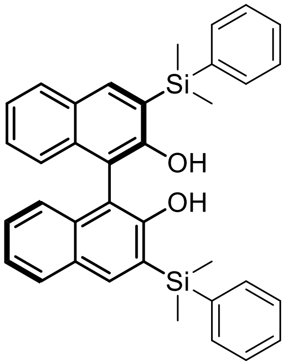
Synthesis of Chiral Tetrahydroisoquinolines with Cu(I)/pybox



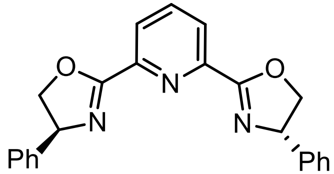
Up to 99% yield, 95% ee

via:





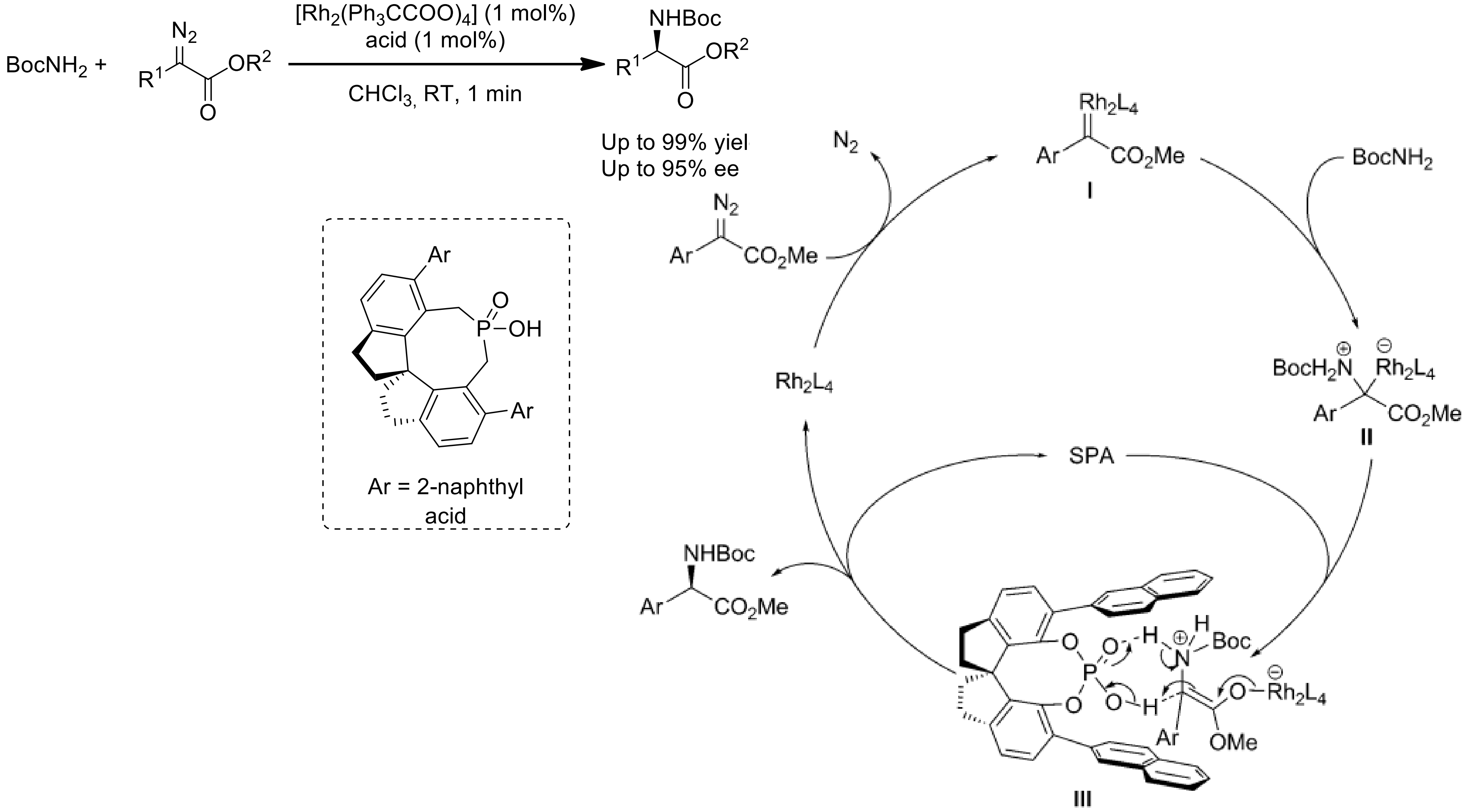
acid



(*R*,*R*)-Ph-pybox

T. Hasimoto, M. Omote, K. Maruoka *Angew. Chem. Int. Ed.* **2011**, *50,* 8952 –8955

Asymmetric N-H Insertion

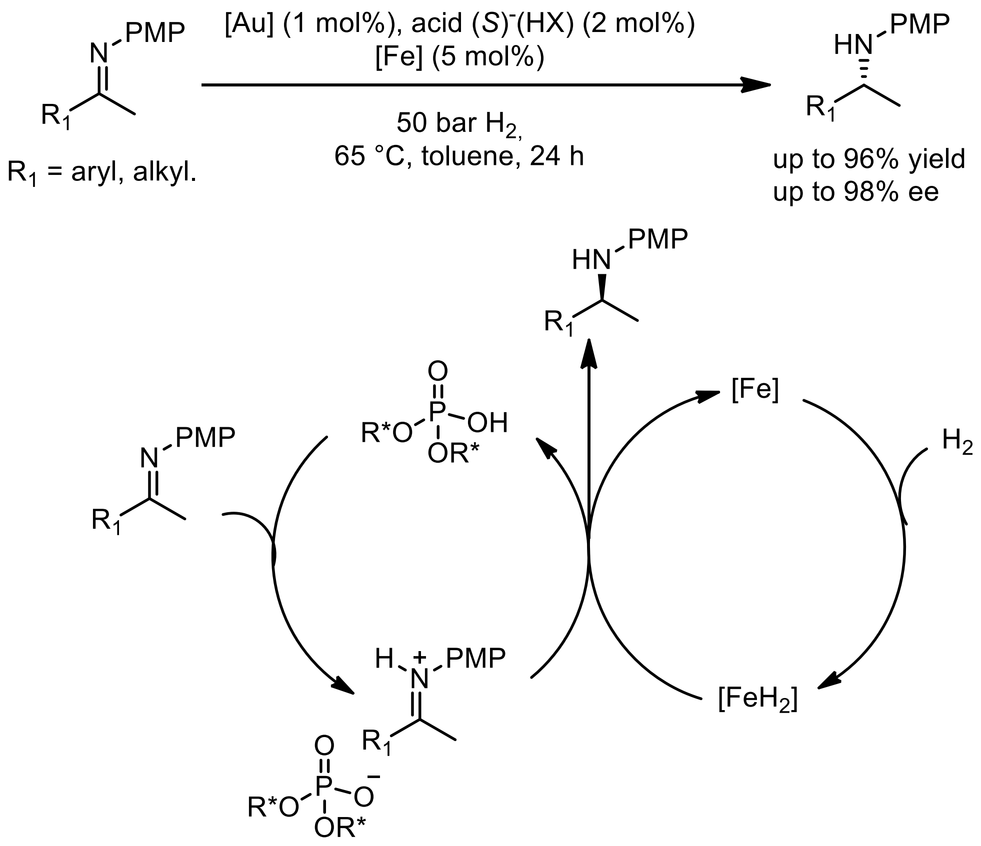


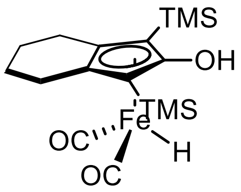
Up to 99% yiel
Up to 95% ee

Ar = 2-naphthyl
acid

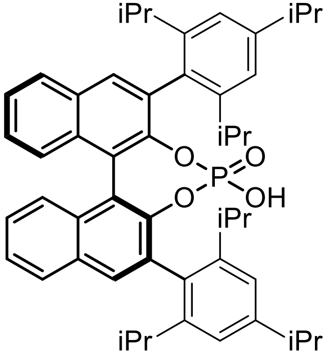
B. Xu, S. Zhu, X. Xie, J. Shen, Q. Zhou *Angew. Chem. Int. Ed.* **2011**, *50*, 11483-11486.

Enantioselective Hydrogenation of Imines





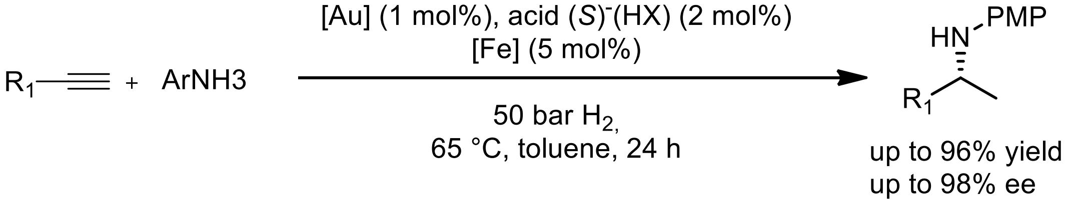
Knölker's complex
[Fe]



acid (*S*)$^-$(HX)

S. Zhou, S. Fleischer, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2011**, 50, 5120-5124.

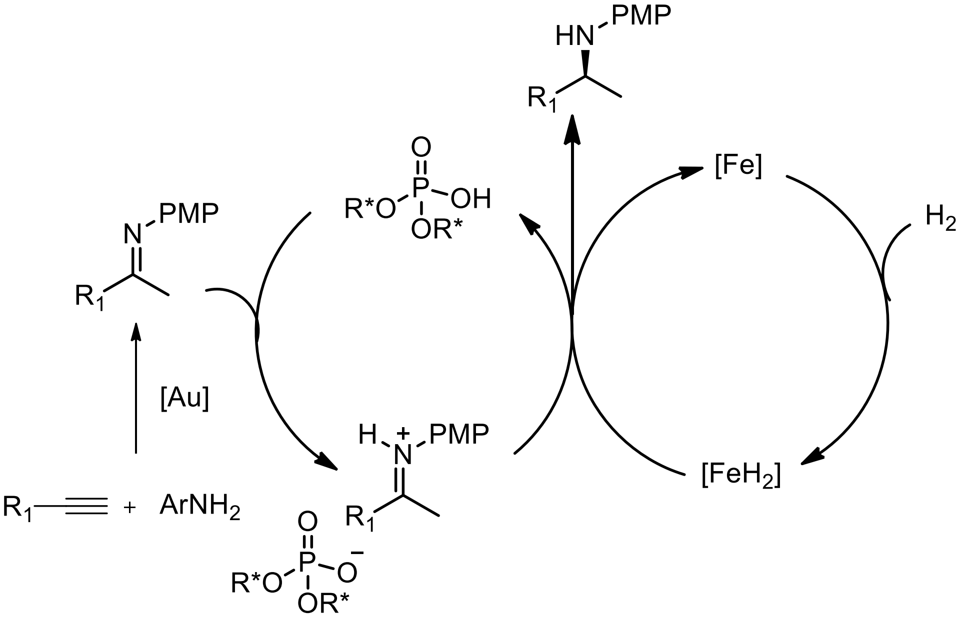
Enantioselective Hydrogenation of in situ Generated Imines

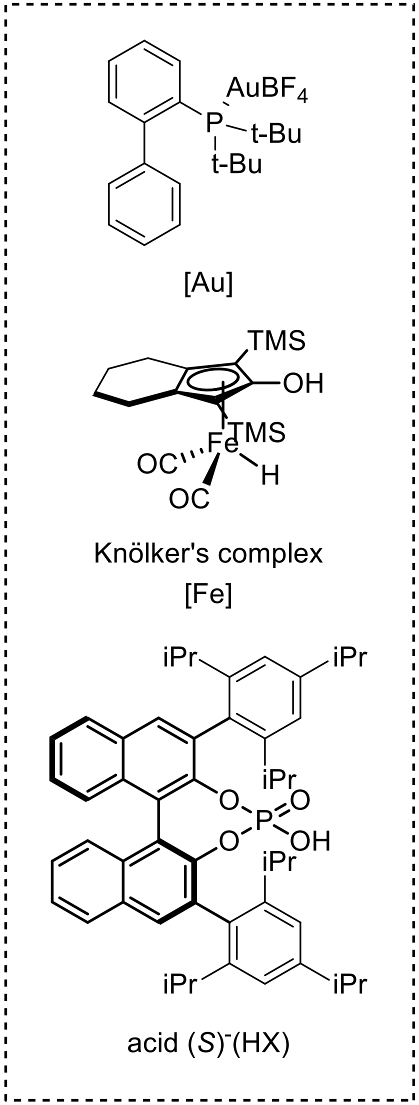


[Au] (1 mol%), acid (*S*)$^-$(HX) (2 mol%)
[Fe] (5 mol%)

50 bar H_2,
65 °C, toluene, 24 h

up to 96% yield
up to 98% ee





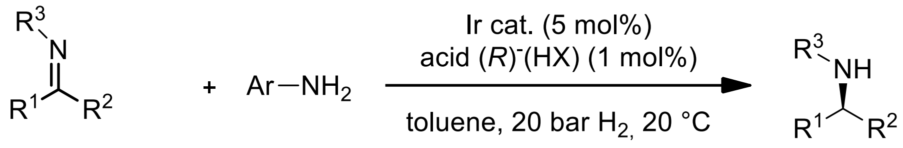
[Au]

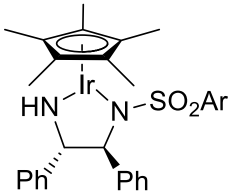
Knölker's complex
[Fe]

acid (*S*)$^-$(HX)

S. Fleischer, S. Werkmeister S., Zhou K. Junge, M. Beller *Chem. Eur. J.* **2012**, *18*, 9005-9008.

Asymmetric Hydrogenation of Imines

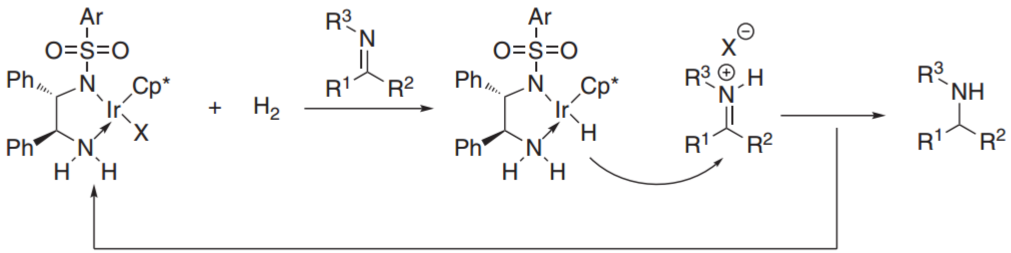


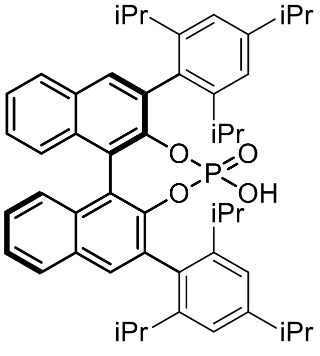


Ar = 2,3,4,5,6,-$(Me)_5C_6$

Ir cat.

via:

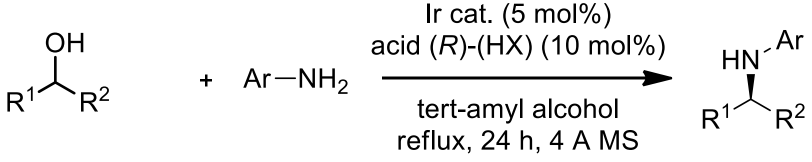


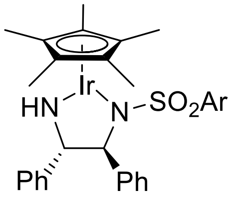


acid (*R*)-(HX)

C. Li, C. Wang, B. Villa-Marcos and J. Xiao *J. Am. Chem. Soc.*, **2008**, *130*, 14450–14451

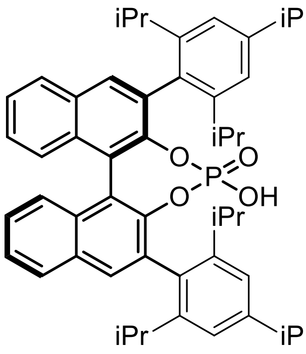
Asymmetric Amination of Alcohols



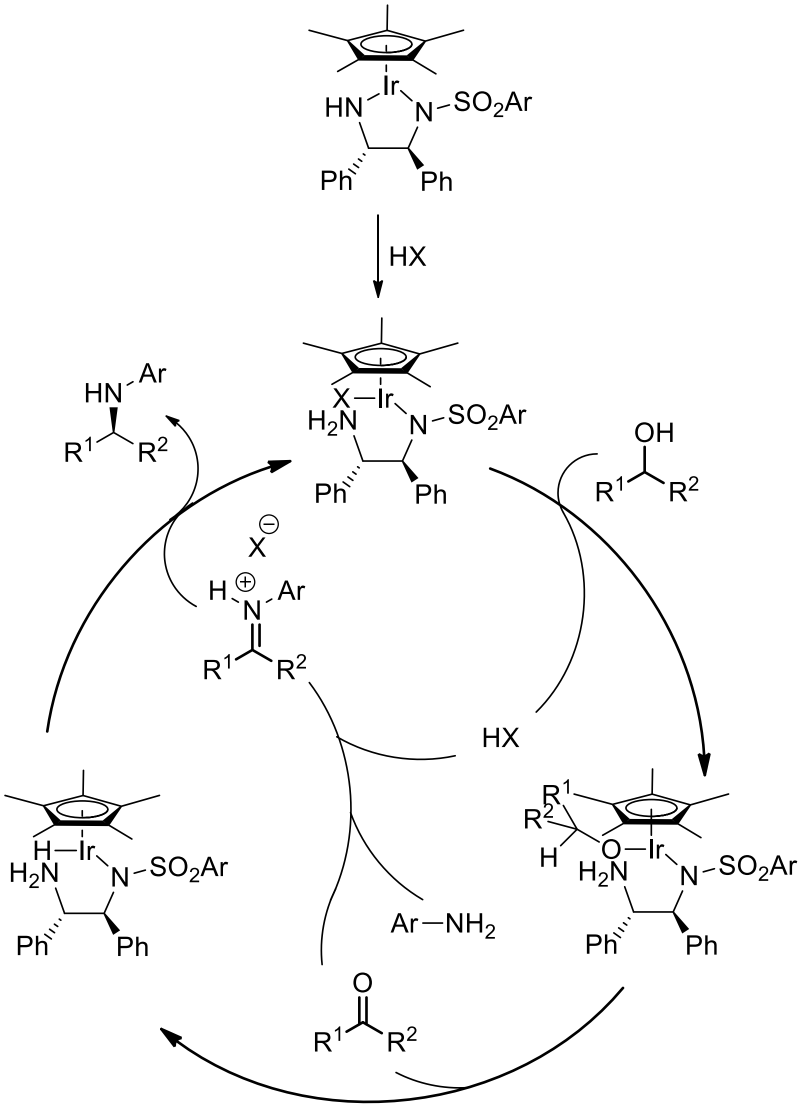


Ar = 2,3,4,5,6,-(Me)$_5$C$_6$

Ir cat.

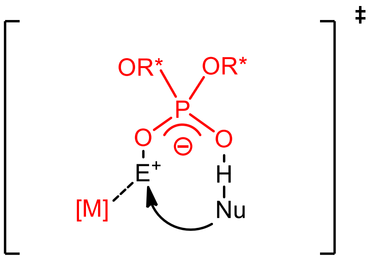


acid (*R*)-(HX)

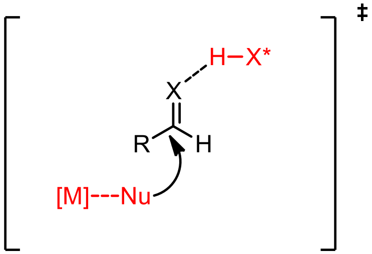


Zhang, Y., Lim, C.-S., Sim, D. S. B., Pan, H.-J. and Zhao, Y. *Angew. Chem. Int. Ed*. **2014**, *53*, 1399–1403.

Summary



Asymmetric Counter Anion Directed Catalysis (ACDC)

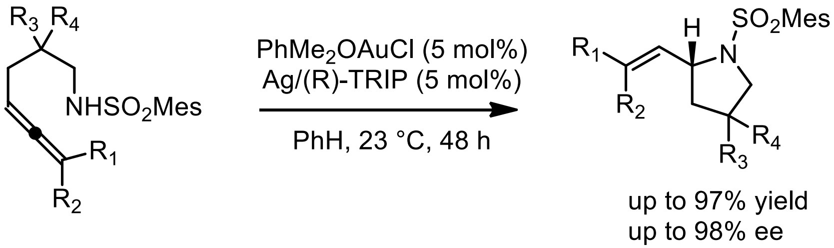


Chiral Brönsted Acid Activation

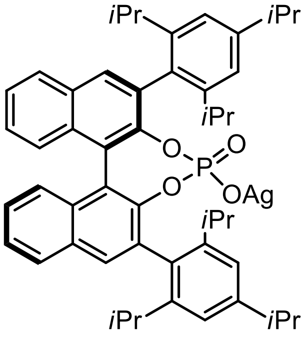
- Bronsted Acid Used Conjugated Base or as Counter Anion
- Versatile Concept
- Many Examples for Catalyses with High Reactivity and Selectivity

Problems

- Can you describe the design of most of the chiral Bronsted. Why is it necessary?
- Why is it for Au(I) chemistry so difficult to form a chiral environment for the substrate and therefore can a chiral counter anion be a solution?



up to 97% yield
up to 98% ee



Ag/(R)-TRIP

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Radical Chemistry in aqueous media, towards C-C bond formation

Marion Garreau

Frontiers in Chemical Synthesis, June 2017

Outline

1. Introduction

Why radical chemistry in aqueous media?

2. Early reports

Indium/Et_3B-mediated radical reactions

3. Photoredox in aqueous media

New developments in the last decade

4. Perspectives and conclusion

1. Introduction

Chemistry in aqueous media, why?

- Origin: Diels-Alder acceleration in aqueous media by Breslow, 1980
- Biological processes, biomolecule compatible reactions

-	+
Solubility of organic molecules	Availability, cost
Reactivity with organometallic species	Nontoxic and nonflammable Redox stability
Waste treatment	High heat capacity
	Simple isolation of organic compounds by phase-separation
	Solubility: biomass feedstock without derivatization

Perchyonok, V. T. *Radical reactions in aqueous media*, **2009**, John Wiley & Sons, Ltd.

Properties of water

- High dielectric constant (78,3/ 1,88 for n-hexane) and dense H-bond network – high polarity
  → solvation ionic species, kinetics of reactions involving charged species

- Internal pressure and cohesive energy density
  → low solubility apolar compounds

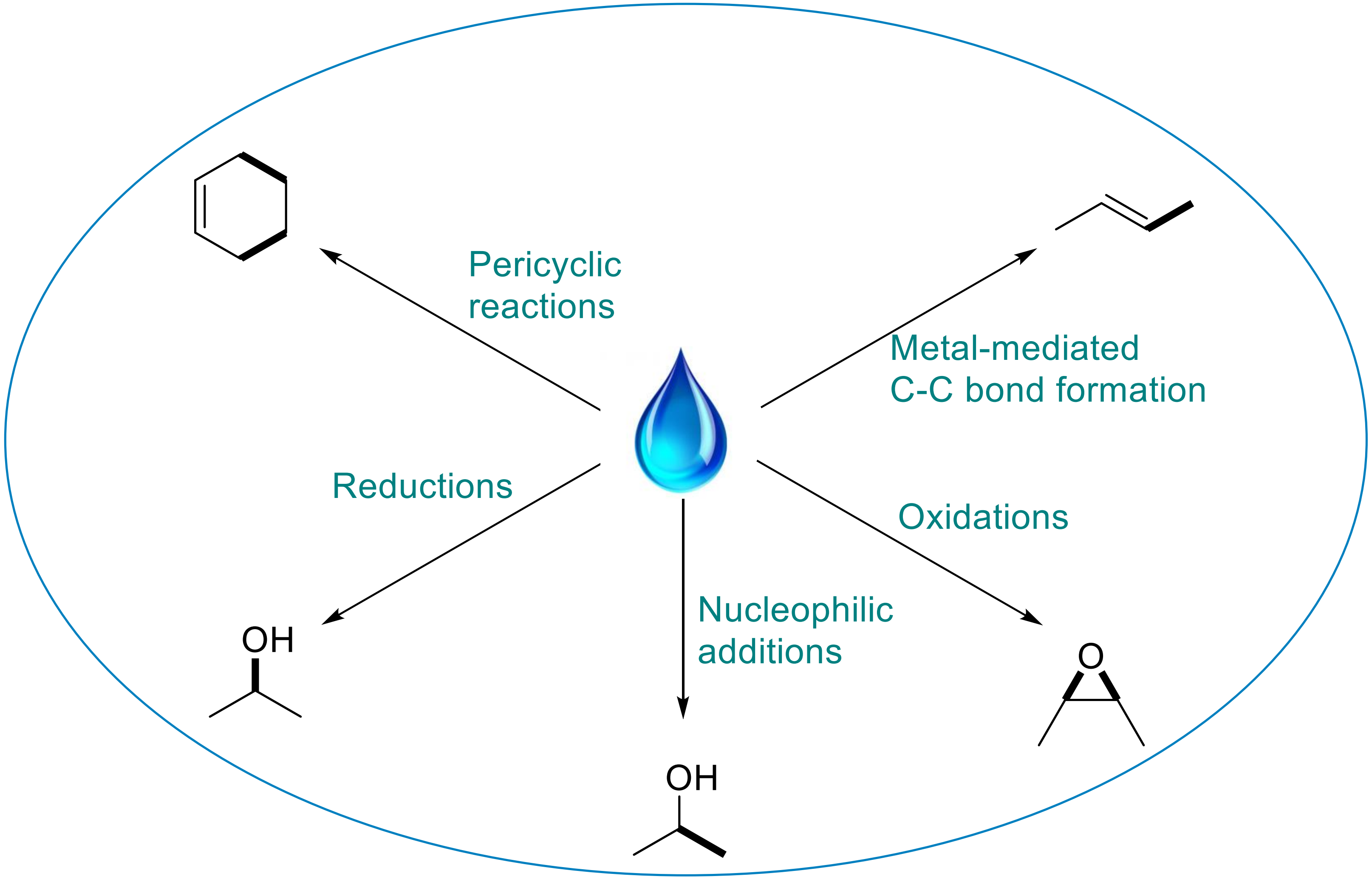
- Hydrophobic interactions
- Adjustable pH
- Hydrogen source

- Increase solubility: organic cosolvent, surfactants, hydrophilic auxiliaries or ionic derivatization

- "On water" approach (Sharpless, 2005): suspension to accelerate reaction

Lindstrom, U. M. *Organic reactions in water: principles, strategies and applications*. **2008**, John Wiley & Sons.

Chemistry in aqueous media, overview

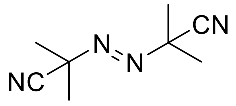


Radical chemistry in water

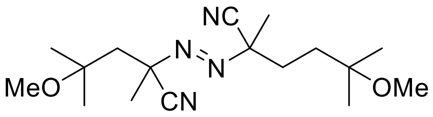
- Radical= uncharged species, orbital-orbital interactions
  → reaction rates unchanged in polar solvent
- Viscosity and internal pressure
- Strong O-H bond

Radical initiators:
- Azo-based (AIBN)
- Peroxides $(tBuO)_2$
- Boranes (Et_3B/O_2)

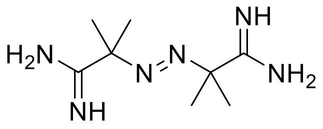
Hydrogen donors:
- Organotin hydrides (Bu_3SnH)
- $(TMS)_3SiH$
- Phosphorous hydrides $(H_3PO_2$, EPHP)



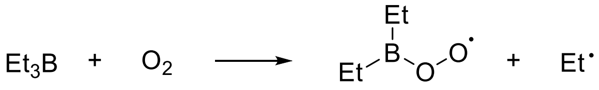
AIBN

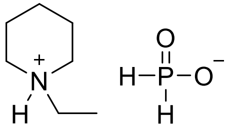


AMVN



AAPH





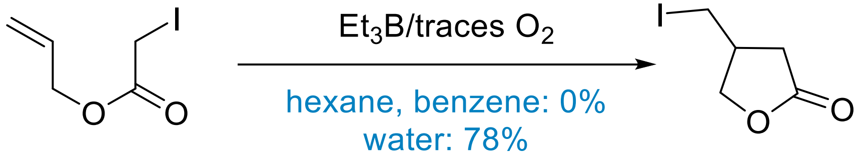
N-ethylpiperidine
Hypophosphite
(EPHP)

TMS_3SiH

2. Early reports

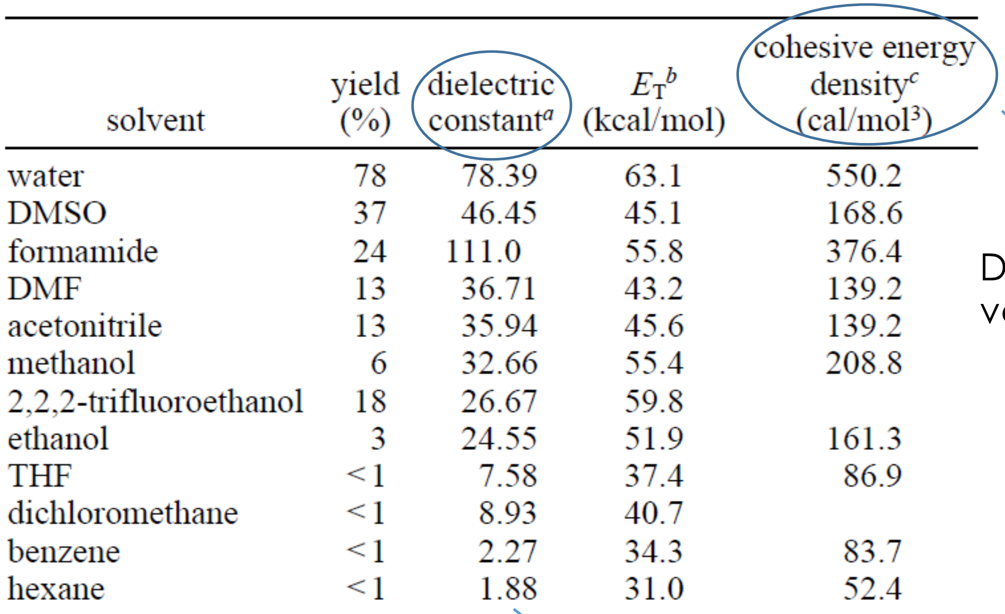
Atom-transfer radical cyclization (ATRC)

Oshima (2000): Solvent effect of water in radical reaction



Et_3B/traces O_2

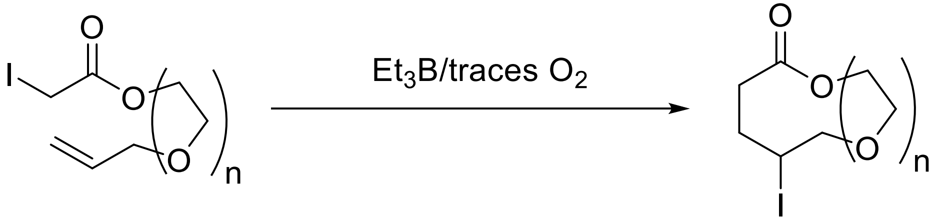
hexane, benzene: 0%
water: 78%



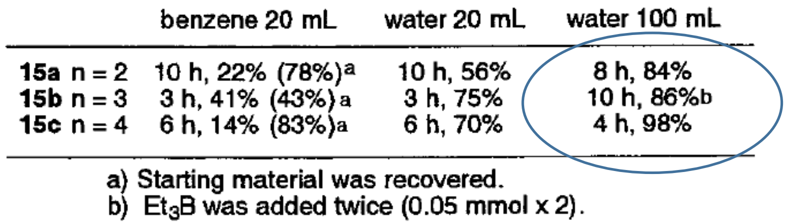
solvent	yield (%)	dielectric constant[a]	E_T[b] (kcal/mol)	cohesive energy density[c] (cal/mol³)
water	78	78.39	63.1	550.2
DMSO	37	46.45	45.1	168.6
formamide	24	111.0	55.8	376.4
DMF	13	36.71	43.2	139.2
acetonitrile	13	35.94	45.6	139.2
methanol	6	32.66	55.4	208.8
2,2,2-trifluoroethanol	18	26.67	59.8	
ethanol	3	24.55	51.9	161.3
THF	<1	7.58	37.4	86.9
dichloromethane	<1	8.93	40.7	
benzene	<1	2.27	34.3	83.7
hexane	<1	1.88	31.0	52.4

Decrease in reactant volume

Lower E barrier of rotation and activation



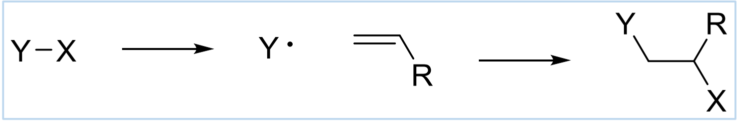
Et_3B/traces O_2



	benzene 20 mL	water 20 mL	water 100 mL
15a n = 2	10 h, 22% (78%)[a]	10 h, 56%	8 h, 84%
15b n = 3	3 h, 41% (43%)[a]	3 h, 75%	10 h, 86%[b]
15c n = 4	6 h, 14% (83%)[a]	6 h, 70%	4 h, 98%

a) Starting material was recovered.
b) Et_3B was added twice (0.05 mmol x 2).

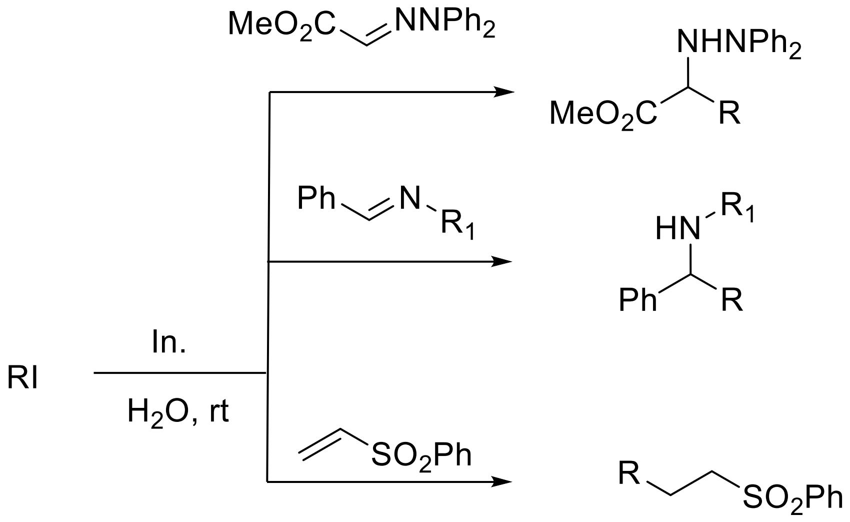
Kharasch-type mechanism



Oshima *et al. J. Am. Chem. Soc.*, **2000**, *122*, 45

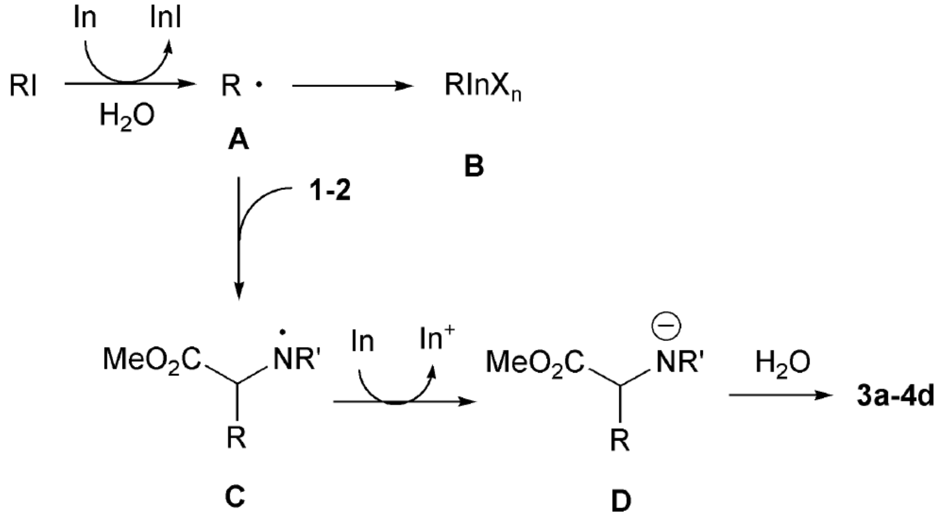
Alkyl addition to double-bonds

Naito (2002): Indium-mediated radical addition to e^- deficient C=N and C=C



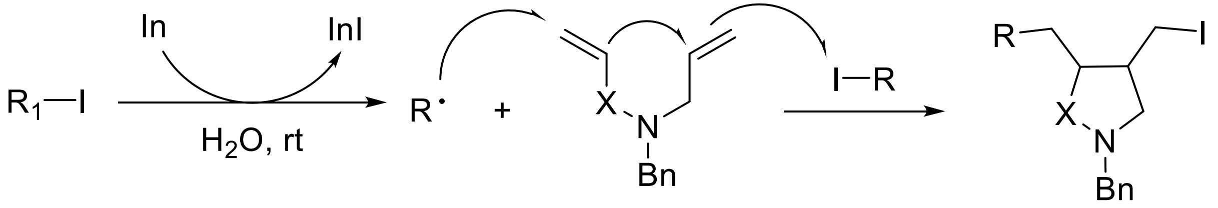
R$_1$= OBn, Ts
R$_3$= iPr, tBu

54-90% yield



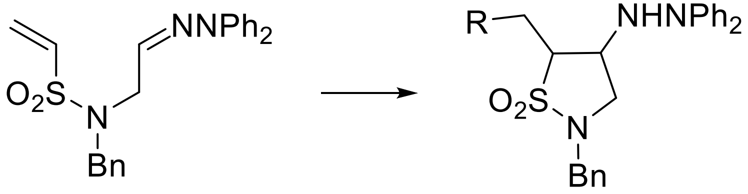
Naito *et al. Org. Lett.*, **2002**, *4*, 1, *Org. Biomol. Chem.*, **2004**, *2*, 1267 – 1270

Tandem radical addition-cyclization trap reaction (ACTR)



R= iPr, tBu
X= CO or SO$_2$

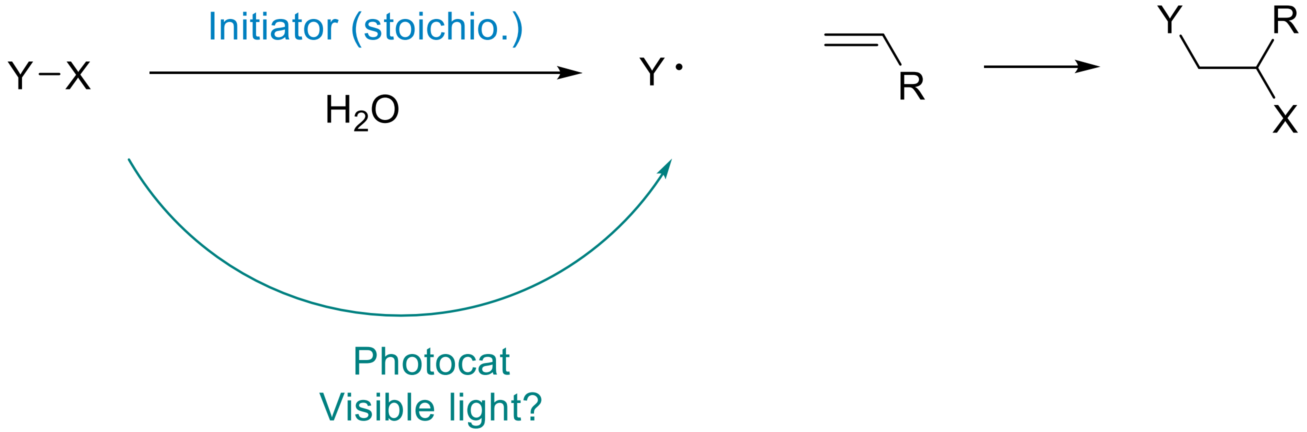
38-84% yield



42-93% yield

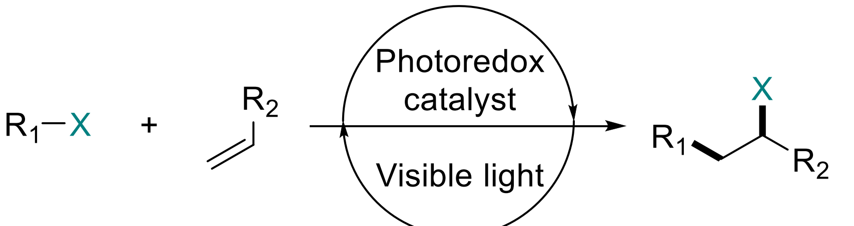
Naito *et al. Org. Biomol. Chem.*, **2004**, *2*, 1267 – 1270

3. Photoredox catalysis in aqueous media



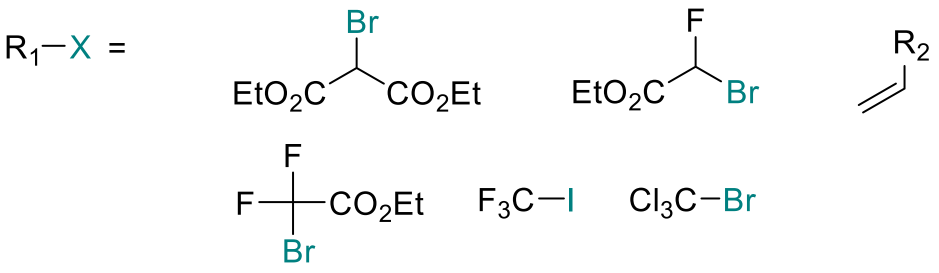
Atom transfer radical addition to olefins (ATRA)

Stephenson (2011): First intermolecular ATRA of haloalkanes and a-halocarbonyls onto olefins

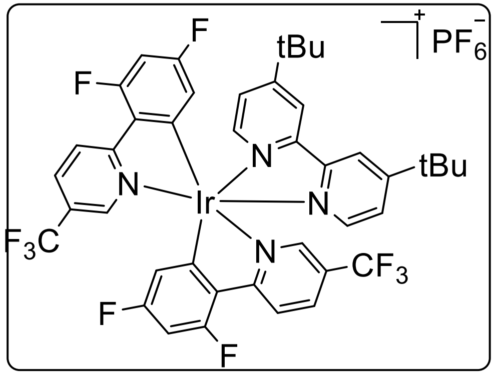


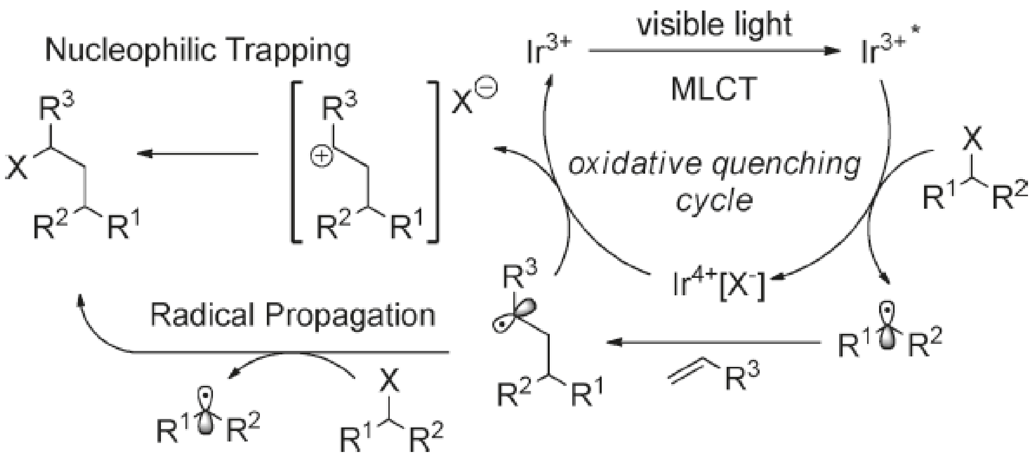
LiBr (2 equiv)
DMF/H_2O 1:4

16 examples
67-99% yield



mono- or disubstituted
-OH, -CO_2R,Ar, alkyl-Br,
enones, carbamates,

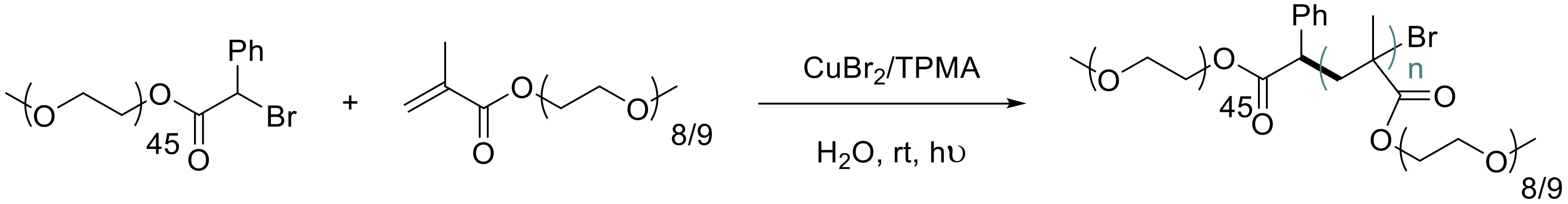




Stephenson *et al. J. Am. Chem. Soc.* **2011**, *133*, 4160–4163

Atom-transfer radical polymerization

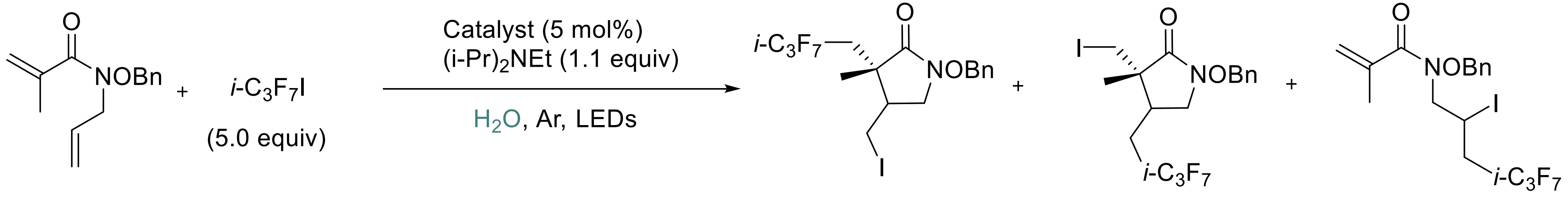
Development of ATRA towards polymerization



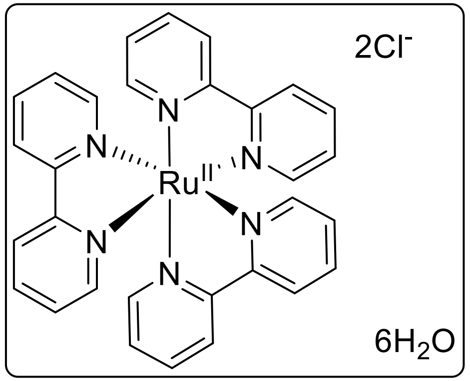
Matyjaszewski, K. *et al. JACS*, **2015**, *137*, 15430-15433.

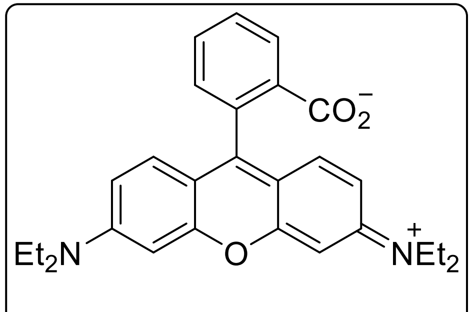
Addition-cyclization-trapping reactions (ACTR)

Miyabe (2015): Photo-induced cascade ACTR using perfluoroalkyl radicals: from Ru to organic dyes

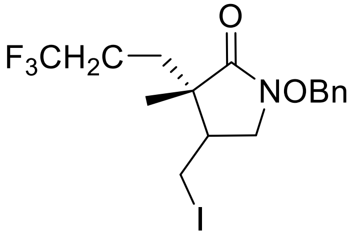


$Ru(bpy)_3Cl_2.6H_2O$ 75% yield	62 cis/trans=77:23	23	15
Rhodamine B 84% yield	64 cis/trans=74:26	29	7

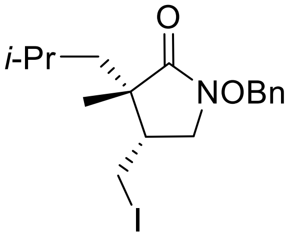




Rhodamine B



61%
cis/trans=58:42

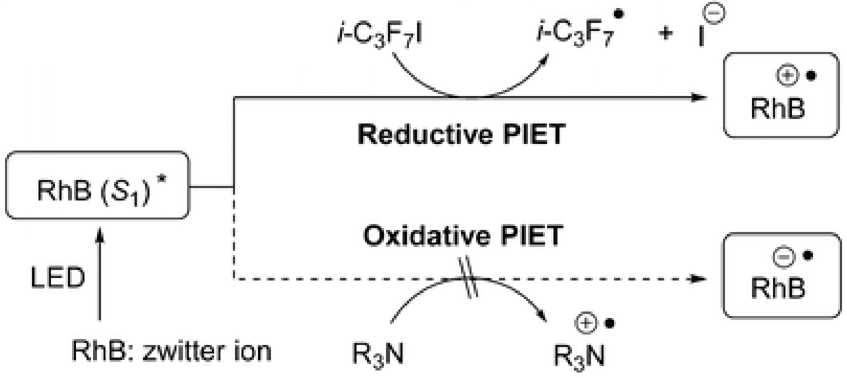


42%
cis/trans=61:39

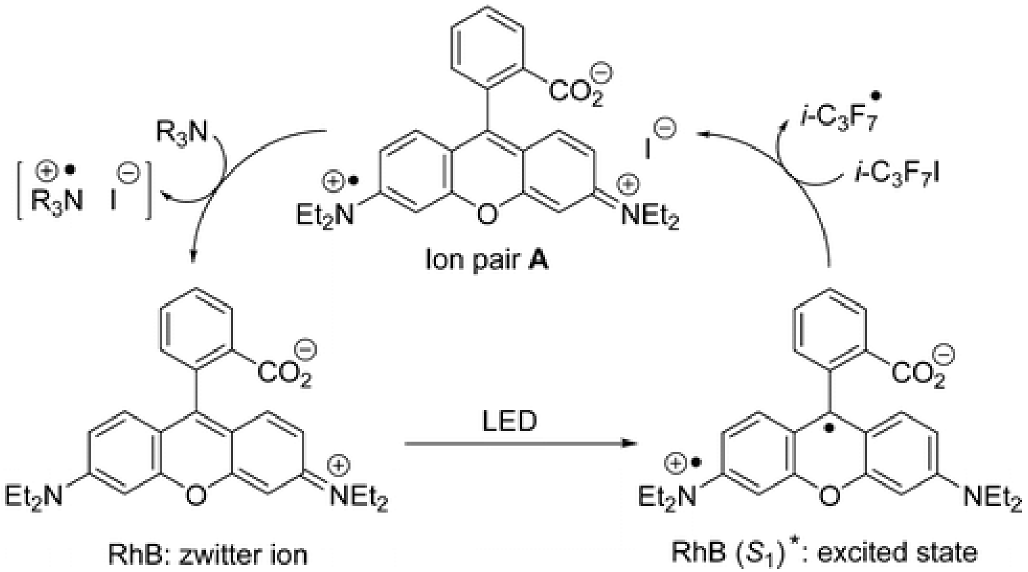
Miyabe *et al. Tetrahedron*, **2015**, *71*, 773-781, *J. Org. Chem.* **2016**, *81*, 7217–7229

Addition-cyclization-trapping reactions (ACTR)

[a] Photo-induced electron transfer (PIET)



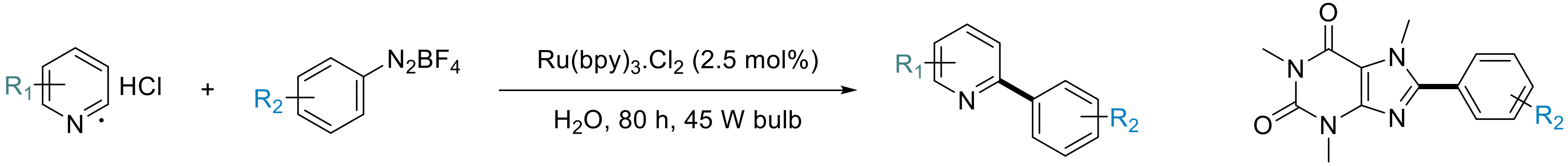
[b] Photo-redox cycle using rhodamine B



Miyabe *et al. Tetrahedron*, **2015**, *71*, 773-781, *J. Org. Chem.* **2016**, *81*, 7217–7229

Arylation of N-heteroarenes

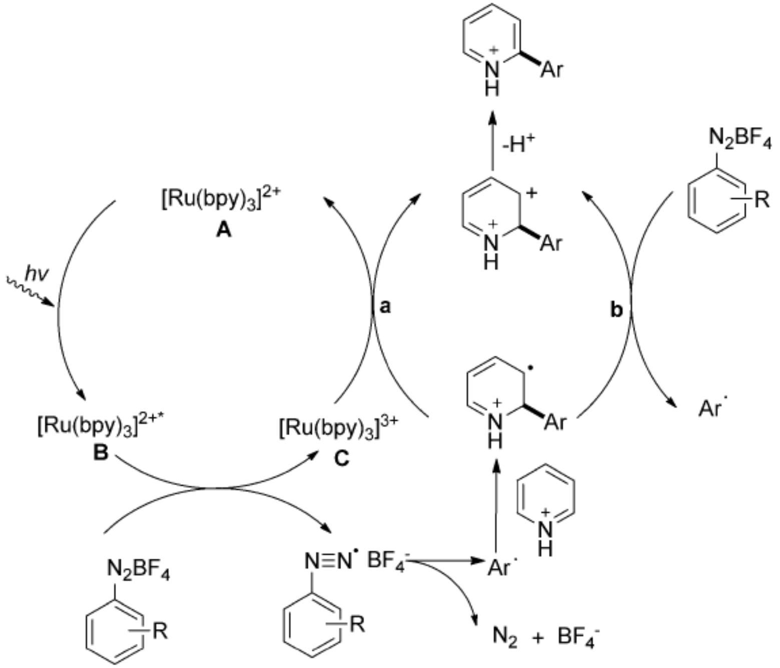
Xiao (2014): Radical coupling N-heteroarenes with aryldiazonium salts



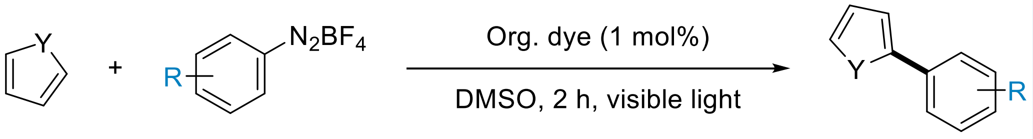
R_1, R_2= Me, CF_3, CN, Br, CO_2Et, OMe

24 examples
50-93% yield

12 examples
42-70% yield



König (2012)

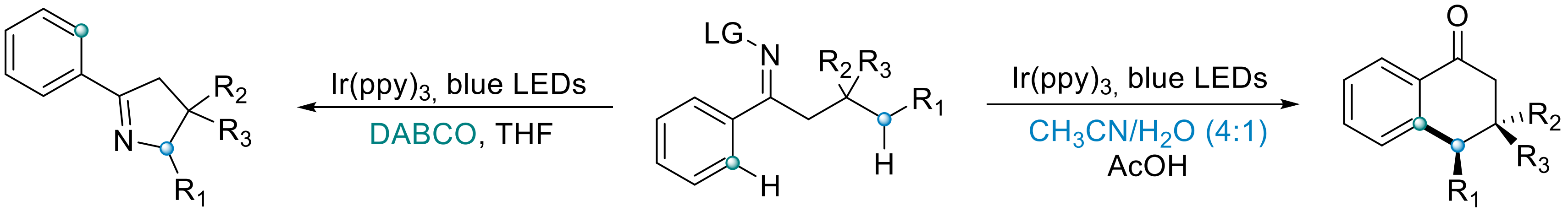


Y= O, S, NBoc

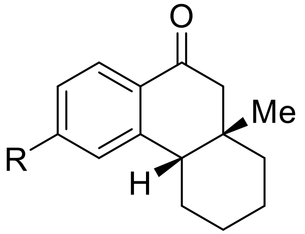
Xiao *et al. Chem. Eur. J.* **2014**, *20*, 2960 – 2965, König *et al. J. Am. Chem.Soc.* **2012**, *134*, 2958–2961

C-H functionalization though 1,5-Hydrogen transfer

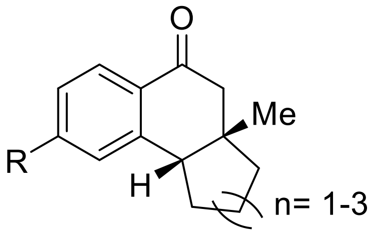
Nevado (2017): Functionalization of aliphatic C(sp^2)-H bonds via iminyl radicals



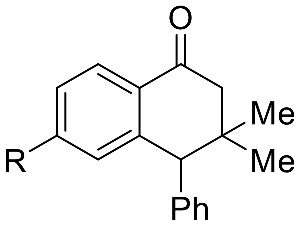
15 examples
57-90% yield



R= H, Cl, Me, F
Single diastereoisomer



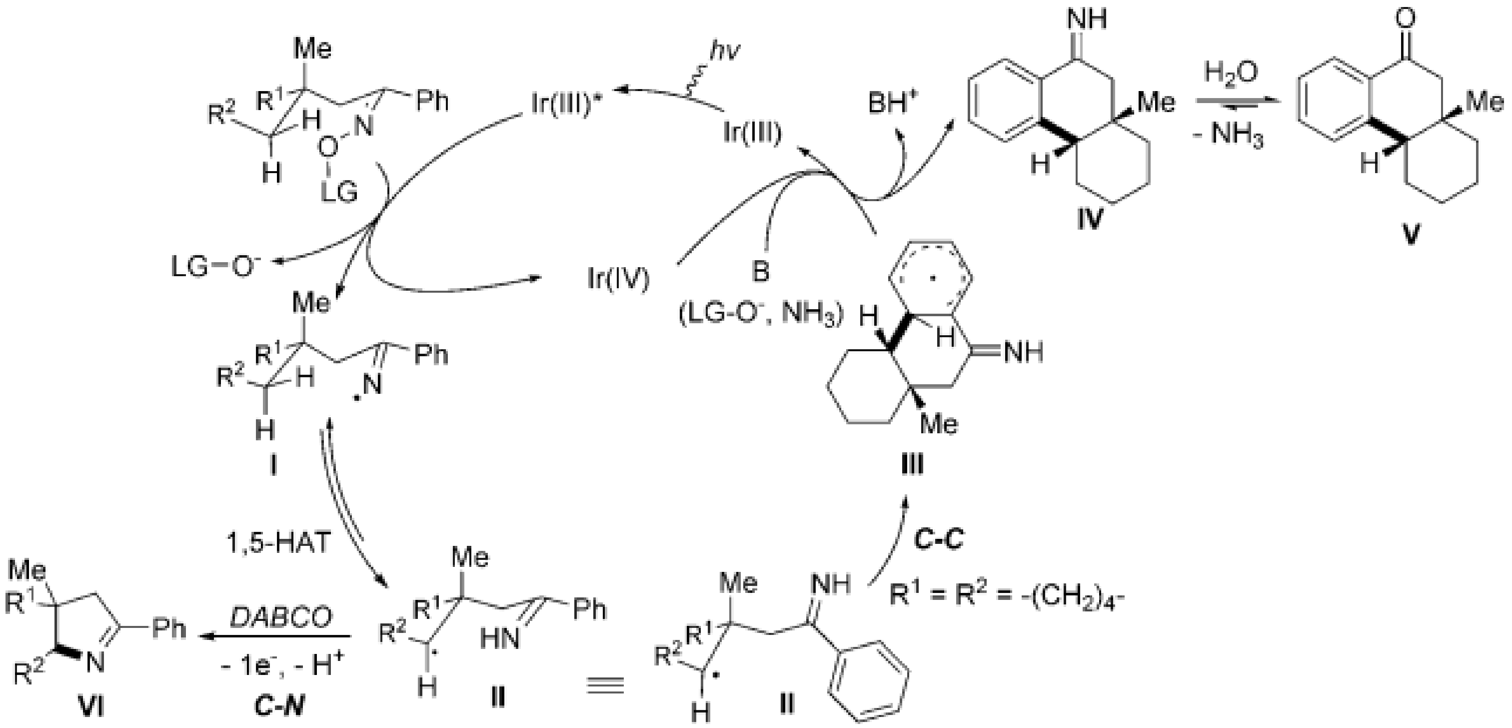
R= H, Cl
Single diastereoisomer



R= H, F

Nevado *et al. Angew.Chem. Int.Ed.* **2017**, *56*,1881 –1884

C-H functionalization though 1,5-Hydrogen transfer

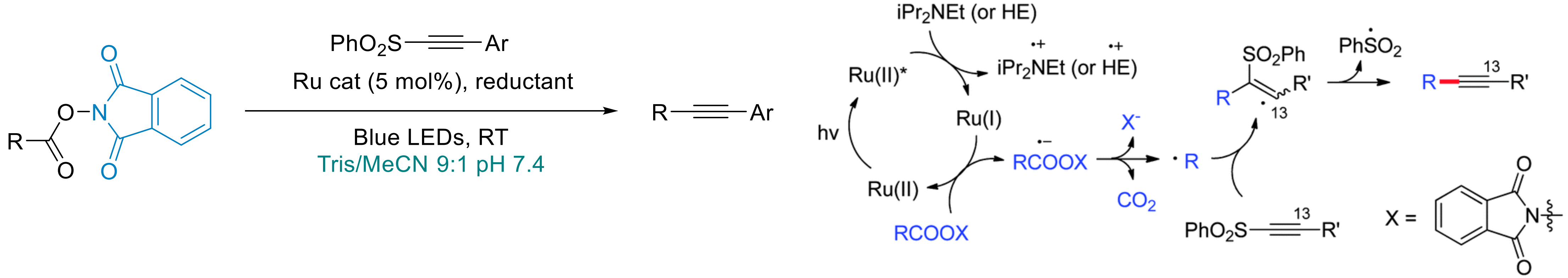


Nevado *et al. Angew.Chem. Int.Ed.* **2017**, *56*,1881 –1884

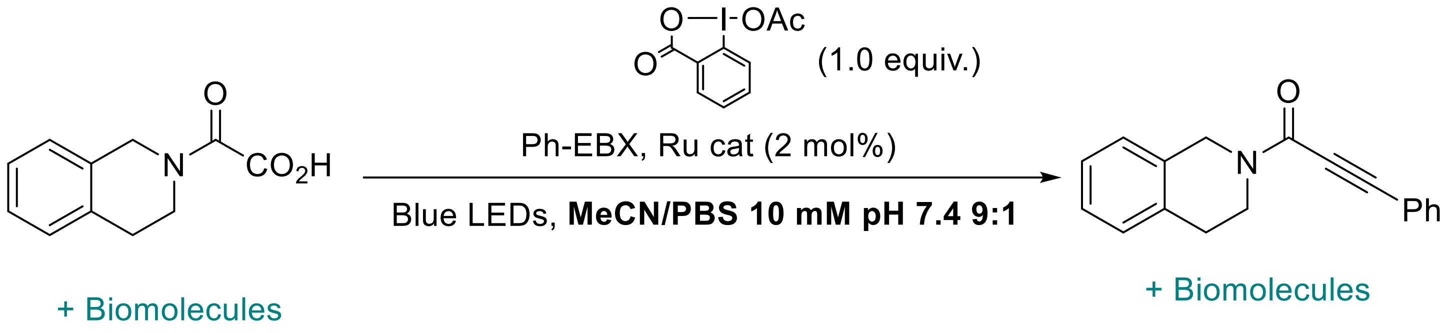
Decarboxylative alkynylation

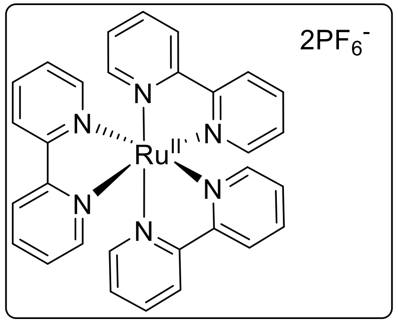
Chen (2015): Decarboxylative C(sp^3)-C(sp) coupling under biomolecule compatible conditions

-From N-hydroxy phtalimide esters in organic solvent to protein alkynylation in neutral buffer



-Similar work: deboronative alkynylation and decarboxylative ynonylation

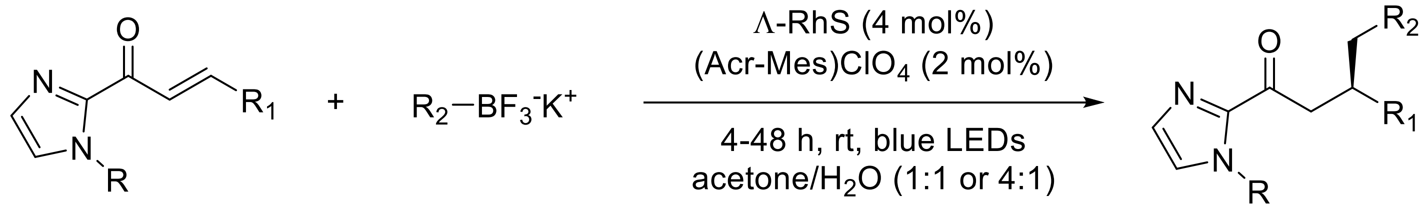




Chen *et al. Chem. Commun.* **2015**, *51*, 5275-5278, *J. Am. Chem. Soc.* **2014**, *136*, 2280–2283, *Angew. Chem. Int. Ed.* **2015**, *54*, 7872-7876.

Addition of alkyl radical to alkenes

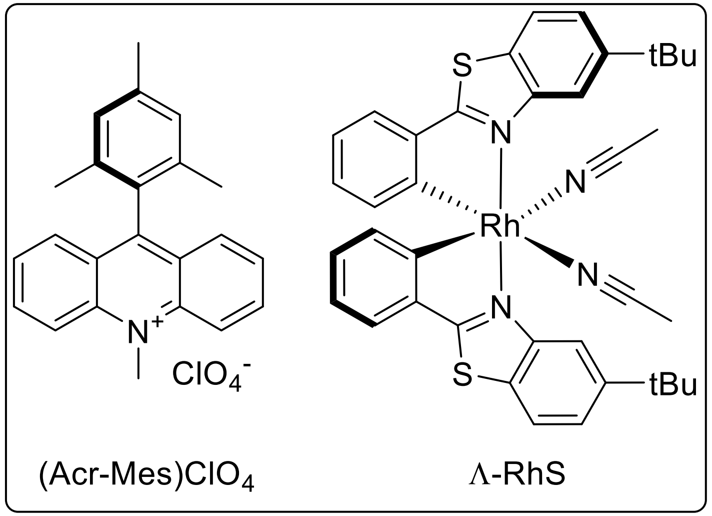
Meggers (2016): Enantioselective and catalytic addition of alkyl radical to acceptor-substituted alkenes



R= Me, Ph
R_1= alkyl, aryl

R_2= Bz, alkoxy, alkyl

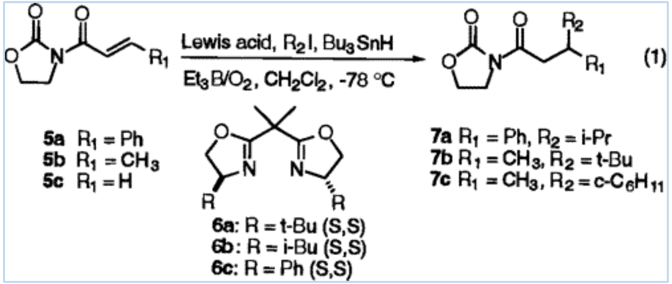
27 examples
up to 97% yield
up to 99% ee



(Acr-Mes)ClO$_4$

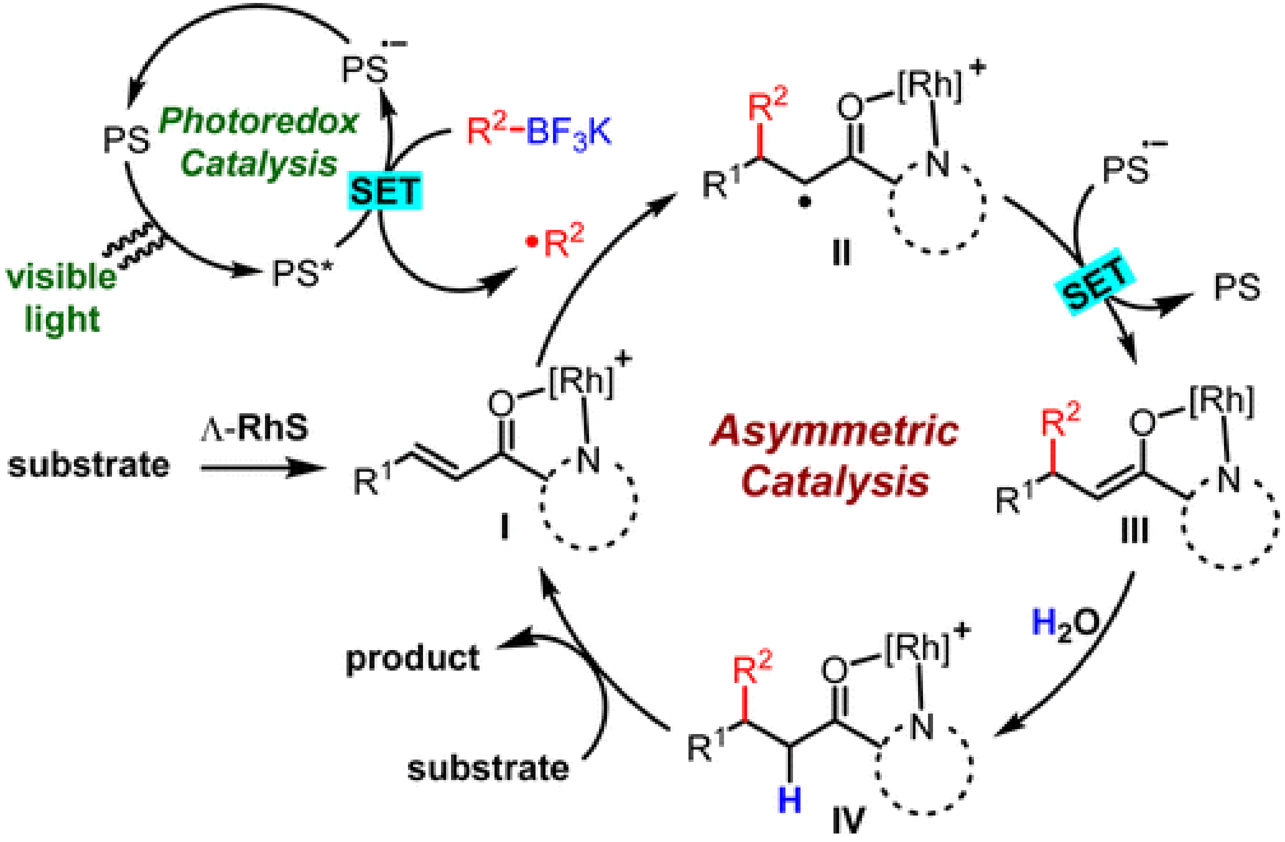
Λ-RhS

Enantioselective conjugate addition (Sibi)



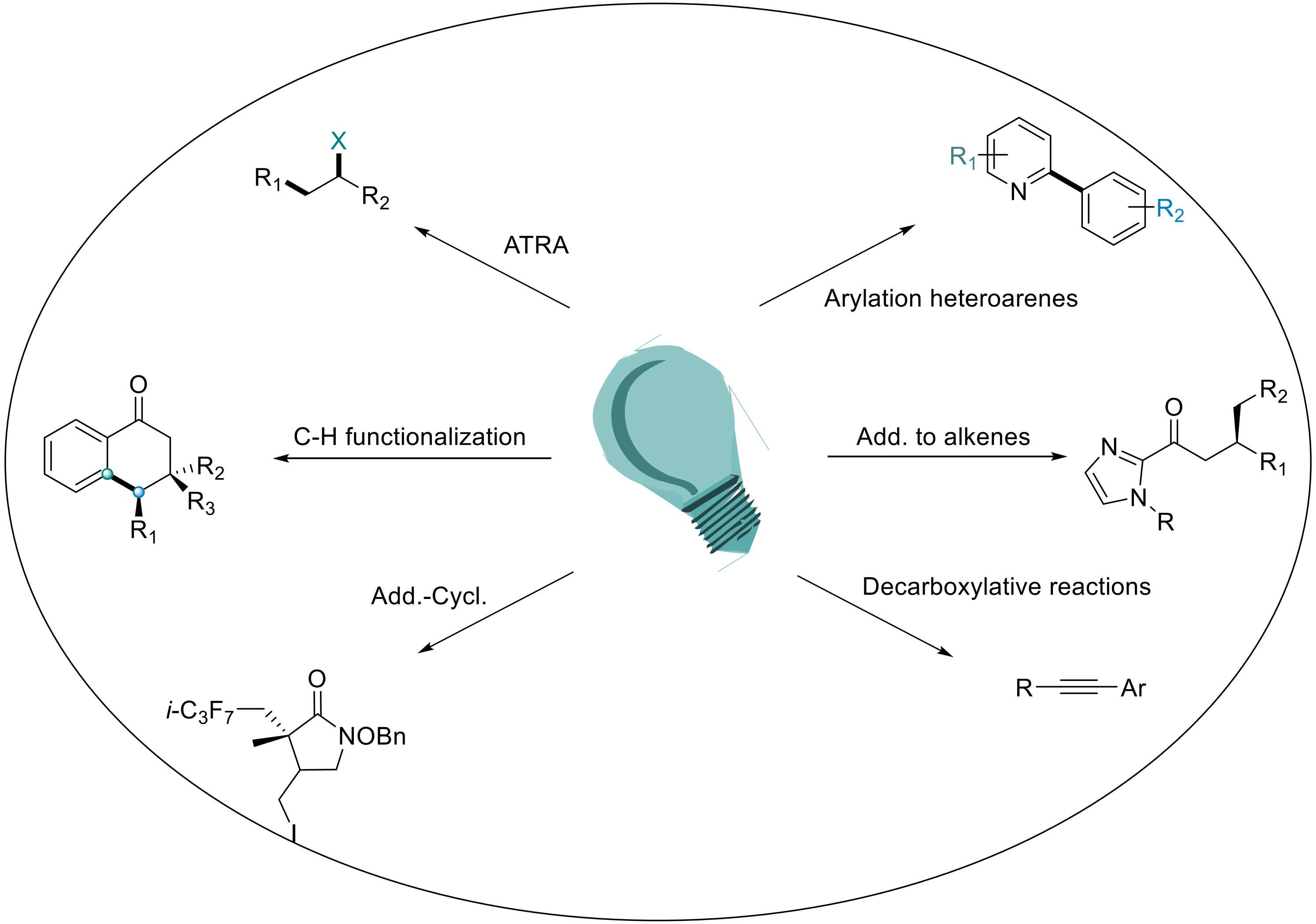
Meggers *et al. J. Am. Chem. Soc.* **2016**, *138*, 6936–6939, Sibi *et al. J. Am. Chem. Soc.* **1996**, *118*, 9200-9201.

Addition of alkyl radical to alkenes



Meggers *et al.* *J. Am. Chem. Soc.* **2016**, *138*, 6936–6939

Advances of photoredox catalysis in aqueous media



ATRA

Arylation heteroarenes

C-H functionalization

Add. to alkenes

Add.-Cycl.

Decarboxylative reactions

Conclusion

- Water compatible/required
- From In., Et_3B to PC
- Efficient C-C bond formation
- Biomolecule functionalization + green chemistry

Perspectives

- Dual transition metal/photoredox catalysis
- New transfornations
- Non-prefunctionalized substrates
- Biomolecule compatible conditions

Thank you for you attention!

Questions?

Questions

- Highlight 3 reasons for positive effect of water on radical reaction rate

- Discuss possible approaches for non-water soluble substrates

Bismuth in Organic Synthesis

Frontiers in Chemical Synthesis
Toward Sustainable Chemistry
by Balàzs Budai

Overview

Properties

- History
- Oxidation states
- Synthesis
- Structure
- Metallochirality

Bismuth (V)

- Oxidation
- Alkylation, Alkenylation
- C, N, O, S - Arylation
- Application

Bismuth (III)

- Cross-coupling
- Lewis acidity and catalysis
  - Aldolization
  - **Alkylation**
  - **Allylation**
  - Amination
  - Arylation
  - Cationic cyclization
  - Cycloaddition
  - Cycloisomerization
  - Epoxide Opening
  - **Etherification**
  - Hydroamination
  - Hydroalkoxylation
  - Hydroalkylation
  - Hydroarylation
  - Oxidation
  - Oxycarbonylation
- New trends

Summary and Outlook

History and General Properties

pre-16th century – Incas used its alloys, tools found in Machu Picchu Rutledge, J. W. *Science* **1984**, *223* (4636)
1753 – Claude Francois Geoffroy: Bismuth is distinct from tin and lead. Wikipedia

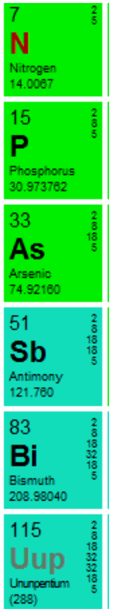
Cosmetics, medical applications(radio-opaque, antiseptic nature)
Peptobismol
Environmentally friendly substituent for lead (fishing, hunting and shooting) ($d = 9.78\ g/cm^3$)
Industrial chem. (Bi-Mo, Bi-Pt), nanochem. ($BiVO_4$, BOI), photochem. (Bi_2O_3, $BiVO_4$, BOI)
Expands on solidification → alloys
Diamagnetic → Maglev trains
Most Bi-salts are less toxic than table salt
64th most abundant (~Cd, Ag) and heaviest stable element **0.3 CHF/g**
Availability ~Fe
Recoverable from reaction mixture

Oxidation potential: $Ph_3N < Ph_3P < Ph_3Sb < Ph_3Bi < Ph_3As$
1.06V 1.31V 1.50V 1.60V 1.63V

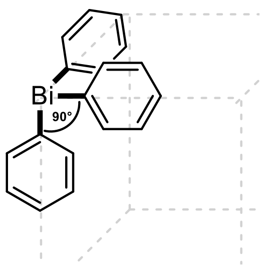
Mostly Bi(V)/Bi(III) redox is employed

Nucleofugality: triphenylbismuthonio group is twice as good leaving group as TfO^-
Matano, Y. *Organometallics* **2000**, *19* (12), 2258–2263.

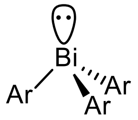
σ – donor : weak ligand in metal complexes
σ and π – acceptor : acceptor with dative-, anionic-, alkyl-, aryl- or even metal ligands
(back donation from d-orbital into Bi-C σ*)



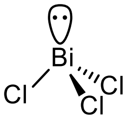
Oxidation States, Structure and Nomenclature



3+

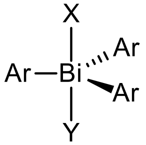


Triarylbismuthine

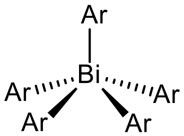


Bismuth chloride

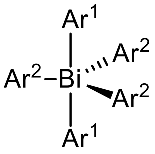
5+

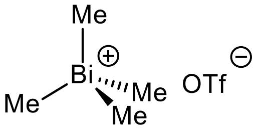


Pentavalent arylbismuthine

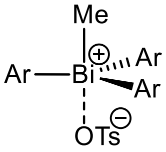


Pentaarylbismuth

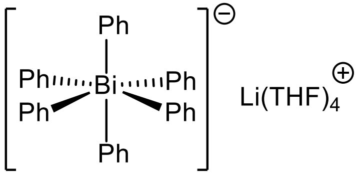




Tetramethylbismuthonium

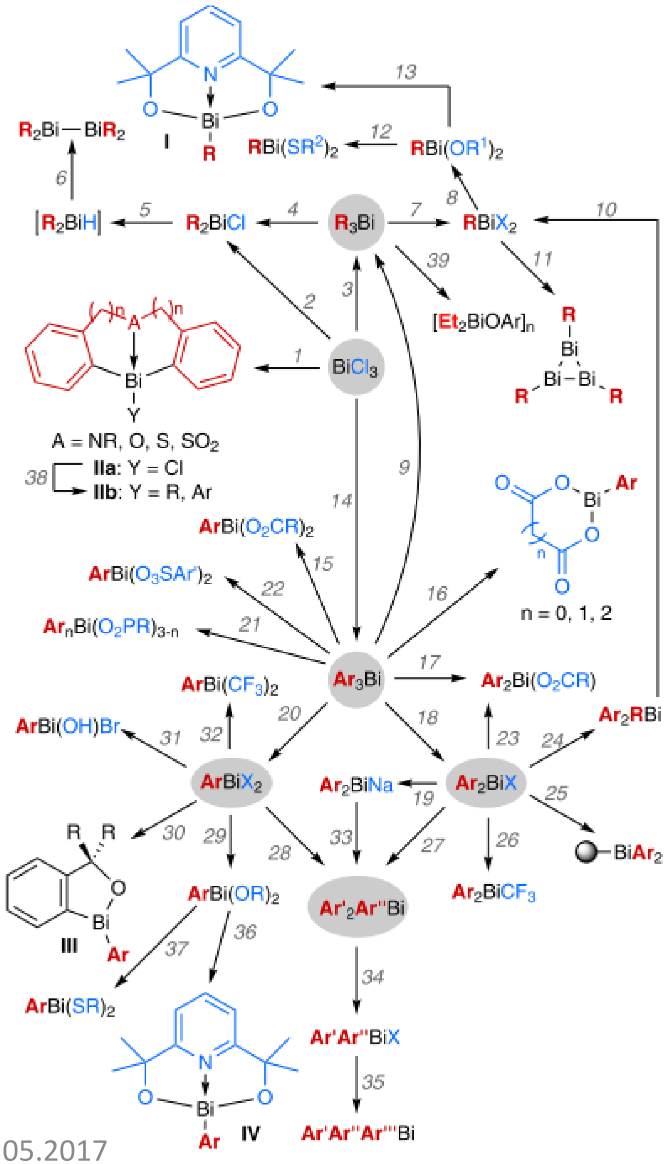


Arylbismuthonium

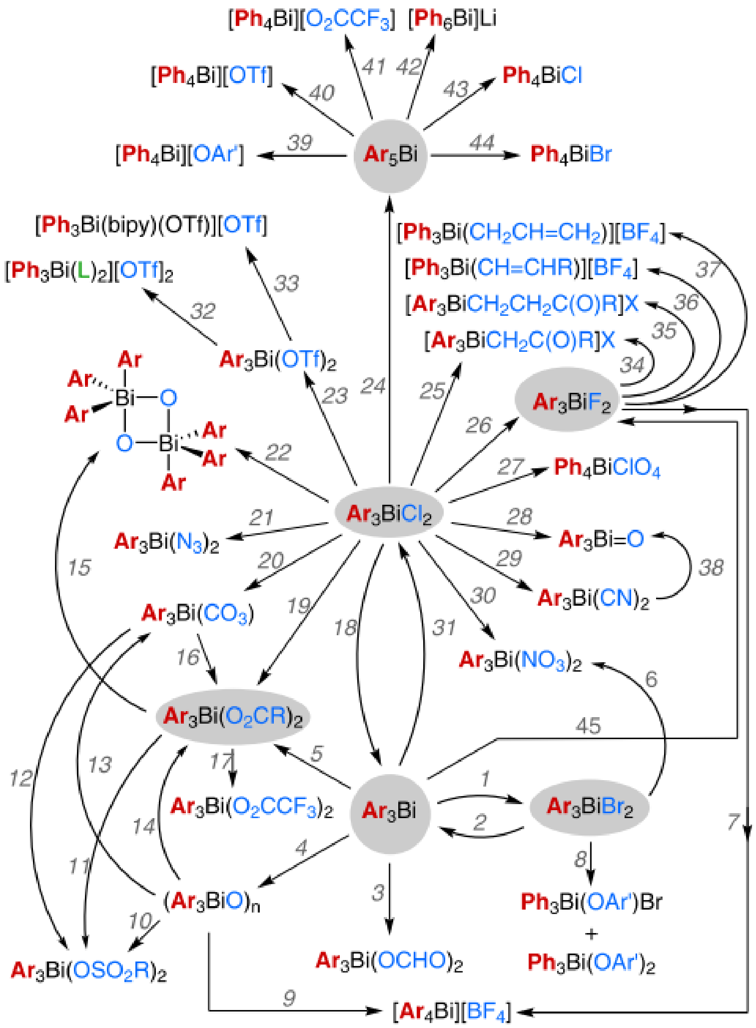


Synthesis

Routes to Bi(III) compounds



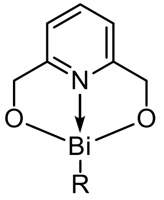
Routes to Bi(V) compounds



Gagnon, A. *Synthesis (Stuttg).* **2017**, *49* (8), 1707–1745.

Hypervalency and Chirality

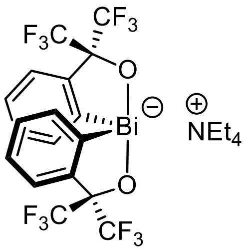
Hypervalency



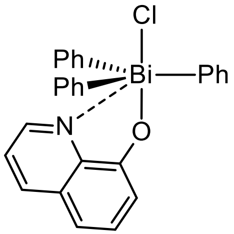
10-Bi-4

electrons around bismuth

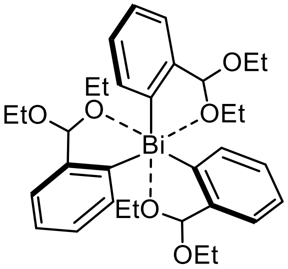
ligands around bismuth



10-Bi-4



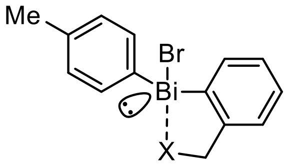
12-Bi-6



14-Bi-6

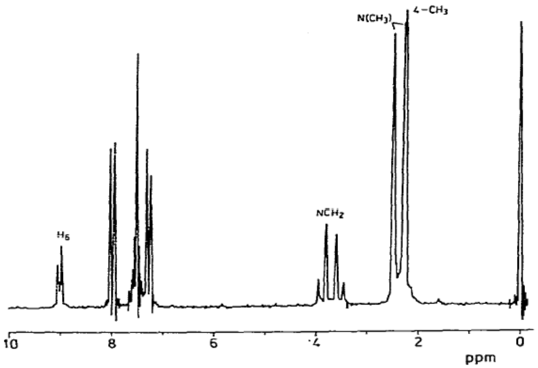
Gagnon, A. *Synthesis (Stuttg).* **2017**, *49* (8), 1707–1745.

Chirality

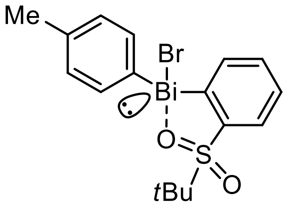


X = NMe_2, OMe

first report: 1981

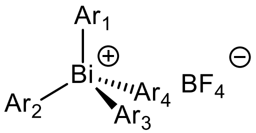


Wolters, J. *J. Organomet. Chem.* **1981**, *212*, C7–C9.



first resolvation: 1992
(Chiral HPLC)

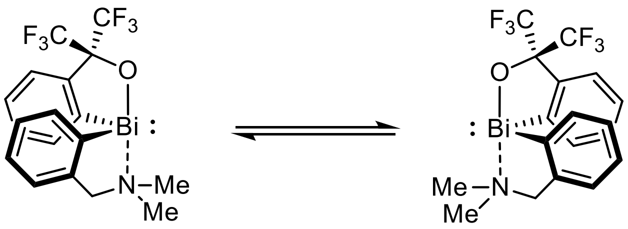
Suzuki, H.; *Chem. Commun.* **1992**, No. 16, 1143.



first chiral tetraarylbismuthonium (1999)
never resolved

Matano, *Organometallics* **1999**, *18* (26), 5668–5681.

Inversion barrier: 34 - 69 kcal/mol
(Phospine: 24 kcal/mol Ammonia: 7 kcal/mol)



Interconversion at:

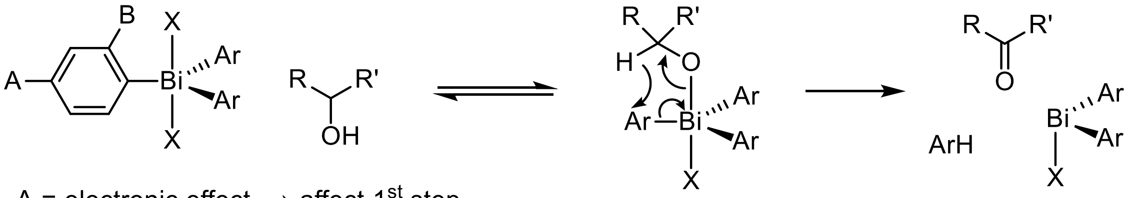
125°C in toluene → $\Delta G^{\#} = 20.5$ kcal/mol
40°C in the presence of pyridine
50°C in DMSO

Gagnon, A. *Synthesis (Stuttg).* **2017**, *49* (8), 1707–1745.

Bismuth (V)

Oxidation

General Mechanism



A = electronic effect → affect 1st step
B = steric effect → affect 2nd step (2x)

- Bi(V)/Bi(III) redox
- Nucleofugality

Evolution of Methodologies

Challenger and Richards
1934

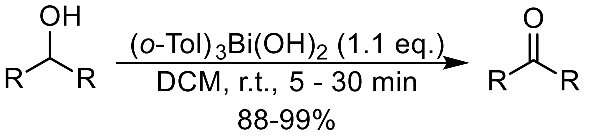
$Ph_3Bi(OH)_2$
Oxidation of simple alcohols to aldehydes

Barton and Dodonov
1978-1985

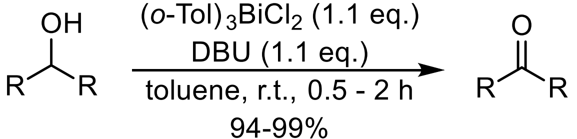
polyphenol bismuth (V) compounds:
Ph_3BiCO_3, $(Ph_3BiCl)_2O$, etc.

Harsh conditions are needed

Matano
2001 and 2002



freshly prepared bismuthate



bench stable starting materials

allylic-1°
allylic-2°
benzylic-1°
benzylic-2°
aliphatic-1°
aliphatic-2°

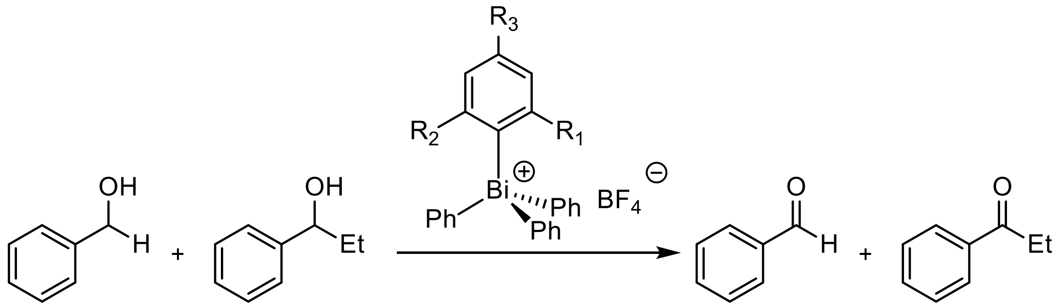
Matano, Y. *J. Org. Chem.* **2001**, *69* (25), 8676–8680.

Matano, Y.; *Angew. Chemie - Int. Ed.* **2002**, *41* (16), 3028–3031.

Bismuth (V)

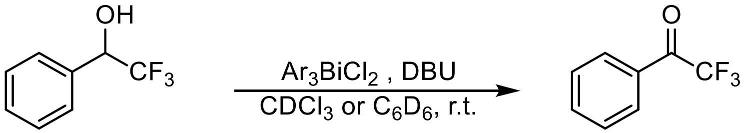
Oxidation

Selectivity and reactivity



Matano Y. *Bull Chem Soc Jpn* **2008**, *81,* 1621

	Aldehyde	Ketone
R_1=R_2=Me R_3=H	92	8
R1=R2=H R3=Me	77	23
Dess-Martin	67	33



Matano, Y.; *Angew. Chemie - Int. Ed.* **2002**, *41* (16), 3028–3031.

entry	Ar	time	yield(%)
1	$o\text{-MeC}_6\text{H}_4$	32 h	98
2	$p\text{-CF}_3\text{C}_6\text{H}_4$	50 min	95<
3	$p\text{-NO}_2\text{C}_6\text{H}_4$	5 min	95<

Order of selectivity:

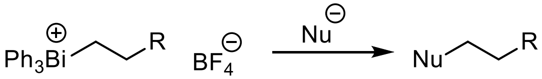
allylic, benzylic > primary > secondary

Advantages	**Drawbacks**
Easy (and cheap) to prepare	Very expensive
Triarylbismuth chloride is bench stable	Triarylbismuth oxides are slowly decomposing in solution
No overoxidation	Moderate thermal stability
Oxidizes less reactive alcohols	
Orthogonal with most FGs	
Excellent selectivities and yields	

Bismuth (V)

C-Alkylation, C-Alkenylation

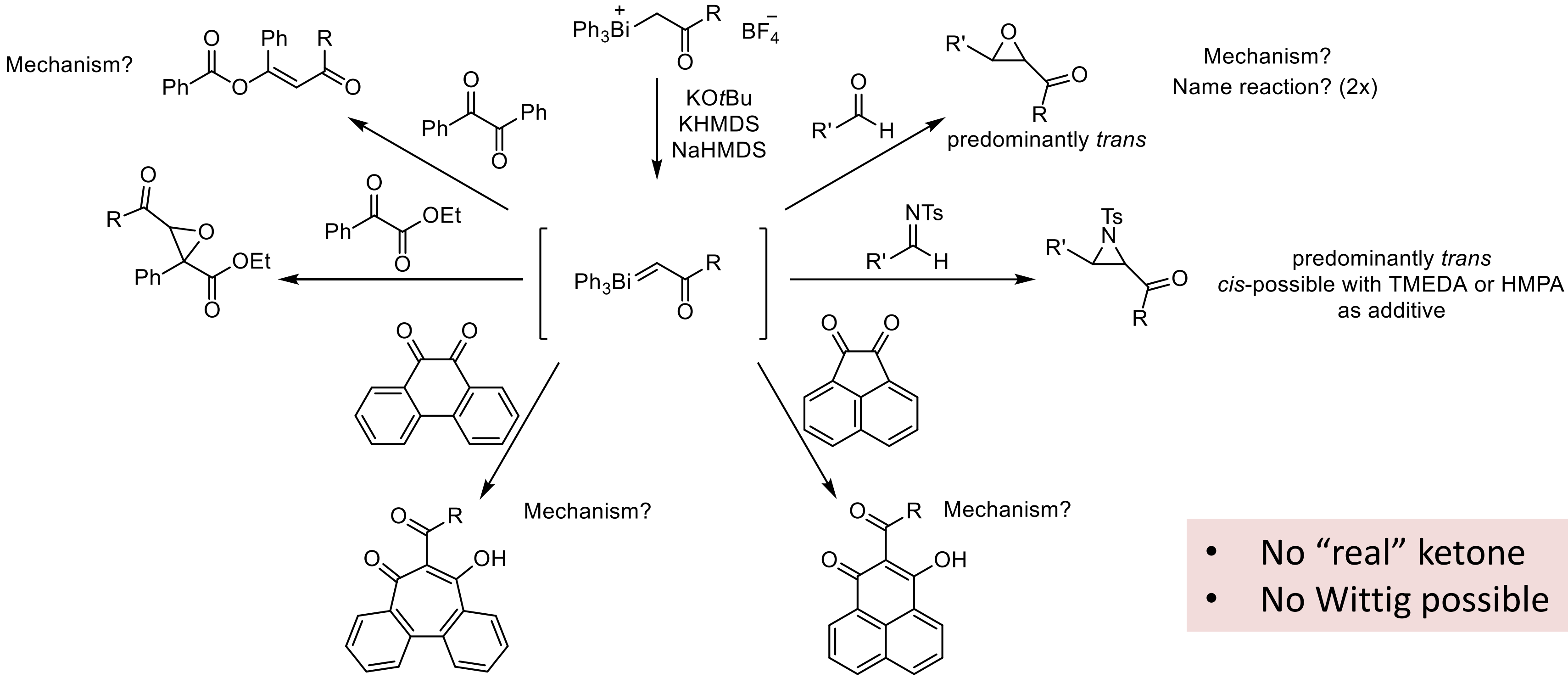
Alkylation



Nu = Me_2S
PPh_3
$PhSO_2Na$
KI
KBr
HNRR'
ROH
enolate
aryl (like FC)

- S_N2-type alkylation
- Bi(V)/Bi(III) redox
- Nucleofugality

Bismuth-ylides



Mechanism?

Mechanism?
Name reaction? (2x)

predominantly *trans*

predominantly *trans*
cis-possible with TMEDA or HMPA as additive

Mechanism?

Mechanism?

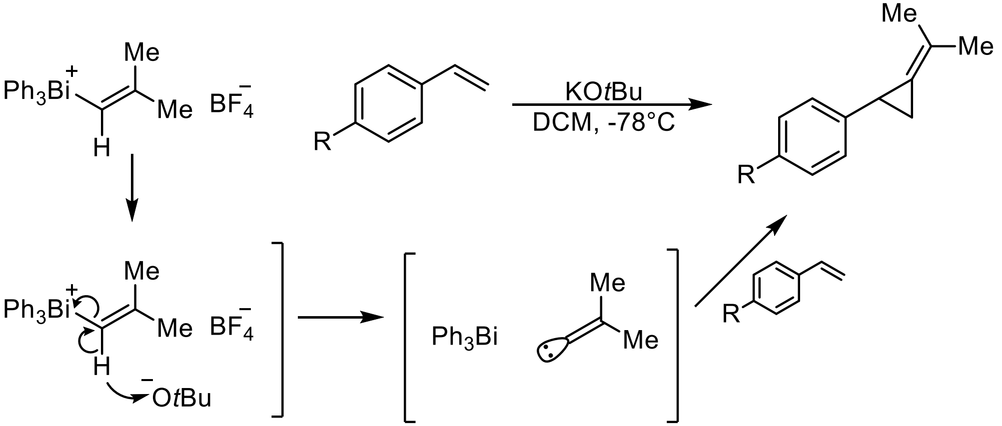
- No “real” ketone
- No Wittig possible

Vinet, L.; Zhedanov, A. *Bismuth-Mediated Organic Reactions*; Ollevier, T., Ed.; Topics in Current Chemistry; Springer Berlin Heidelberg: Berlin, Heidelberg, 2012; Vol. 311.

Bismuth (V)

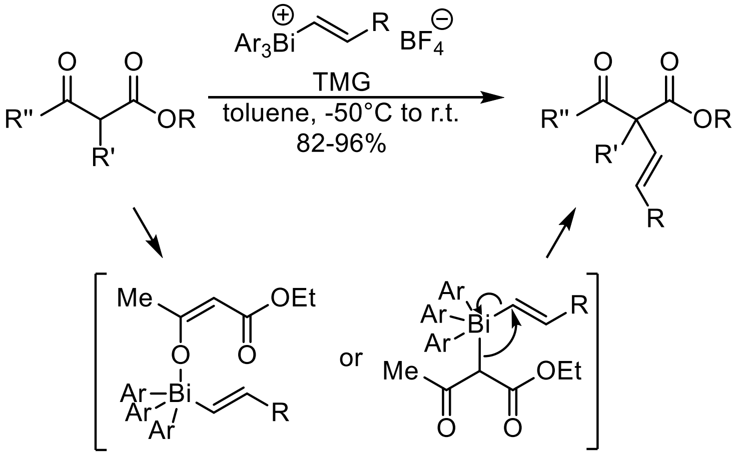
C-Alkylation, C-Alkenylation

Ylide → Carbenoid



R = Me 93%
H 84%
Cl 86%

Alkenylation



Mechanism	Observation
SN1	Retention of E/Z ratio
SN2	Retention of E/Z ratio
Addition-Elimination	No beta-EWG → no stabilization
Carbene / C-H insertion	Parallel pathway
Ligand-exchange, then ligand-coupling	Explains stereochemical outcome and substituent effects

Mukaiyama, T.; *Chem. Lett.* **2006**, *35* (10), 1140–1141.

Selectivity of **alkenyl vs aryl** transfer with regard to alkenyl's β-substituents:

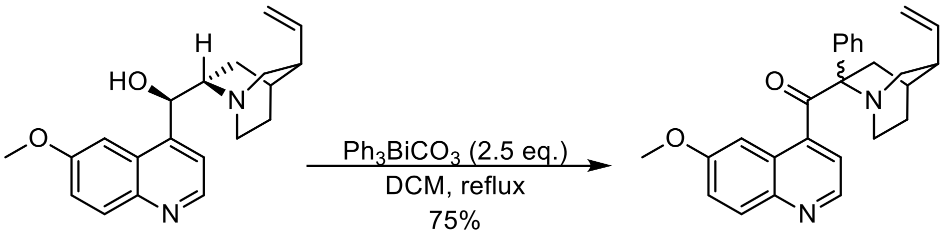
β-alkyl > β-phenyl > β-methyl > β,β-dimethyl

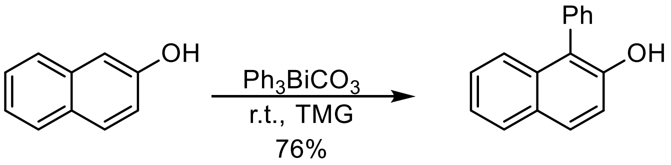
← preference of alkenyl migration

Bismuth (V)

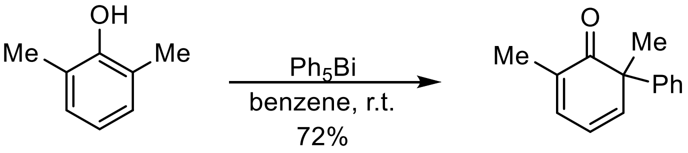
C- and O-Arylation

Barton 1980-1981

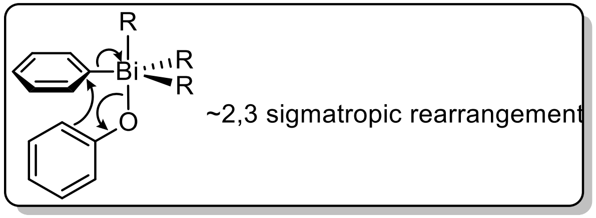




Barton, D. H. R.; *J. Chem. Soc., Chem. Commun.* **1980**, *8* (5), 246–247.



Barton, D. H. R.; *J. Chem. Soc. Chem. Commun.* **1981**, No. 10, 503.



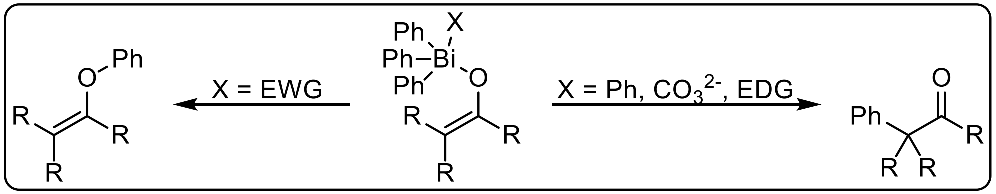
Bismuth (V)

C- and O-Arylation

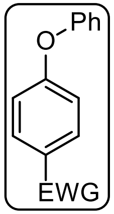
O- vs C- selectivity

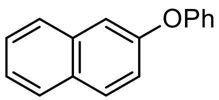
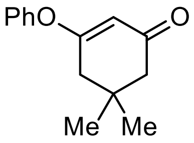
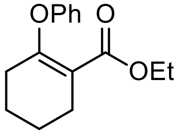
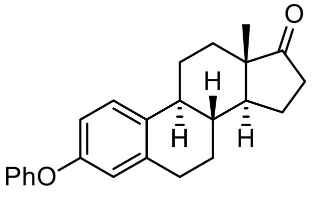
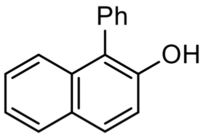
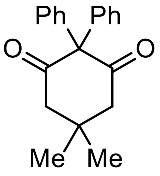
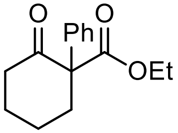
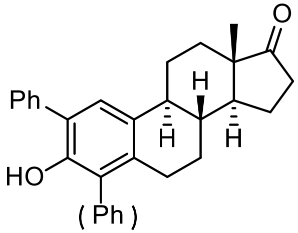
Chemoselectivity depends on:

- Counter anion of Bi-salt
- Electronics of substrate
- pH of reaction mixture



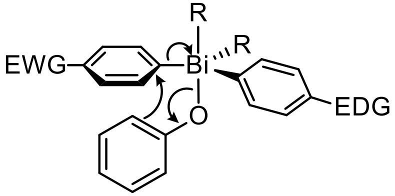
Barton *Tetrahedron Lett.* **1982**, *23*, 3365.



Neutral and acidic condition (yield (%) neutral), (yield (%) acidic)	 75%, 90%	 55%, 85%	 30%, 57%	 68%
Basic condition (yield (%))	 90%	 15%	 91%	 18%, (41% brsm)

Relative migratory aptitude of aryl groups depends on:

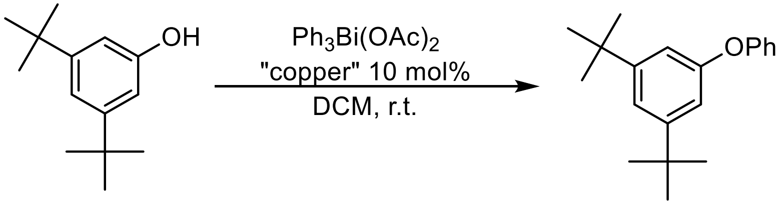
- Electronics of aromatic ligands
- The lower the electron density, the higher aptitude it have



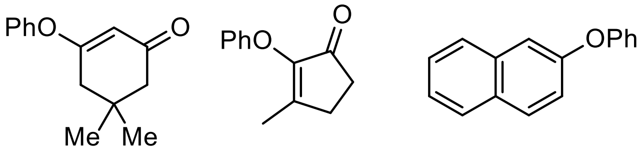
Bismuth (V)

O-Arylation

Phenol



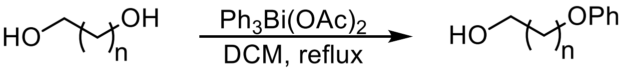
no copper: 86% (23 h)
Cu(OAc)$_2$: 77% (1h)
Cu(0): 90% (4h)



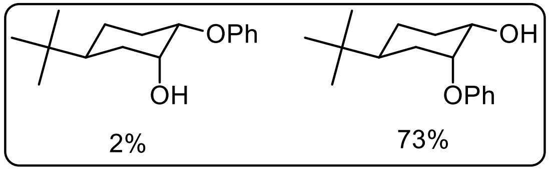
88% 96% 84%

Matano Y. *Bull Chem Soc Jpn*, **2008,** 81:1621

Aliphatic alcohol

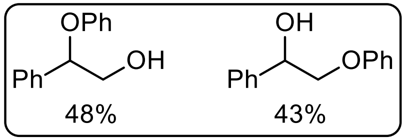


n=1 : 85%
n=2 : 87%
n=3 : 80%
n=4 : 50%
n=5 : 40%

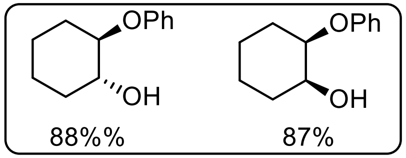


2% 73%

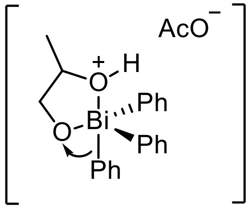
conformationally fixed substrate
trans-4-tertbutyl-cis-cyclohexane-1,2-diol



48% 43%



88%% 87%



Advantages

- Selective for axial alcohol
- High yields are obtained

Drawbacks

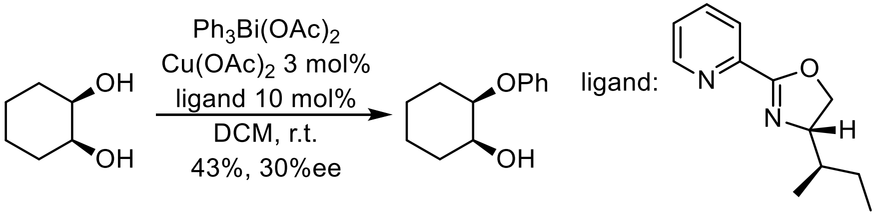
- Only diols work
- No tertiary alcohol
- Not selective for 1° / 2° alcohol
- Not selective for relative configuration

Gagnon, A. *Synthesis (Stuttg).* **2017**, *49* (8), 1707–1745.

Bismuth (V)

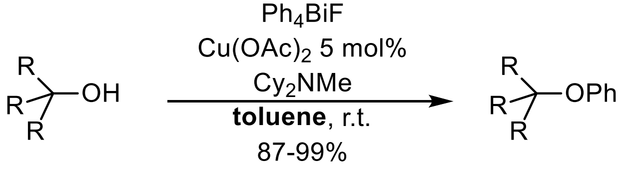
O-Arylation

Attempt on desymmetrization



$Ph_3Bi(OAc)_2$
$Cu(OAc)_2$ 3 mol%
ligand 10 mol%
DCM, r.t.
43%, 30%ee

Mukaiyama



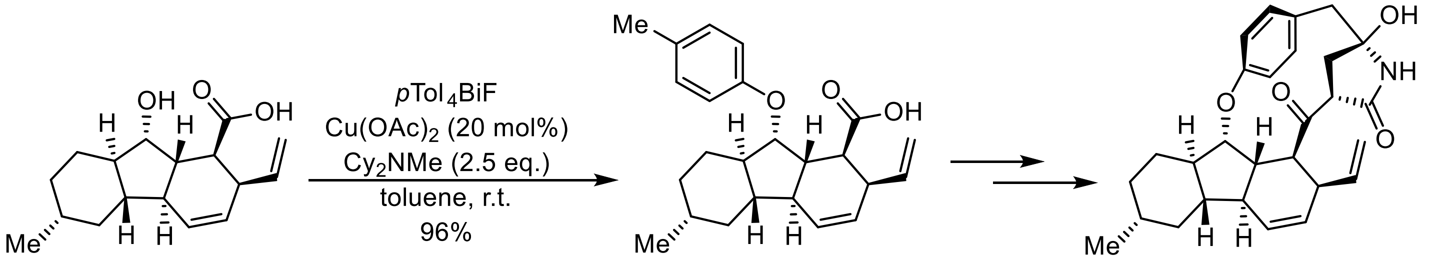
Ph_4BiF
$Cu(OAc)_2$ 5 mol%
Cy_2NMe
toluene, r.t.
87-99%

arylates tertiary alcohols

“Mukaiyama-modified Barton etherification”

Chem. Lett. **2006**, *35* (10), 1140–1141.

Nicolaou

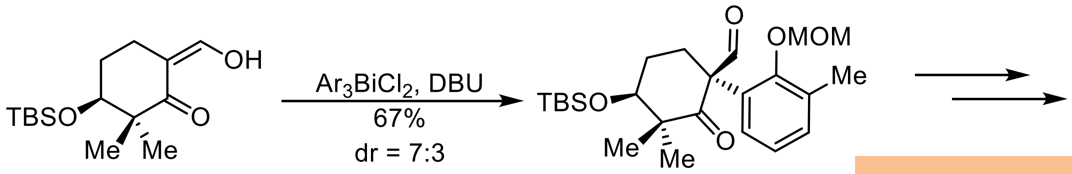


pTol$_4$BiF
$Cu(OAc)_2$ (20 mol%)
Cy_2NMe (2.5 eq.)
toluene, r.t.
96%

Angew. Chemie Int. Ed. **2009**, *48* (37), 6870–6874.

Hirsutellone B

Baran



Ar_3BiCl_2, DBU
67%
dr = 7:3

Attempt on Maeocrystal V

Matano-Barton condition, still, oxidation is not possible!

Org. Lett. **2009**, *11* (21), 4774–4776.

Bismuth (III)

Lewis acidity and catalysis

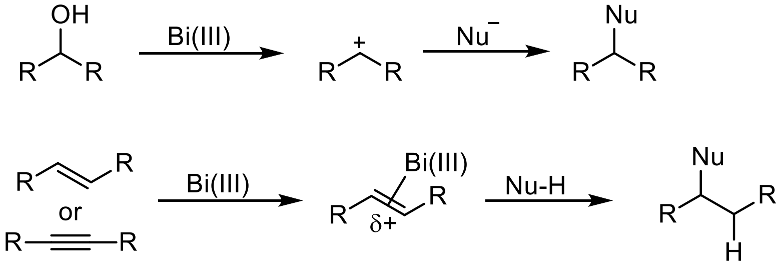
Base or acid?

Lewis acidity is a result of :

1. the counteranion and its free acid TfOH
2. backdonation from the full d-orbital to the Bi-C σ^* orbital
3. an antibonding σ^* MO, which originates from an unoccupied p-orbital of the Bi (III) atom.
   Electron-deficient ligands or counterions such as TfO^- can lower the energy of this antibonding orbital and subsequently increase its reactivity.

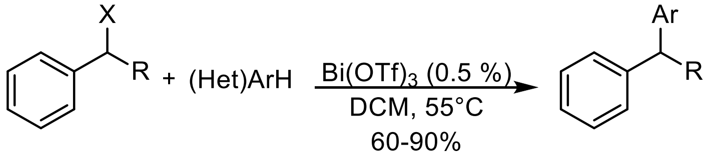
Take home this:

- 99% of the cases $Bi(OTf)_3$ or $BiCl_3$ is the catalyst.
- Bismuth(III) activates alcohol and unsaturated C-C bonds.
- Typical transformations to consider screening Bi(III) compounds:
    - Sakurai allylation
    - Silyl-enol ether activation
    - Tsuji-Trost-type allylic / propargylic substitution
    - Friedel-Crafts (mild)
    - Diels-Alder reaction



Bismuth (III)
Alkylation

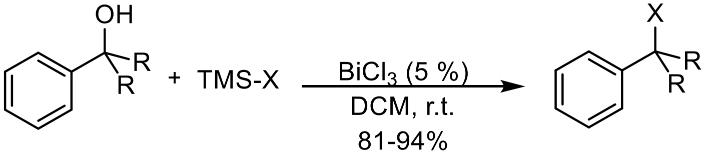
Friedel-Crafts benzylation



X = OH, OAc
R = H, Me

Rueping, M.; *Adv. Synth. Catal.* **2006**, *348* (9), 1033–1037.

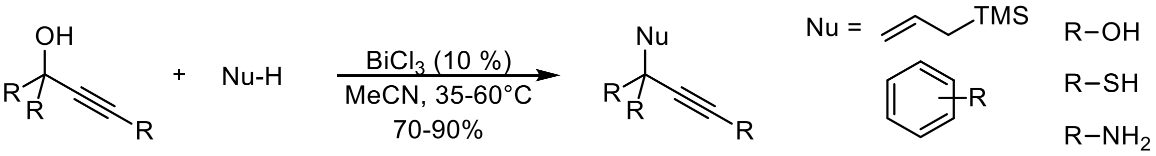
Deoxygenative allylation



R = aryl, alkyl, diaryl, dialkyl
X = allyl, propargyl, alkynyl

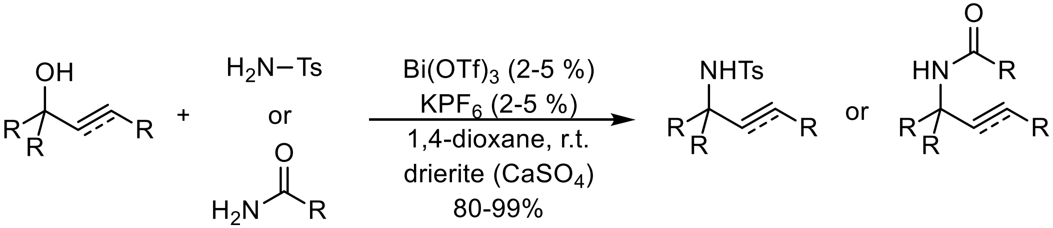
Gibbs, R. A. *Tetrahedron Lett.* **2005**, *46* (48), 8345–8350.

Propargylic substitution



Zhan, Z.; *Chem. Commun.* **2006**, *1* (31), 3352.

Direct allylic / propargylic substitution

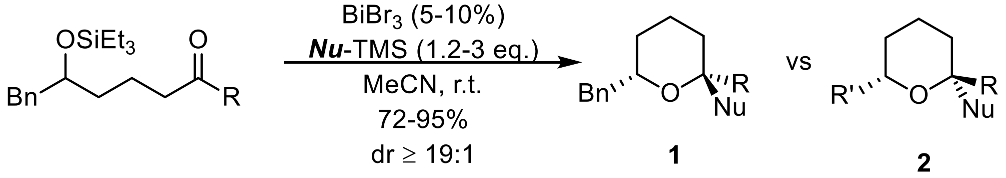


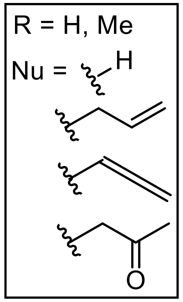
Shibasaki, M. *Angew. Chemie - Int. Ed.* **2007**, *46* (3), 409–413.

Bismuth (III)

Etherification – P. A. Evans

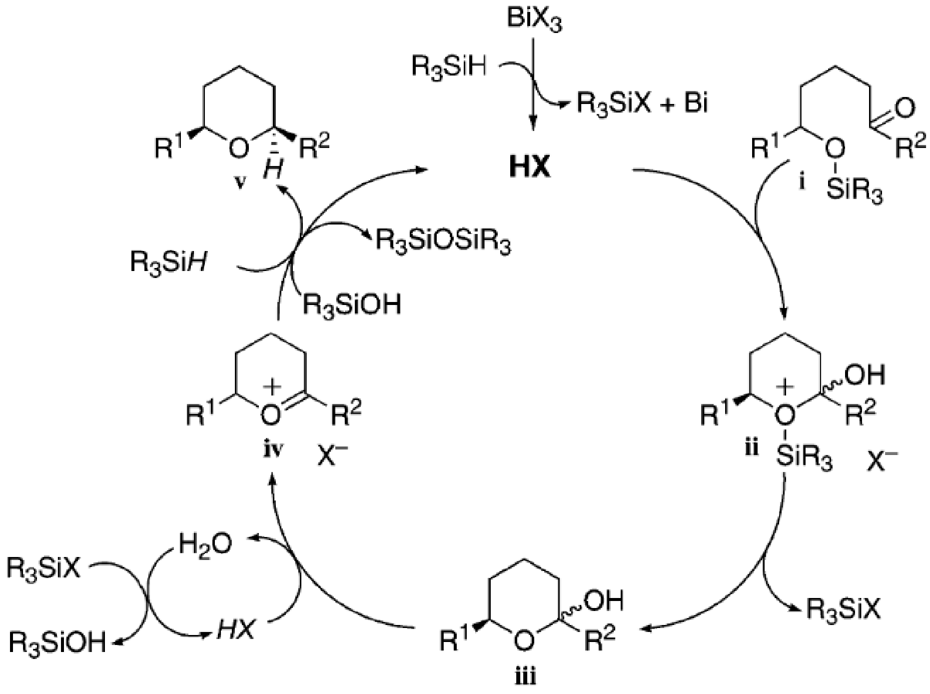
Tandem Etherification





Evans, P. A.; *J. Am. Chem. Soc.* **2003**, *125* (38), 11456–11457.

Catalytic cycle

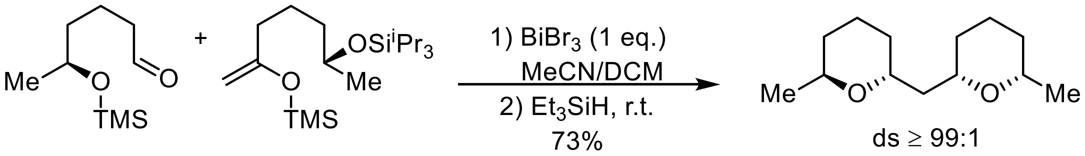


Evans, P. A.; *J. Am. Chem. Soc.* **2003**, *125* (38), 11456–11457.

Bismuth (III)

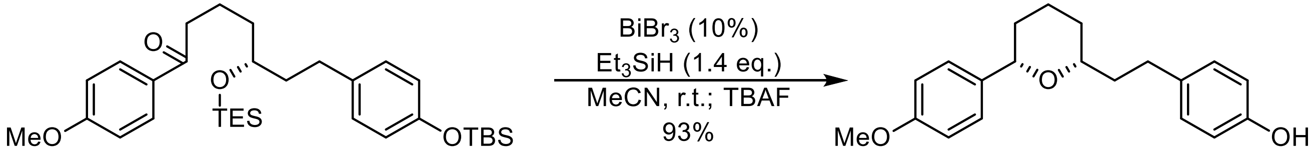
Etherification – P. A. Evans

Tandem etherification



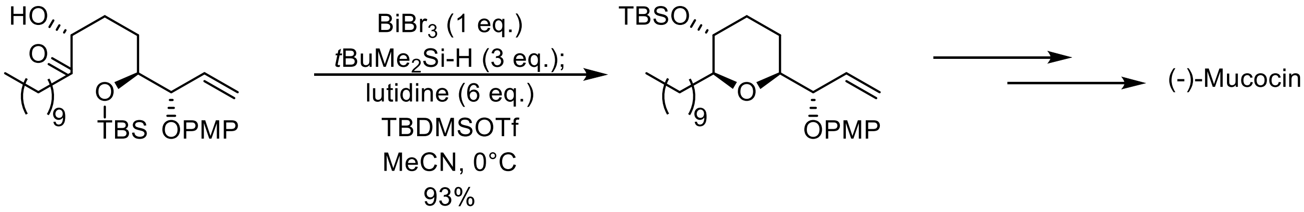
Evans, P. A.; *J. Am. Chem. Soc.* **2003**, *125* (38), 11456–11457.

Total Syntheses



(-)-Centrolobine

Evans, P. A.; J. *Org. Lett.* **2003**, *5* (21), 3883–3885.

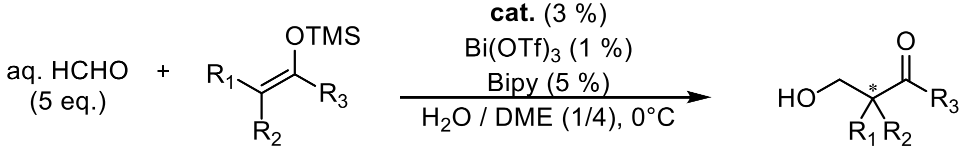


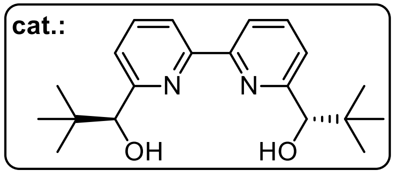
Evans, P. A.; *J. Am. Chem. Soc.* **2003**, *125* (48), 14702–14703

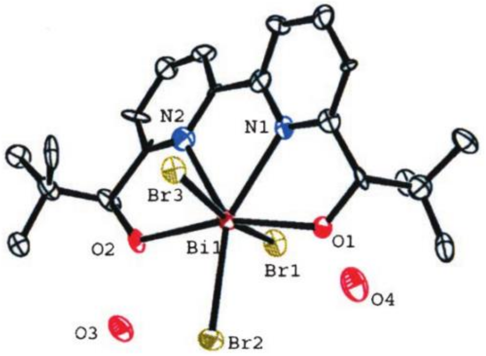
Bismuth (III)

Reaction in Aqueous Media

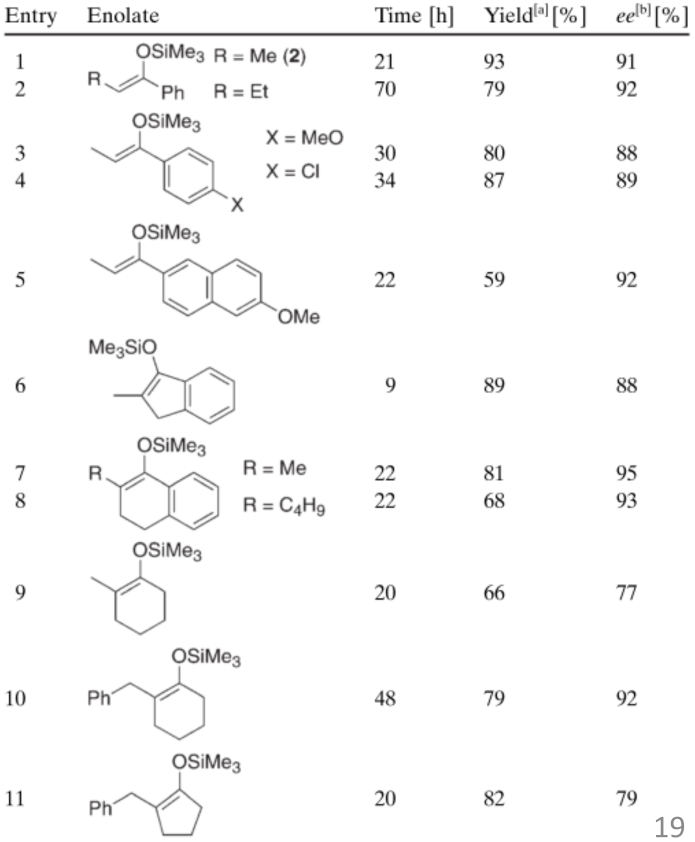
Mukaiyama aldol in aq. media







Kobayashi, S.; *Chem. - A Eur. J.* **2006**, *12* (23), 5954–5960.



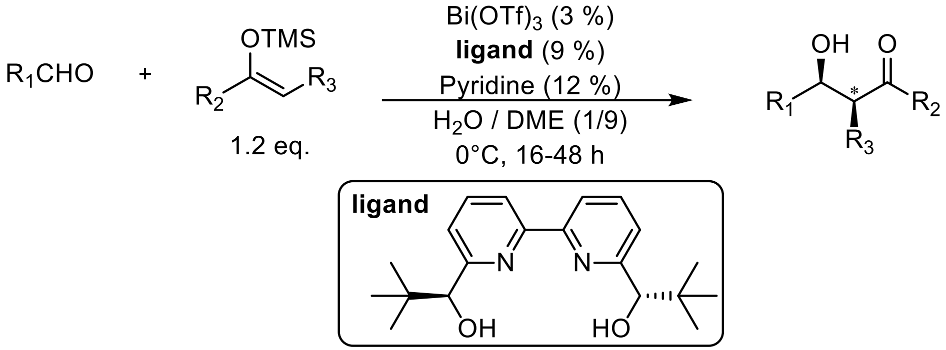
Entry	Enolate	Time [h]	Yield[a] [%]	ee[b] [%]
1	R = Me (**2**)	21	93	91
2	R = Et	70	79	92
3	X = MeO	30	80	88
4	X = Cl	34	87	89
5		22	59	92
6		9	89	88
7	R = Me	22	81	95
8	R = C_4H_9	22	68	93
9		20	66	77
10		48	79	92
11		20	82	79

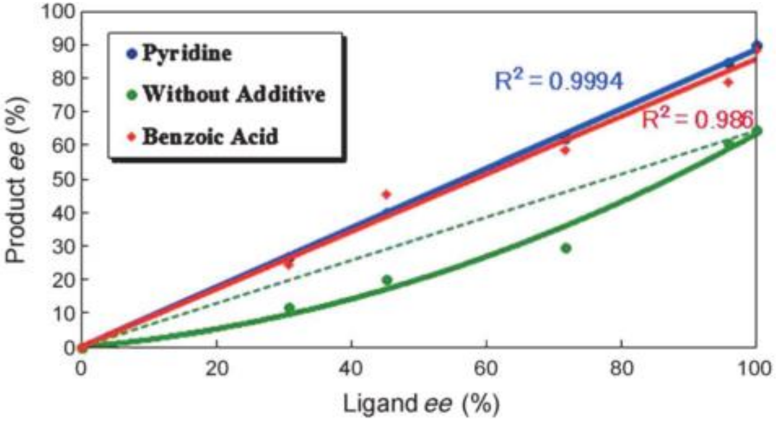
- Most chiral catalysts are unstable in water
- Lewis acids are typically non-stable in aqueous media
- $Bi(OTf)_3$ is known to hydrolyze is water

Bismuth (III)

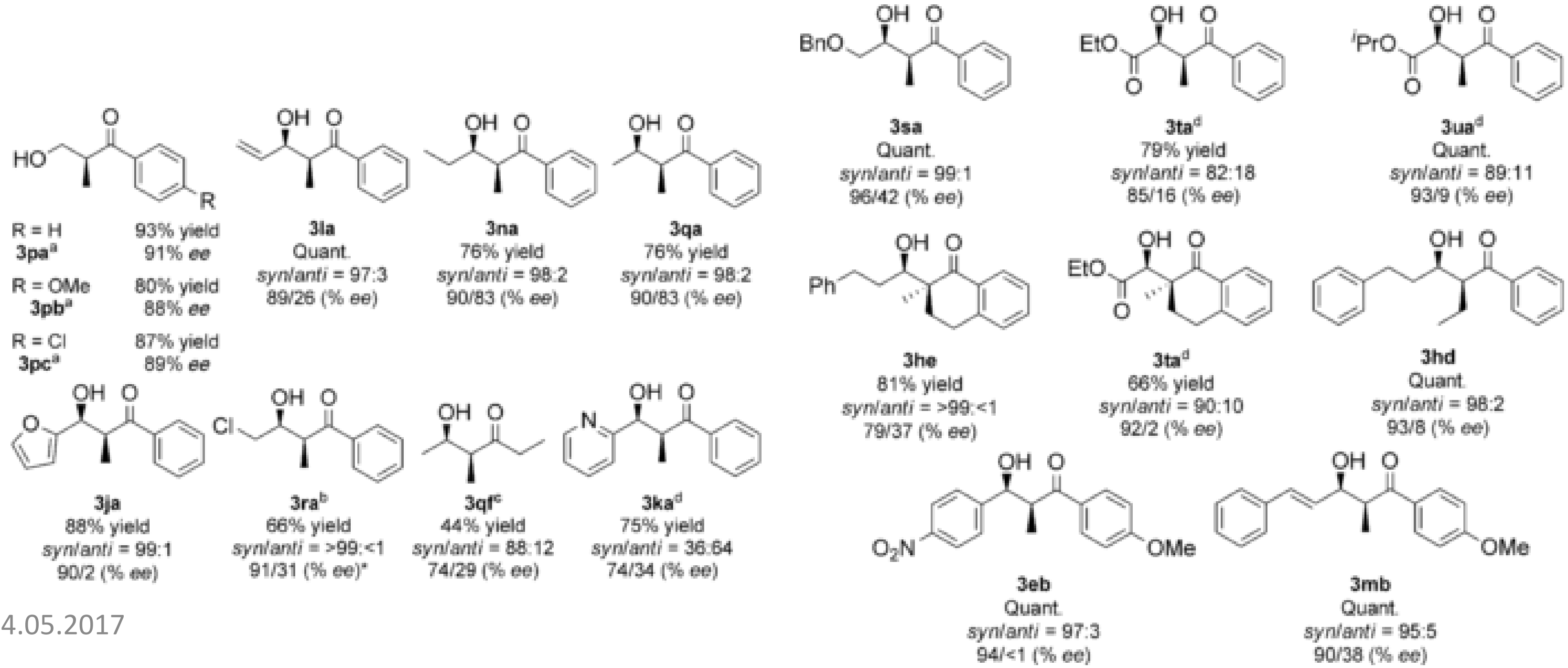
Reaction in Aqueous Media

State of the Art





Kobayashi, S. *Chem. - An Asian J.* **2013**, *8* (12), 3051–3062.



R = H **3pa**[a] 93% yield 91% *ee*

R = OMe **3pb**[a] 80% yield 88% *ee*

R = Cl **3pc**[a] 87% yield 89% *ee*

3la Quant. *syn*/*anti* = 97:3 89/26 (% *ee*)

3na 76% yield *syn*/*anti* = 98:2 90/83 (% *ee*)

3qa 76% yield *syn*/*anti* = 98:2 90/83 (% *ee*)

3ja 88% yield *syn*/*anti* = 99:1 90/2 (% *ee*)

3ra[b] 66% yield *syn*/*anti* = >99:<1 91/31 (% *ee*)[*]

3qf[c] 44% yield *syn*/*anti* = 88:12 74/29 (% *ee*)

3ka[d] 75% yield *syn*/*anti* = 36:64 74/34 (% *ee*)

3sa Quant. *syn*/*anti* = 99:1 96/42 (% *ee*)

3ta[d] 79% yield *syn*/*anti* = 82:18 85/16 (% *ee*)

3ua[d] Quant. *syn*/*anti* = 89:11 93/9 (% *ee*)

3he 81% yield *syn*/*anti* = >99:<1 79/37 (% *ee*)

3ta[d] 66% yield *syn*/*anti* = 90:10 92/2 (% *ee*)

3hd Quant. *syn*/*anti* = 98:2 93/8 (% *ee*)

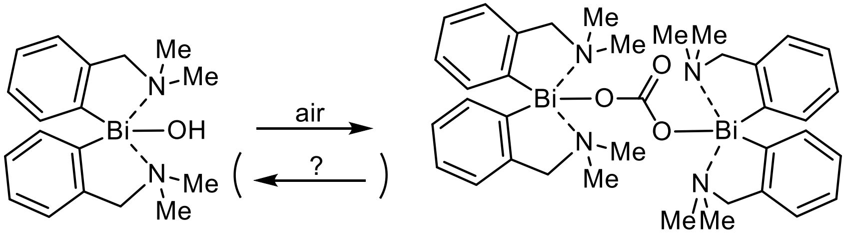
3eb Quant. *syn*/*anti* = 97:3 94/<1 (% *ee*)

3mb Quant. *syn*/*anti* = 95:5 90/38 (% *ee*)

Bismuth (III)

Carbon-dioxide fixation

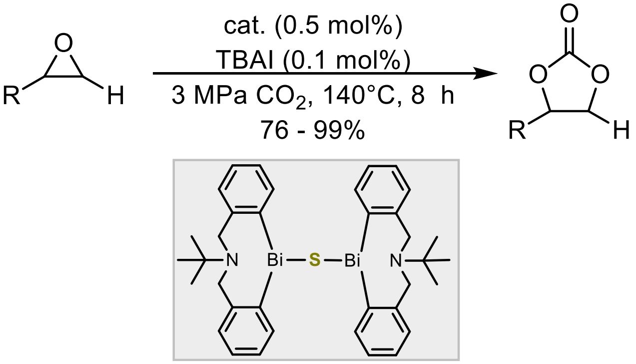
The very first report



solid, thermally stable

Breunig, H. J.*Dalt. Trans.* **2008**, *9226* (14), 1831.

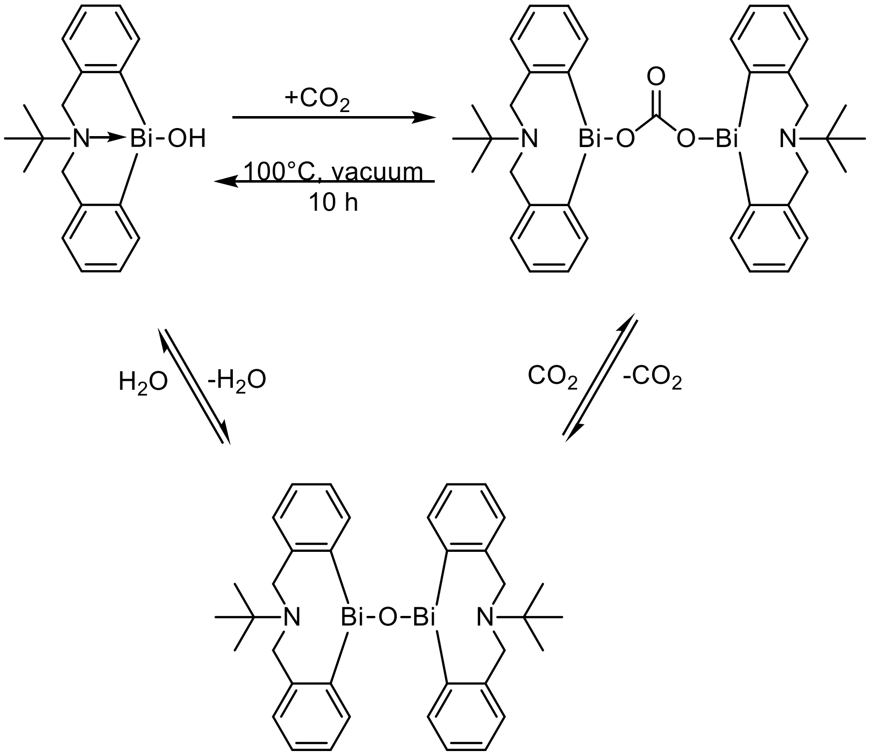
Application



"…**intramolecular coordination of the sulfur atom to the bismuth atom is expected to be very flexible,** as observed for the dibenzoazabismocine framework,17 **and can adjust the Lewis acidity of the bismuth atom and facilitate the exchange of the product and the reactant.**"

Yin, S.-F.; Shimada, S. *Chem. Commun.* **2009**, No. 9, 1136.

Reversibility demonstrated



Shimada, S. *Angew. Chemie Int. Ed.* **2008**, *47* (35), 6590–6593.

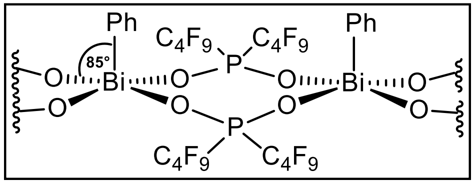
Review: Yin, S. *RSC Adv.* **2014**, *4* (23), 11907.

Bismuth (III)

State of the Art Complexes

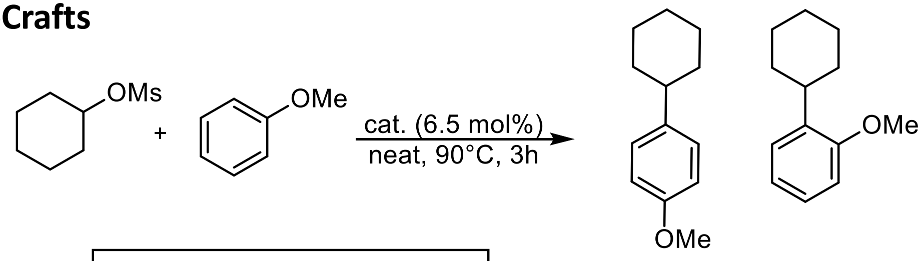
Synthesis and structure

$$BiPh_3 \xrightarrow[\text{MeOH, reflux, 24 h; - 2 benzene}]{2\,(C_2F_5)_2P(O)OH} Ph(Bi[(C_2F_5)_2PO_2]_2$$



Demonstration of activity and stability

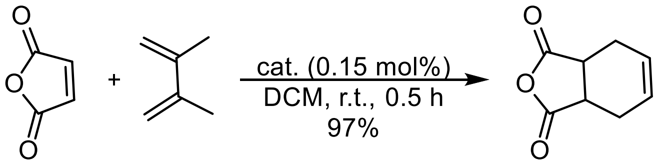
Friedel-Crafts



Alternative:
$Sc(OTf)_3$ and $Cu(OTf)_3$ 10 mol%

1 : 1
97%

Diels-Alder



Hoge, B. *Chem. - A Eur. J.* **2017**, *23* (7), 1568–1575.

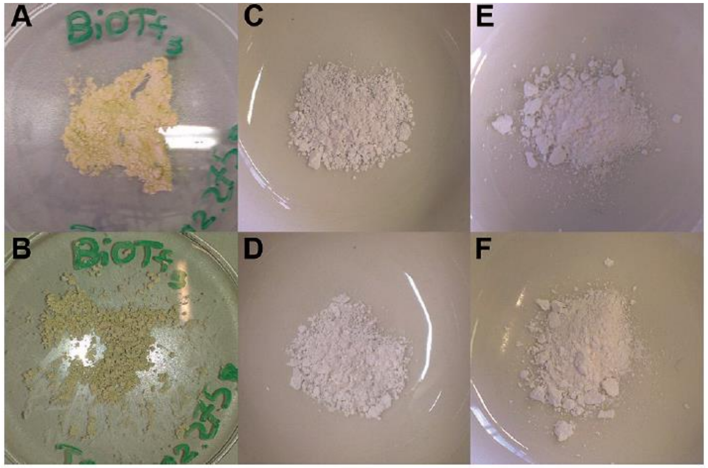


Figure 4. Illustrations of the 24 h hygroscopicity studies of $Bi(OTf)_3$ and bismuth(III) compounds **2** and **3**; **A** $Bi(OTf)_3$ before, **B** after storing at ambient air; **C** $PhBi[(C_2F_5)_2PO_2]_2$ before, **D** after storing at ambient air; **E** $Bi[(C_2F_5)_2PO_2]_3$ before, **F** after storing at ambient air.

Overview and Outlook

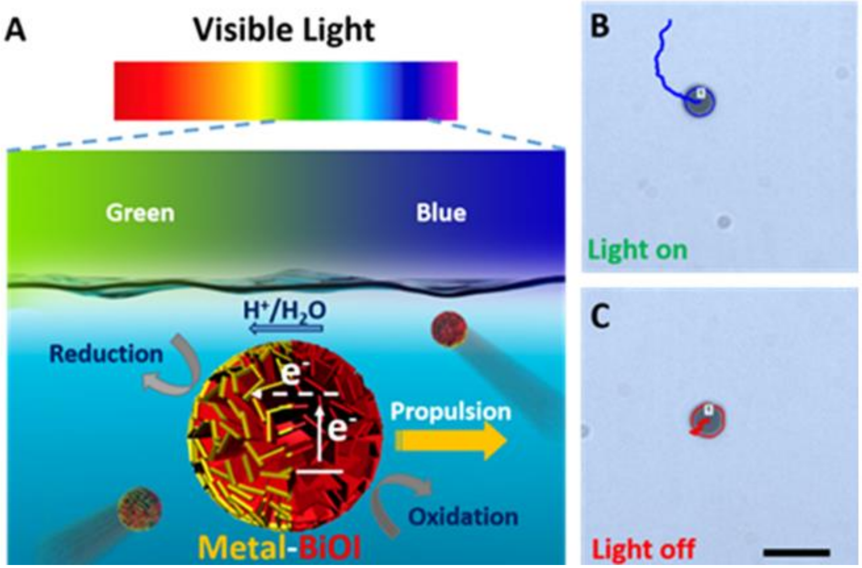
Bismuth is great, because:

- Mild, non-toxic and inexpensive reagent
- Easy and established methods to prepare its derivatives
- B(V):
  - As oxidant: More stable and selective, than DMP
  - C, O arylation and C-alkenylation without prefunctionalization
  - Epoxidation and ring expansion with Bi-ylides
- Bi(III):
  - Activation of allylsilanes and silyl-enolethers
  - Mild Friedel-Crafts and Diels-Alder catalyst
  - Benzylic-, allylic-, propargylic-substitution
  - CO_2 activation

Why bismuth never made it to mainstream chemistry?

- Few enantioselective transformations
- Facile inversion of chirality
- Bi(III)/Bi(V) oxidation potential → catalytic regeneration?
- Low AE
- We do not completely understand its properties and reactivity

Bonus Slide



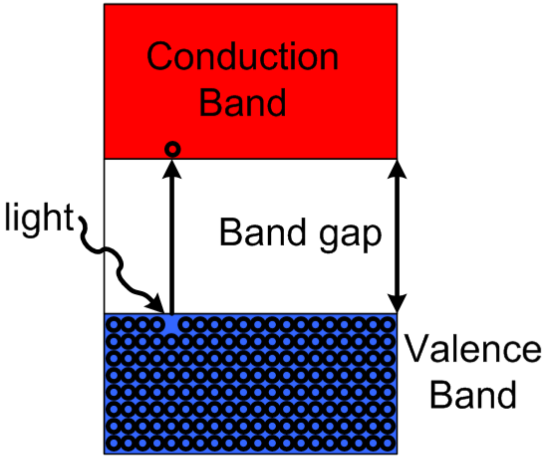
For the BiOI side:

$$\mathrm{BiOI} + h\nu \rightarrow e^{-} + h^{+}$$

$$2H_2O + 2h^{+} \rightarrow 2H^{+} + 2^{\bullet}OH$$

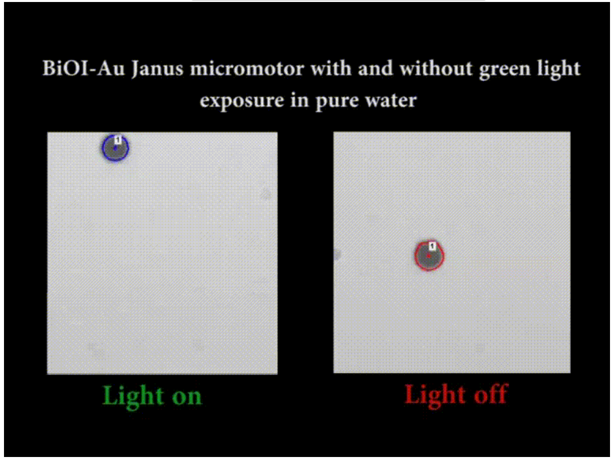
For the gold side:

$$O_2 + 2e^{-} + 2H^{+} \rightarrow 2^{\bullet}OH$$



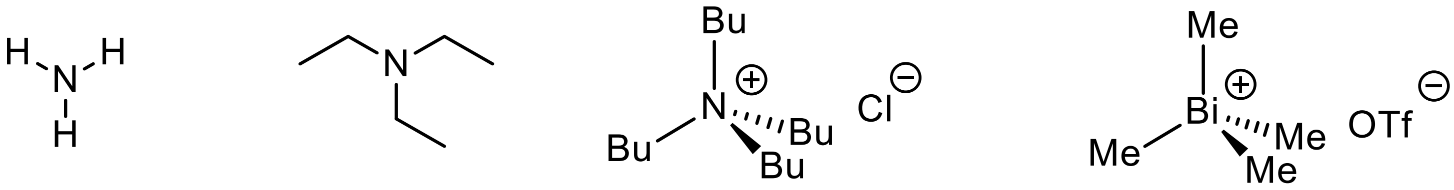
- Works from green to the blue end of the spectrum
- Not complicated preparation
- 1.62 µm/s 43 kilolux of green light (~strong headlamp, weaker end of spectrum)
- 0.6 µm/s = Brownian movement

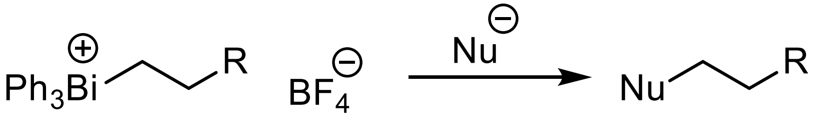
- Imagine controlling objects/instrument in the space!


BiOI-Au Janus micromotor with and without green light exposure in pure water

Dong, R.; Hu, Y.; Wu, Y.; Gao, W.; Ren, B.; Wang, Q.; Cai, Y. *J. Am. Chem. Soc.* **2017**, *139* (5), 1722–1725.

Oxidation state?





Nu = Me_2S

PPh_3

$PhSO_2Na$

KI

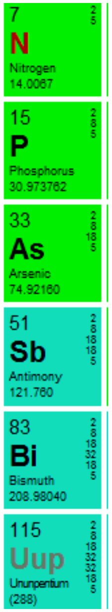
KBr

HNRR'

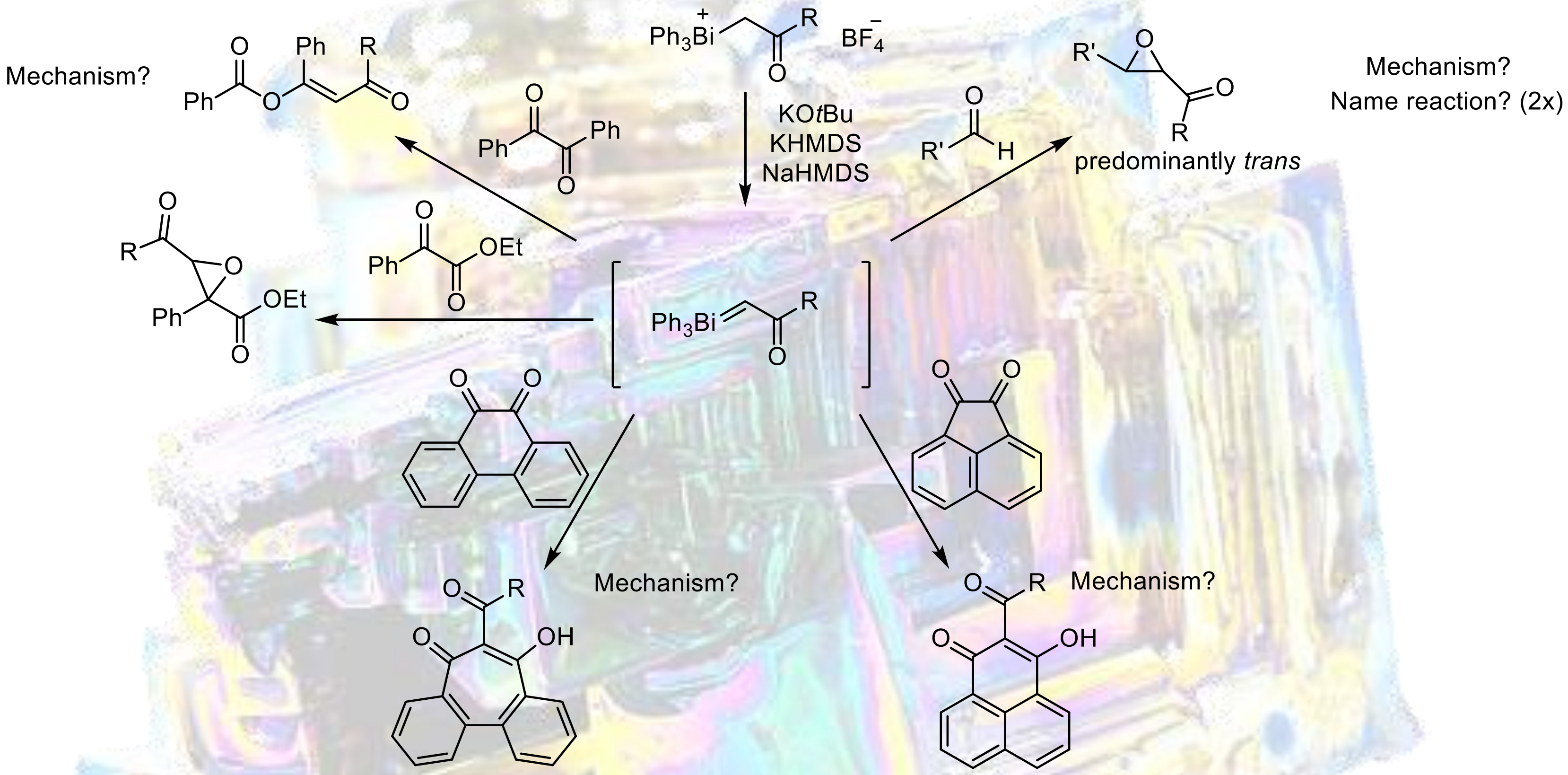
ROH

enolate

aryl (like FC)



Mechanism



Mechanism?

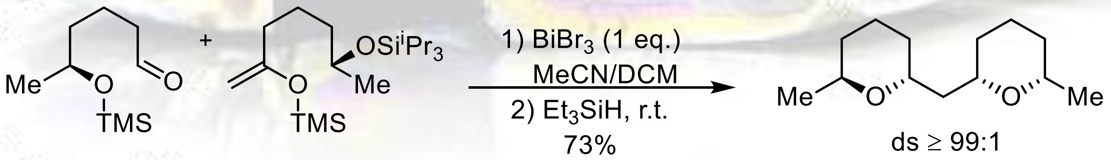
Mechanism?
Name reaction? (2x)

predominantly *trans*

Mechanism?

Mechanism?

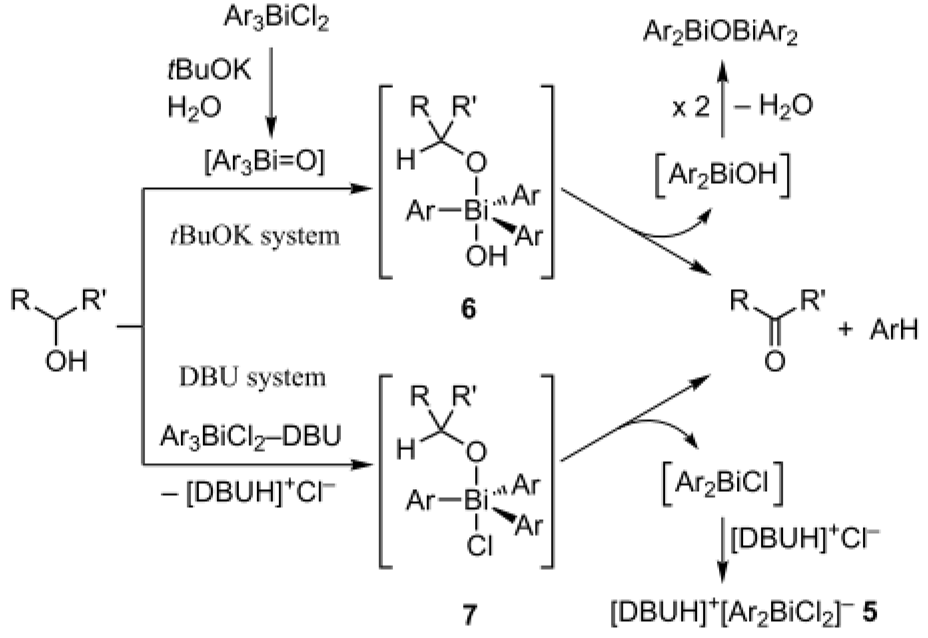
Tandem etherification



1) $BiBr_3$ (1 eq.)
MeCN/DCM
2) Et_3SiH, r.t.
73%

ds ≥ 99:1

Thank you for your attention!



Scheme 1. Plausible reaction mechanisms for the oxidation of alcohols by

Incorporation of CO_2 into Organic Molecules with Transition Metal Catalysis

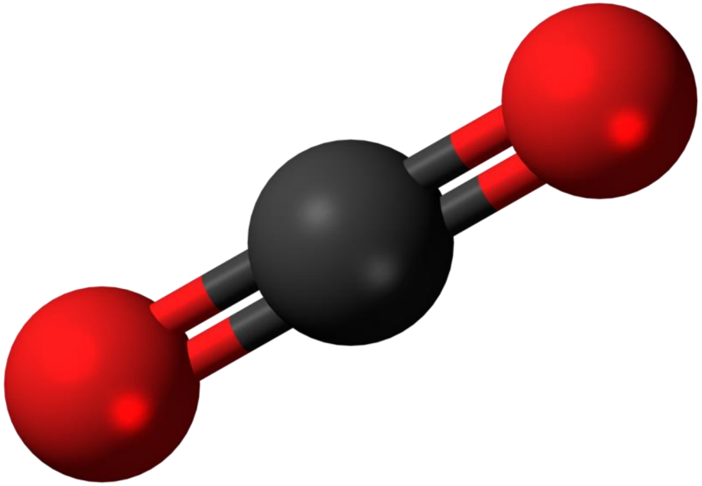
Phillip Greenwood

Plan

- Introduction
    - CO_2 as a reagent

- Examples in Literaure
    - Carboxylation
        - First examples
        - Cross electrophile coupling
        - Reductive carboxylation

    - Carbonates
        - Epoxide opening
- Conclusion



Using CO_2 as a chemical feedstock

Green Chemistry and Sustainable Technology
Bhalchandra M. Bhanage
Masahiko Arai *Editors*
Transformation and Utilization of Carbon Dioxide
Spring

ELSEVIER
Carbon Dioxide Utilisation: Closing the Carbon Cycle
Peter Styring, Elsje Alessandra Quadrelli, and Katy Armstrong

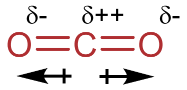
Topics in Organometallic Chemistry 53
Xiao-Bing Lu *Editor*
Carbon Dioxide and Organometallics
Springer

Edited by Michele Aresta
WILEY-VCH
Carbon Dioxide as Chemical Feedstock

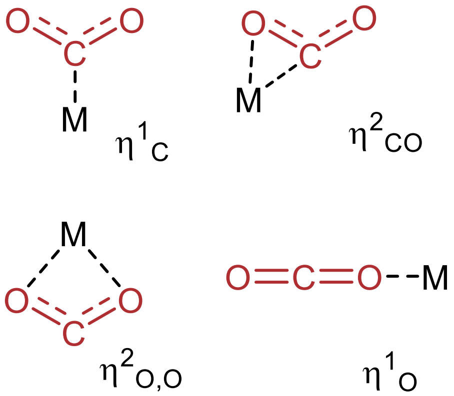
ELSEVIER
studies in surface science and catalysis
153
CARBON DIOXIDE UTILIZATION FOR GLOBAL SUSTAINABILITY
Sang-Eon Park
Jong-San Chang
Kyu-Wan Lee
(editors)

CO_2 as a reagent

- Advantages
  - Inherent greenness
  - Atom and step economy
  - Abundance
- Disadvantages
  - Inherent stability
  - Often needs high pressures

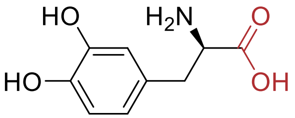


No net dipole
Linear
Amphoteric reactivity

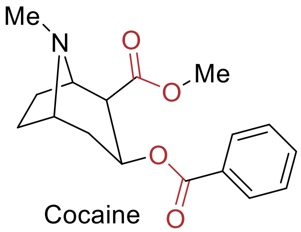


Prevalence of CO_2 in chemicals

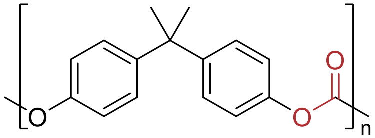
- “The carboxylic acid functional group plays a cardinal role in the biochemistry of living systems as well as in drug design.” [1]



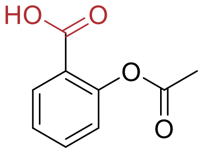
Levadopa



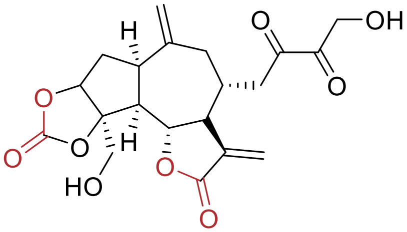
Cocaine



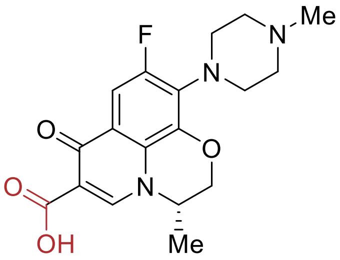
BPA polycarbonate



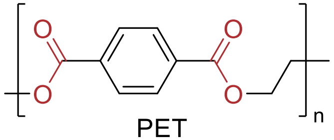
Asprin



Hololeucin derivative



Levaquin



PET

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1) ChemMedChem 2013, 8, 385 – 395

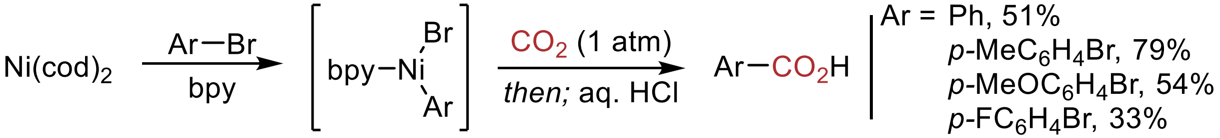
Carboxylation

- Organolithium and Grignard reagents reaction with CO_2

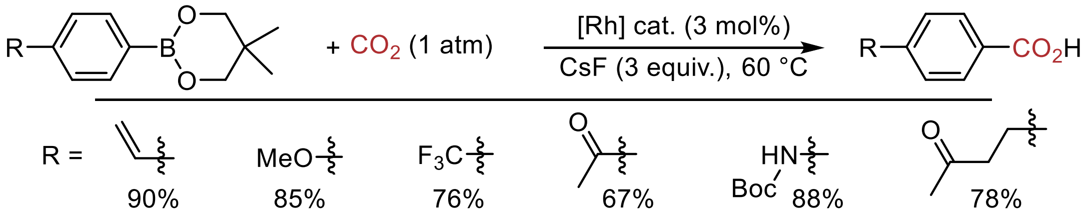
$$R{-}M \xrightarrow{CO_2} R{-}CO_2H$$

M = Li or MgX

- First example of transition metal mediated carboxylation of aryl bromides (stoichiometric Ni; 1994)[1]



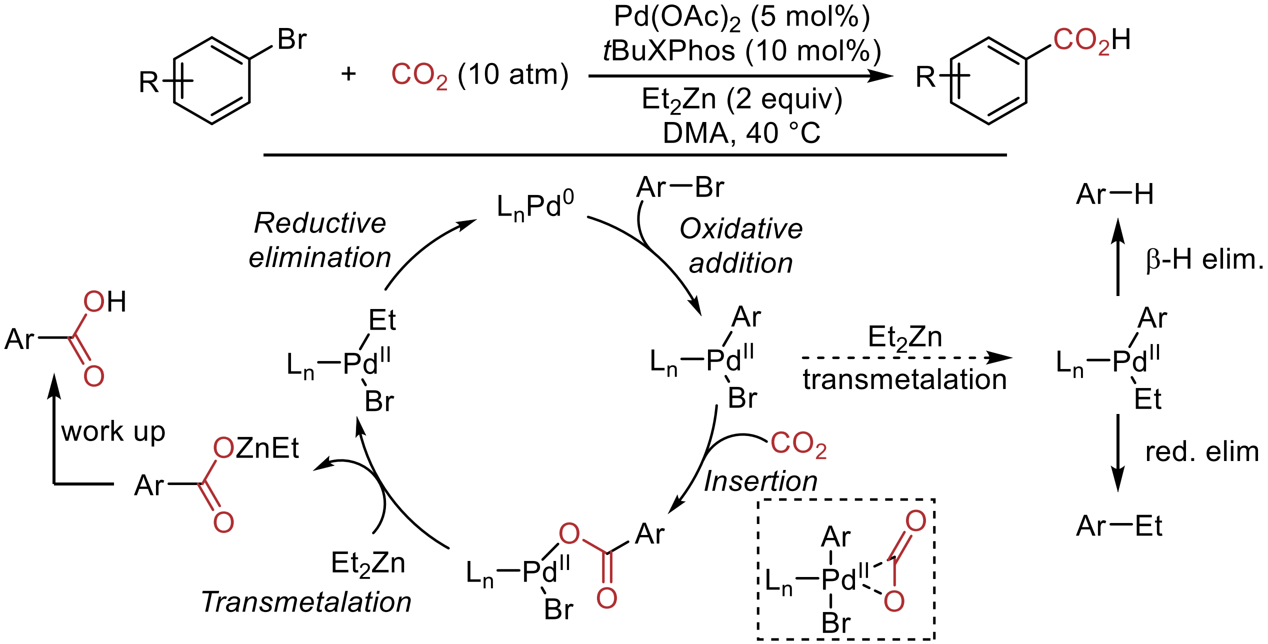
- First TM-catalysed coupling reaction with CO_2 (Iwasawa, 2006)[2] later developed to Cu catalysis (2008)[3]



1) T. Yamamoto, Organonmetallics, 1994, 4645; 2) N. Iwasawa, JACS, 2006, 8706; 3) N. Iwasawa, Org. Lett., 2008 2697

Cross electrophile reactions

- Ruben Martin (2009)[1]



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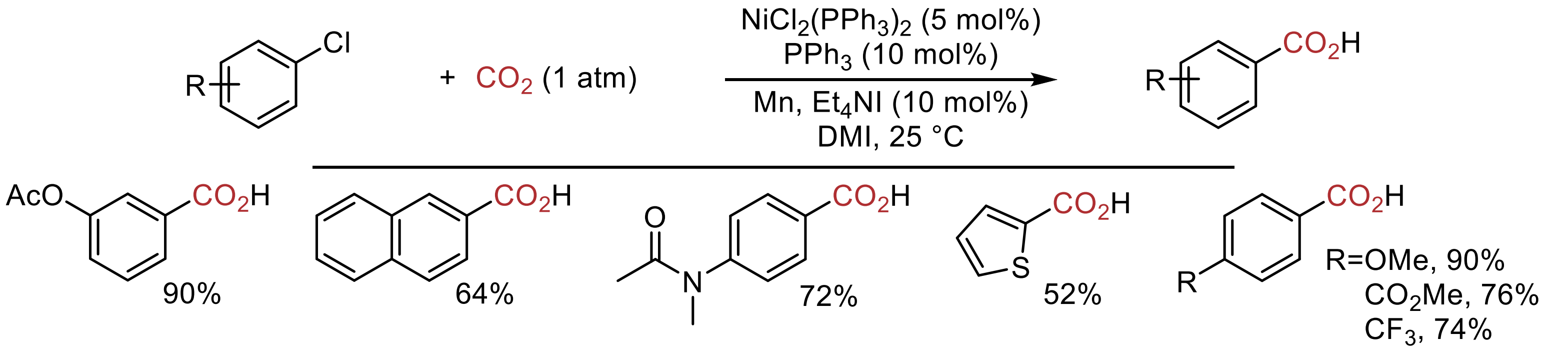
1) A. Correa and R. Martin, J. Am. Chem. Soc. 2009, 131, 15974-15975

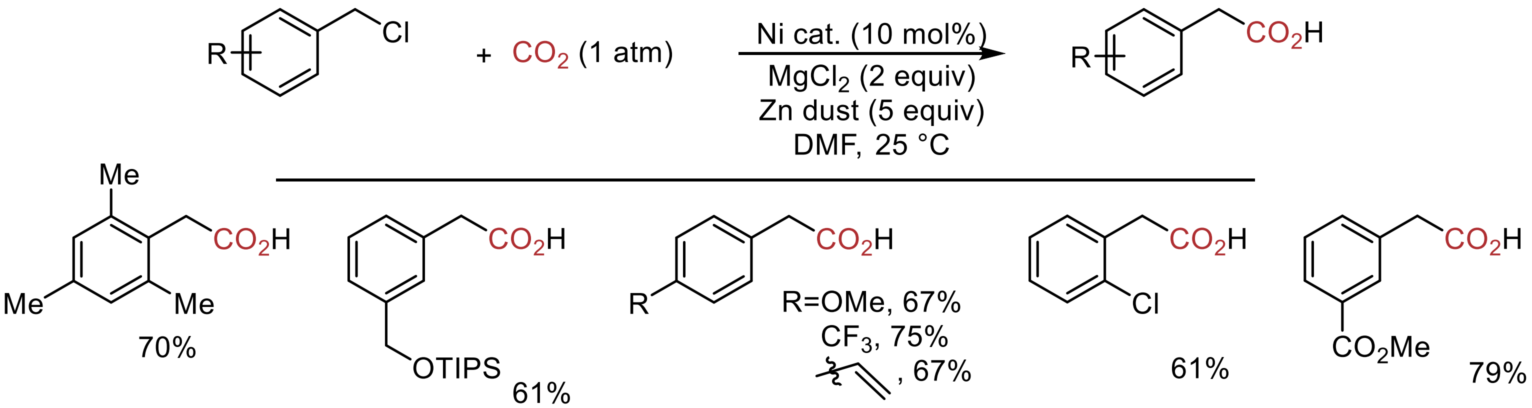
Cross electrophile reactions

- Aryl Chlorides (Yasushi Tsuji, 2012)[1]



examples of OTf, OTs and vinyl chlorides also demonstrated

- Benzyl chlorides (Ruben Martin, 2013)[2]



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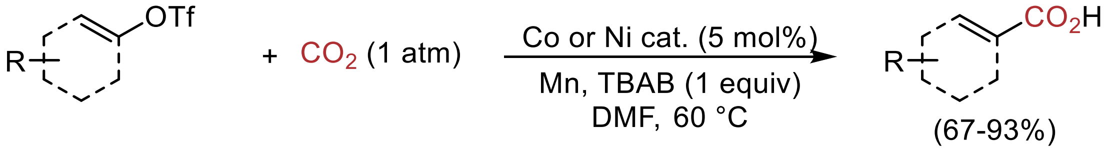
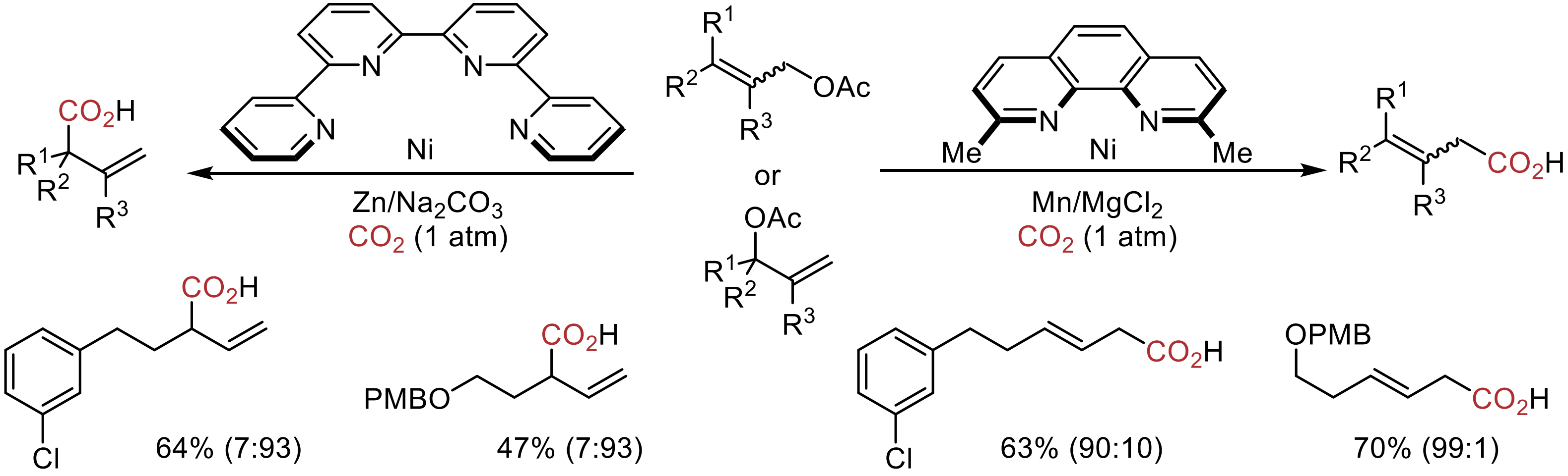
1) T.Fujihara, Y. Tsuji *et al*, JACS, 2016, 9106; 2) T. León, R. Martin *et al*. JACS. 2013, 135, 1221.

Cross electrophile reactions

- Aryl and vinyl triflates - Yasushi Tsuji (2015)[1]



- Allylic acetates - Ruben Martin (2014)[2]



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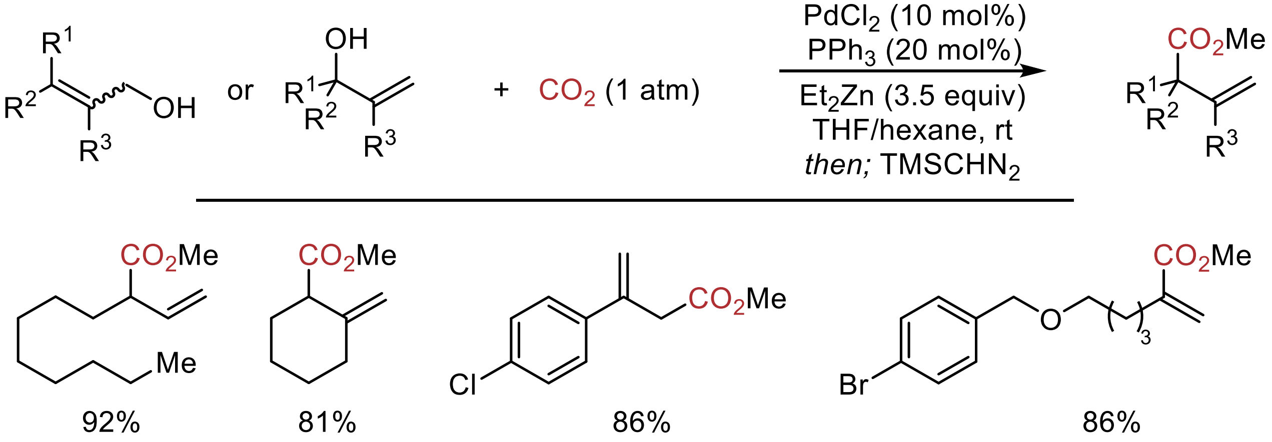
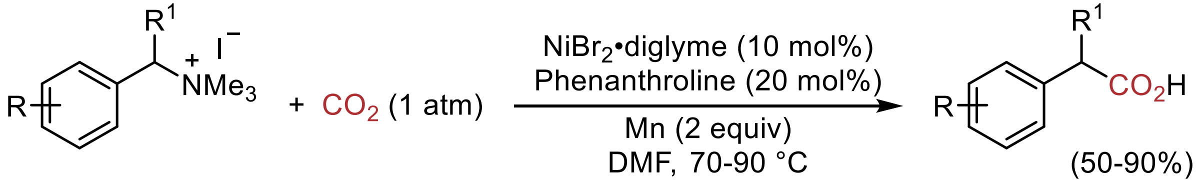
1) K. Nogi, Y. Tsuji *et al.*, JOC. 2015, 80, 11618; 2) T. Moragas, J. Cornella, R. Martin, JACS, 2014, 136, 17702.

Cross electrophile reactions

- Allylic alcohols - Yoshihiro Sato (2015)[1]



- Quaternary ammonium iodides - Ruben Martin (2016)[2]



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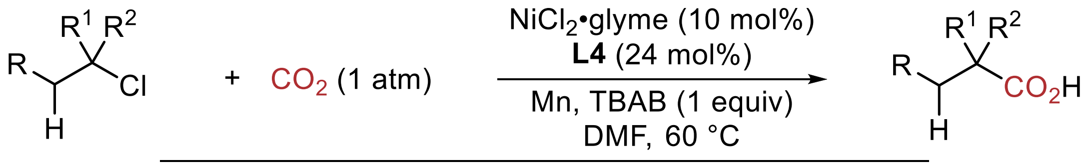
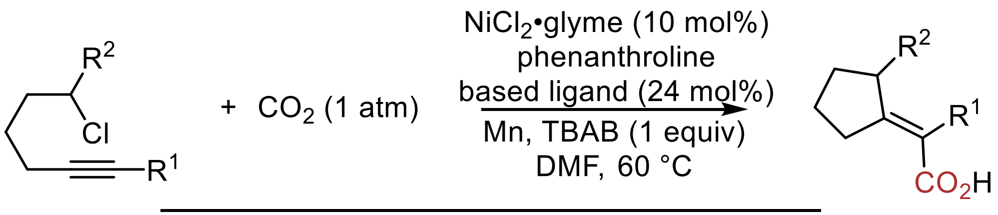
1) T. Mita, Y. Higuchi, and Y. Sato Chem. Eur.J.2015, 21,16391 ; 2) T. Moragas, M. Gaydou, and R. Martin, ACIE, 2016, 55, 5053.

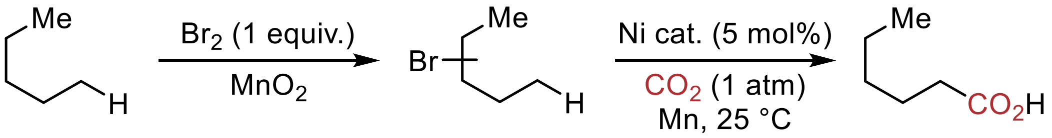
Cross electrophile reactions

- Ruben Martin (2016)



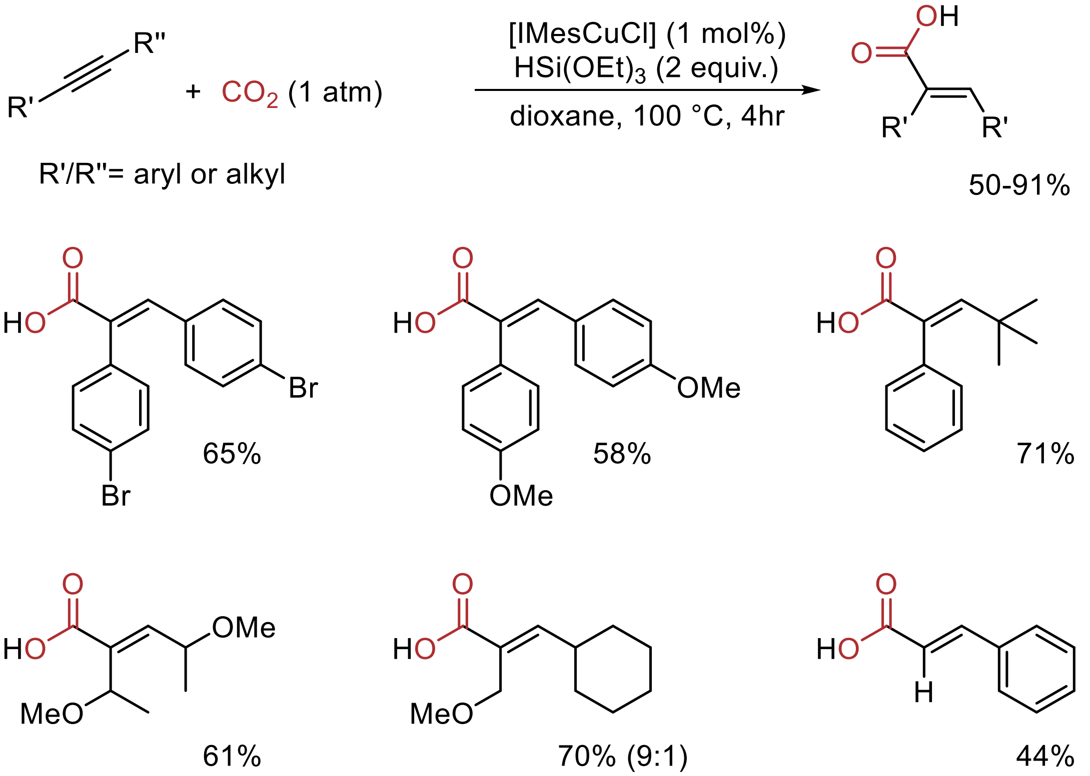


- Ruben Martin (2017)



1) M. Börjesson, T. Moragas, and R. Martin, JACS, 2016, 138, 7504; 2) F. Juliá-Hernández1, R. Martin *et al.*, Nature, 2017, 84

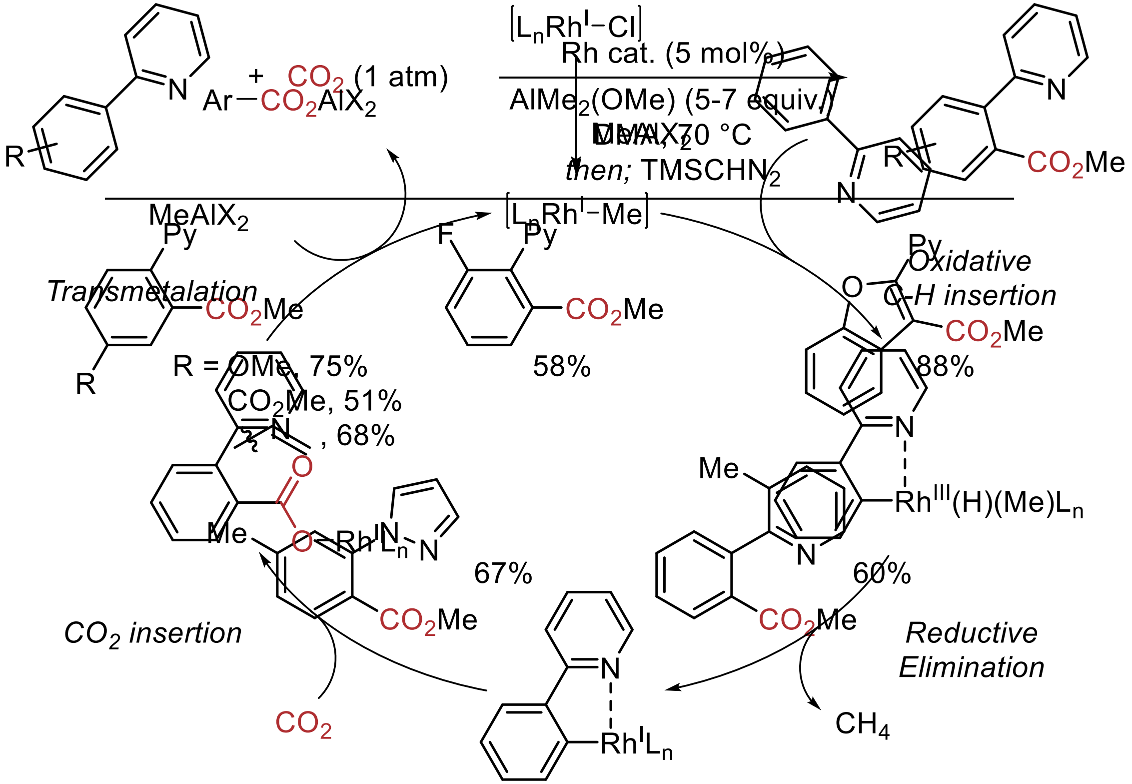
Reductive carboxylation of alkynes



1) T. Fujihara, Yasushi Tsuji *et al.* Chem. Int. Ed. 2011, 50, 523 –527; 2) xxx.

Directed C—H carboxylation

- Nobuharu Iwasawa (2011)[1]



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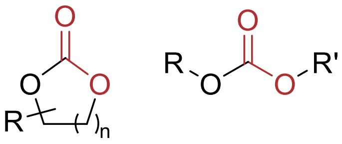
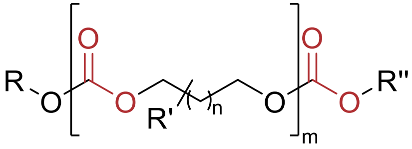
1) H. Mizuno, J. Takaya, and N. Iwasawa, JACS, 2011, 1251

(Poly)carbonates



- Open and Cyclic carbonates
  - Use as ‘green’ solvent
  - Plasticisers
  - DMC (dimethyl carbonate) used as mild methylating reagent.
  - Electrolytes for Li-ion batteries
  - Additives for cleaning/degreasing agents.
  - Fuel additive
  - Building blocks for fine chemical synthesis (flavours and fragrance)
  - Polymer synthesis
- Polycarbonate
  - High optics grade plastic
  - Impact resistant “glass”

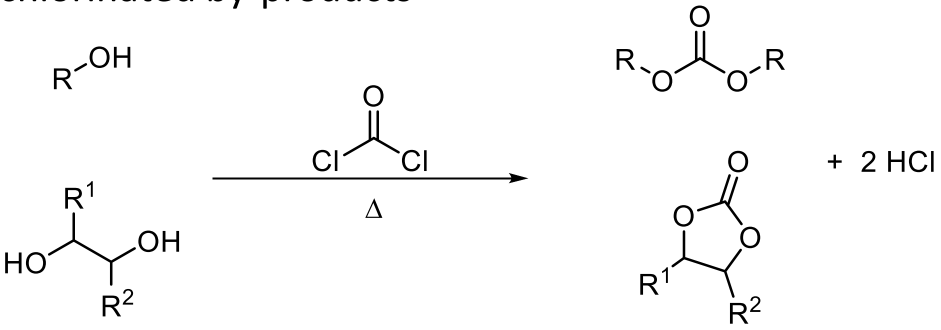


---

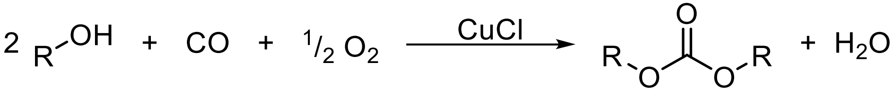
1) Buysch, H.-J. *Carbonic Esters: Ullmann’s Encyclopedia of Industrial Chemistry*; Wiley-VCH , 2000; pp 54–71.

Industrial synthesis

- Phosgenation. (major process)
  - Hazardous reagent
  - HCl and other chlorinated by-products



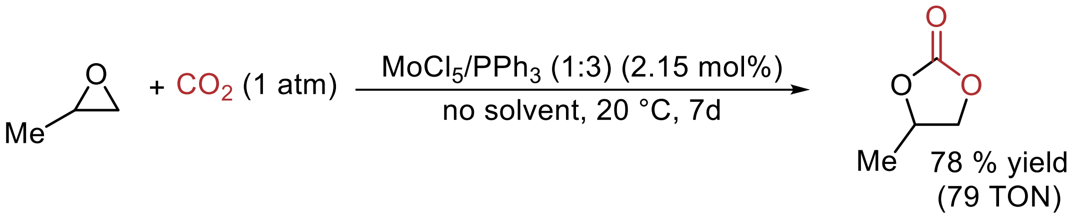
- Oxidative carbonylation. (minor process)
  - Hazardous reagent
  - H_2O detrimental to reaction
  - CO_2, HCl and other chlorinated by-products



1) Buysch, H.-J. *Carbonic Esters: Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH , 2000; pp 54–71.

First use of TM catalysis

- Epoxide ring opening with CO_2 (Kisch 1980)



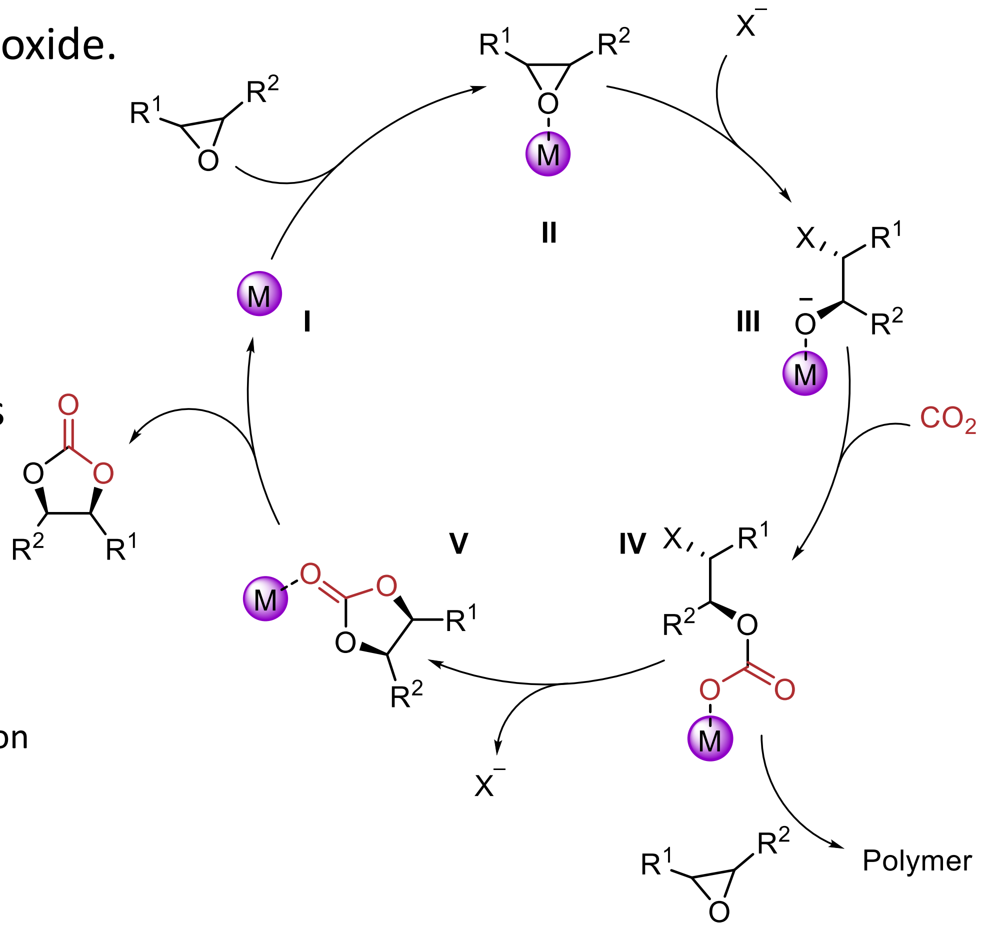
- Prior to this, reactions required high pressures and temperatures.
  - Suffers from low turn over numbers and long reaction times

---

1) M. Ratzenhofer, H. Kisch. ACIE, 1980, 317

General mechanism- Epoxides

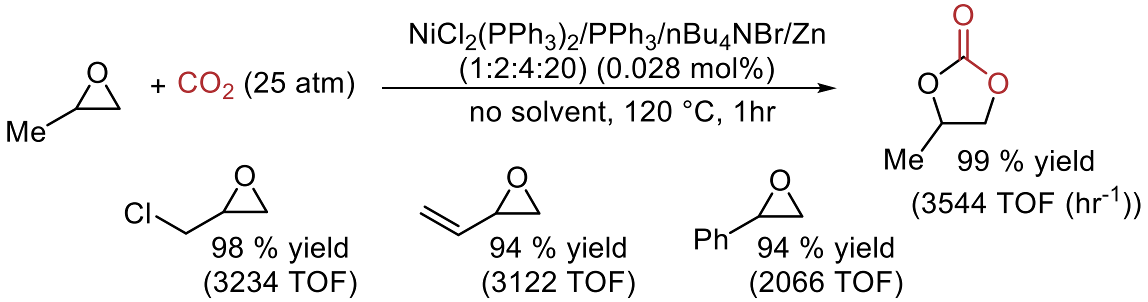
- Lewis acid complex coordinates epoxide.
- Anion, acting as nucleophile,
  opens epoxide.
- CO_2 insertion into M-O bond
- Cyclisation to form carboxylate
- Addition of epoxide to **IV** produces polymer



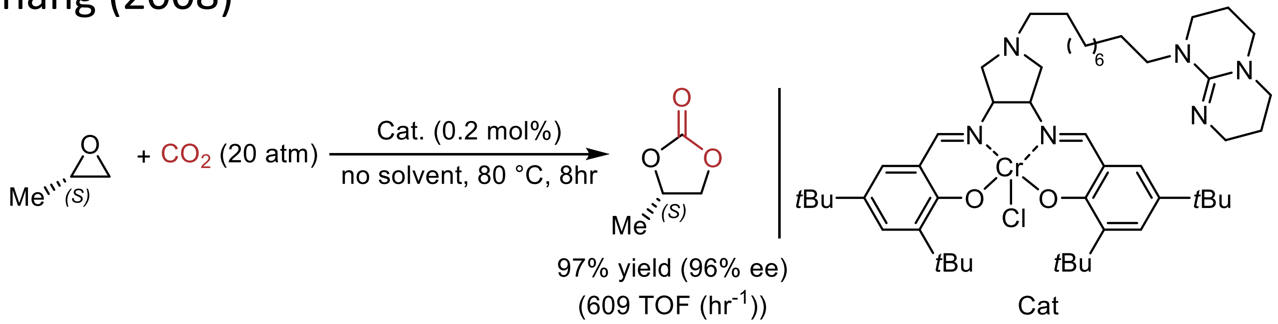
  - Cyclic carbonate vs. polymer production determined be catalyst tuning.

Linear and cyclic carbonates

- Contemporary examples.
  - Chungu Xia (2003)



  - Zhang (2008)



1) Chungu Xia, Chem. Commun., 2003, 2042–2043; 2) X. Zhang, Tet. Lett., 2008, 6589.

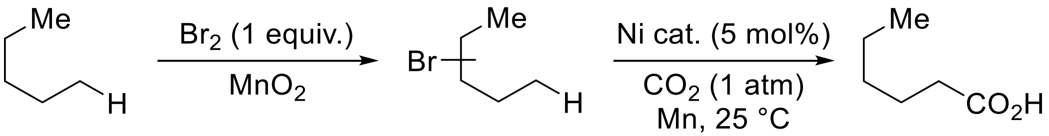
Conclusion

- Summery
  - CO_2 has genuine applications as reagent in TM catalysed reaction.
  - Greener and sometimes safer alternative.
  - Can be used under mild conditions.
  - Often can achieve good selectivity.

- Perspective
  - More effort needs to be made to incorporate CO_2 into small and large scale processes
  - Plastics and chemicals as a means of CO_2 storage

- Questions:

1) What characteristic of the catalyst aids for this reaction.



2) Carbonates can be formed be direct carboxylation of alcohol or diols however this process has major issues. Identify one.

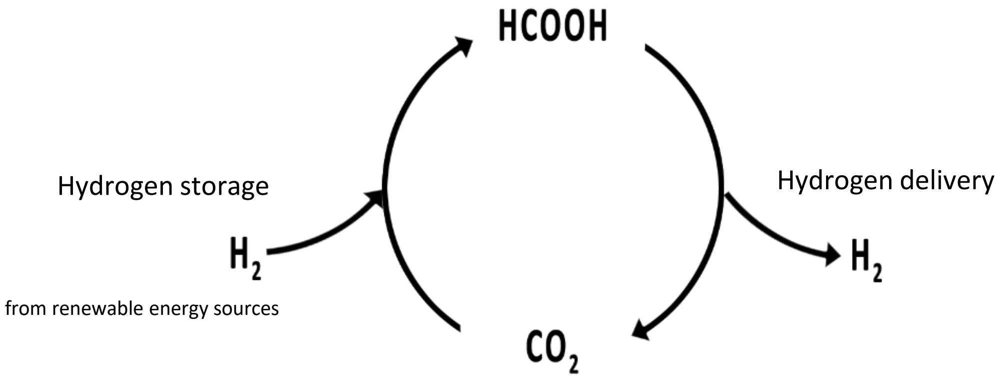
Group of Catalysis for Energy and Environment - Laboratory of Organometallic and Medicinal Chemistry

Catalytic Reduction of Carbon Dioxide with Molecular Dihydrogen by Transitions Metal Complexes to Formic Acid

Cornel FINK

2nd June 2017, EPFL, Lausanne

Formic Acid in Hydrogen Storage



HCOOH

Hydrogen storage

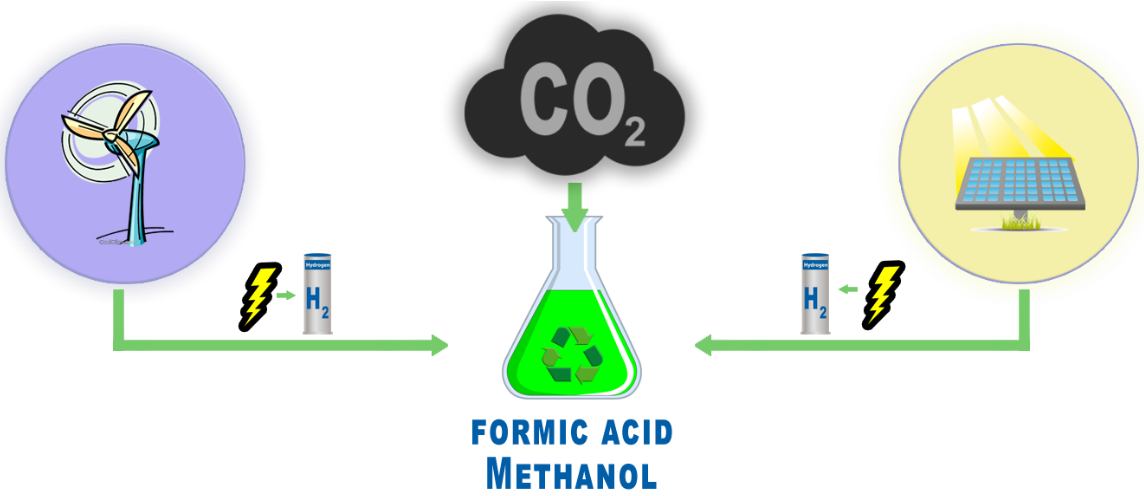
H_2

from renewable energy sources

Hydrogen delivery

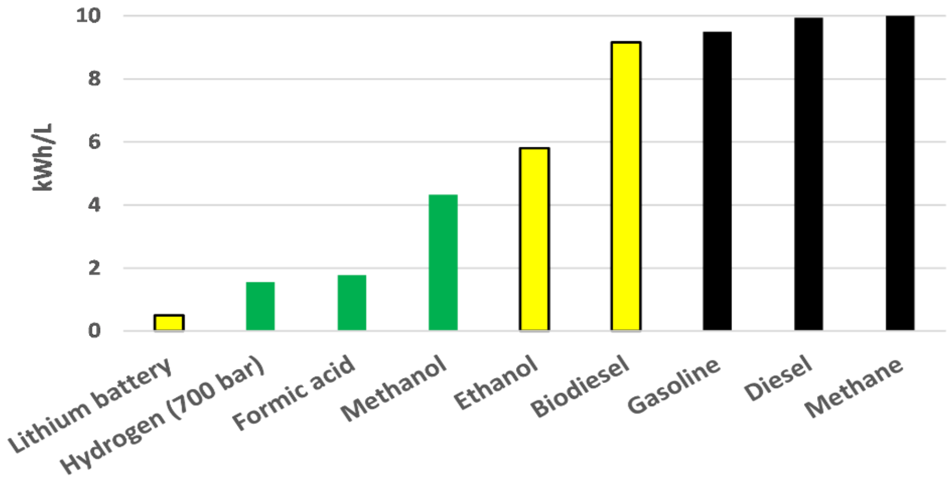
H_2

CO_2



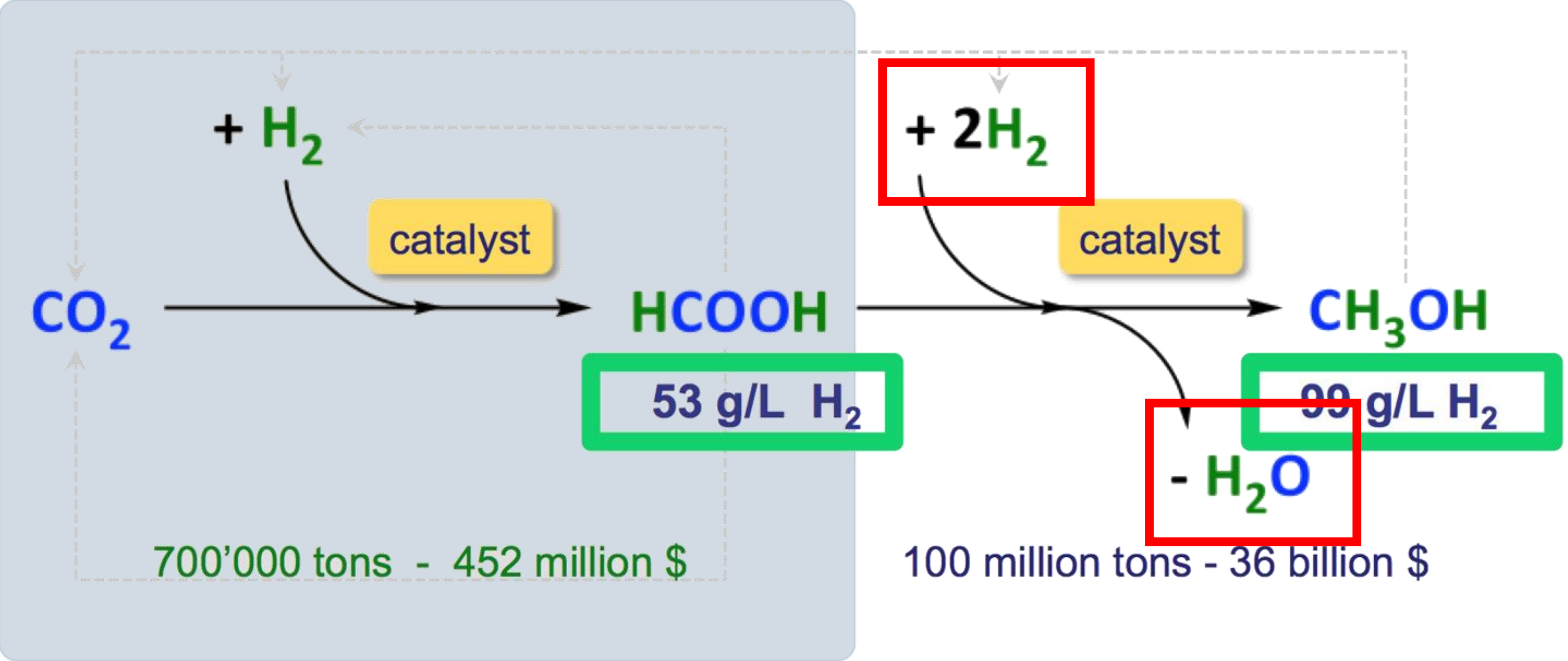
H. Takeda, C. Cometto, O. Ishitani, M. Robert, ACS Catalysis **2017**, 7, 70-88.

Formic Acid in Hydrogen Storage



W.-H. Wang, Y. Himeda, J.T. Muckerman, G.F. Manbeck, Chem Rev **2015**, 115, 12936-12973.

CO_2 – Formic Acid - Methanol



CO_2

+ H_2

catalyst

HCOOH

53 g/L H_2

700’000 tons - 452 million $

+ $2H_2$

catalyst

CH_3OH

99 g/L H_2

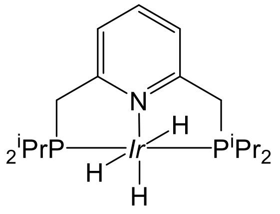
- H_2O

100 million tons - 36 billion $

	Energy content [MJ/kg]	Storage efficiency [%]
$H_2 + CO_2 \rightleftharpoons HCO_2H$	5.22	100
$3H_2 + CO_2 \rightleftharpoons CH_3OH + H_2O$	15.2	66.6
$4H_2 + CO_2 \rightleftharpoons CH_4 + 2H_2O$	30.15	50

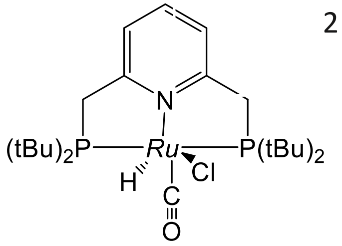
K. Sordakis, A. Tsurusaki, G. Laurenczy, ACS Catalysis, **2017**, 7, 1123-1131.

Hydrogenation of Carbon Dioxide to Formates



[1]

120°C / 60 bar
1 M KOH aq. / THF
TON$_{48\ h}$ 3 500 000



[2]

120°C / 40 bar
DMF / DBU
TOF$_{1\ h}$ 1 100 000

$$HCO_3^- \xrightarrow{\text{basic conditions}} HCOO^-$$

HCOOK
HCOOH * amine

---

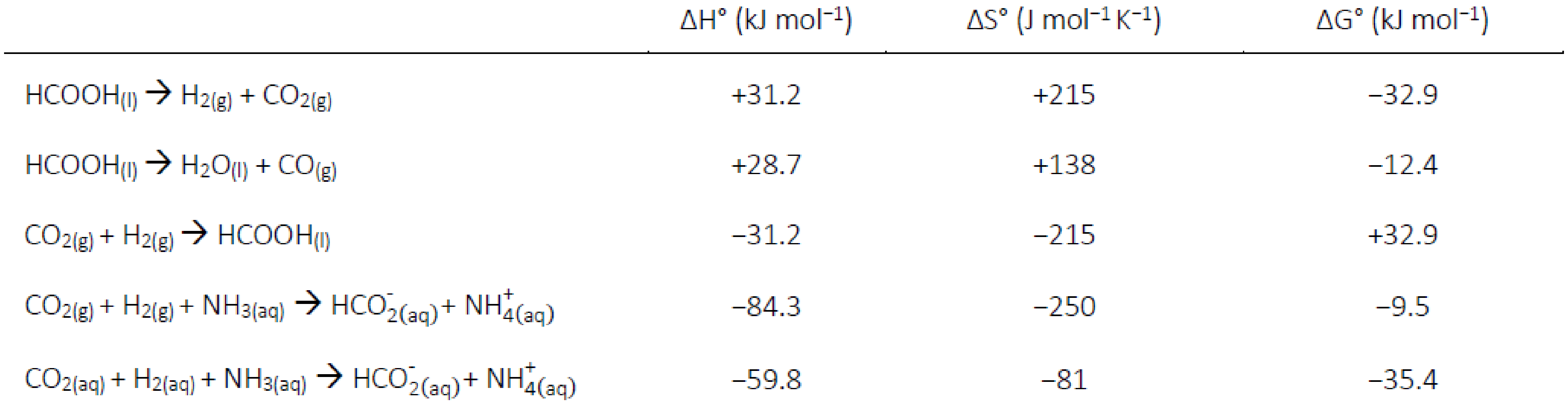
[1] R. Tanaka; M. Yamashita; K. Nozaki; J. Am. Chem. Soc. **2009**, 131, 14168-14169.

[2] G.A. Filonenko, E.J.M. Hensen, ChemCatChem **2014**, 6, 1526-1530.

A.G. Boddien, Laurenczy, Gábor; Beller, Matthias, CHIMIA International Journal for Chemistry **2011**, 65, 214-218(5).

T. Schaub, R.A. Paciello, Angew Chem Int Ed **2011**, 50, 7278-7282.

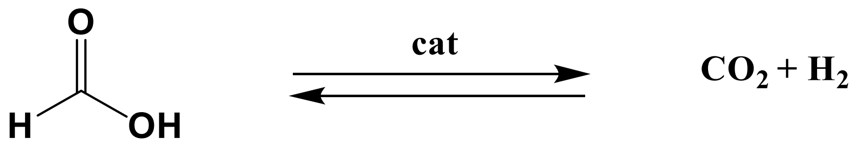
Thermodynamic data



	ΔH° (kJ mol^{-1})	ΔS° (J mol^{-1} K^{-1})	ΔG° (kJ mol^{-1})
$HCOOH_{(l)} \rightarrow H_{2(g)} + CO_{2(g)}$	+31.2	+215	−32.9
$HCOOH_{(l)} \rightarrow H_2O_{(l)} + CO_{(g)}$	+28.7	+138	−12.4
$CO_{2(g)} + H_{2(g)} \rightarrow HCOOH_{(l)}$	−31.2	−215	+32.9
$CO_{2(g)} + H_{2(g)} + NH_{3(aq)} \rightarrow HCO^-_{2(aq)} + NH^+_{4(aq)}$	−84.3	−250	−9.5
$CO_{2(aq)} + H_{2(aq)} + NH_{3(aq)} \rightarrow HCO^-_{2(aq)} + NH^+_{4(aq)}$	−59.8	−81	−35.4

Jessop, P. G.; Ikariya, T.; Noyori R.; Chem. Rev. **1995**, 95 (2), 259–272.
Loges, B.; Boddien, A.; Gärtner, F.; Junge, H.; Beller, M.; Top. Catal. **2010**, 53 (13–14), 902–914.
Aresta, M.; Dibenedetto, A.; Quaranta, E. Reaction Mechanisms in Carbon Dioxide Conversion, 1st ed.; Springer: Heidelberg, **2016**.

Requirements for Ligands



Formic acid dehydrogenation

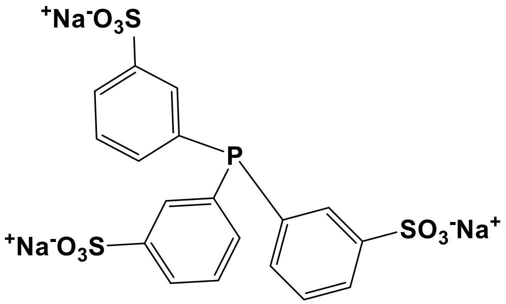
- Low pH values
- Reducing environment => FA
- Elevated temperatures

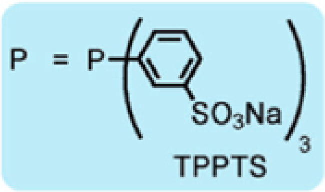
CO_2 hydrogenation

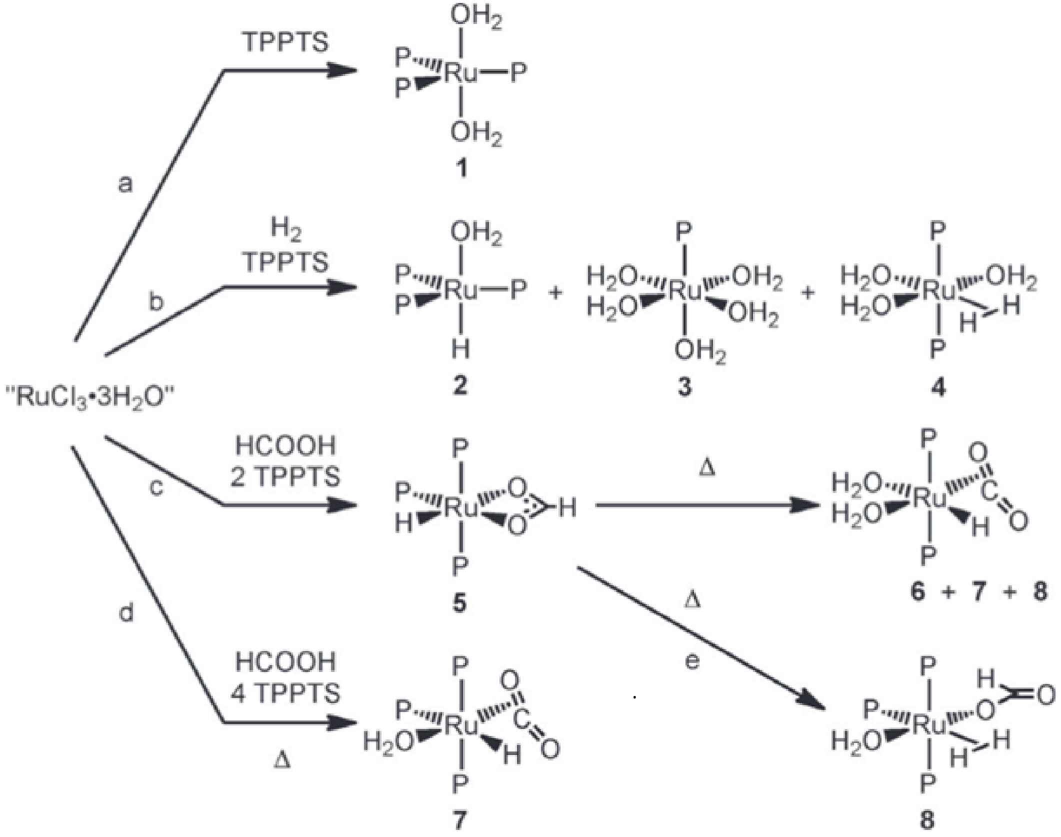
- pH can be basic for acidic
- Reducing environment => H_2 pressure
- Elevated temperatures

- Protect the metal against reduction
- Water soluble
- long-term stability

$[Ru^{II}(TPPTS)_3(H_2O)_2]$

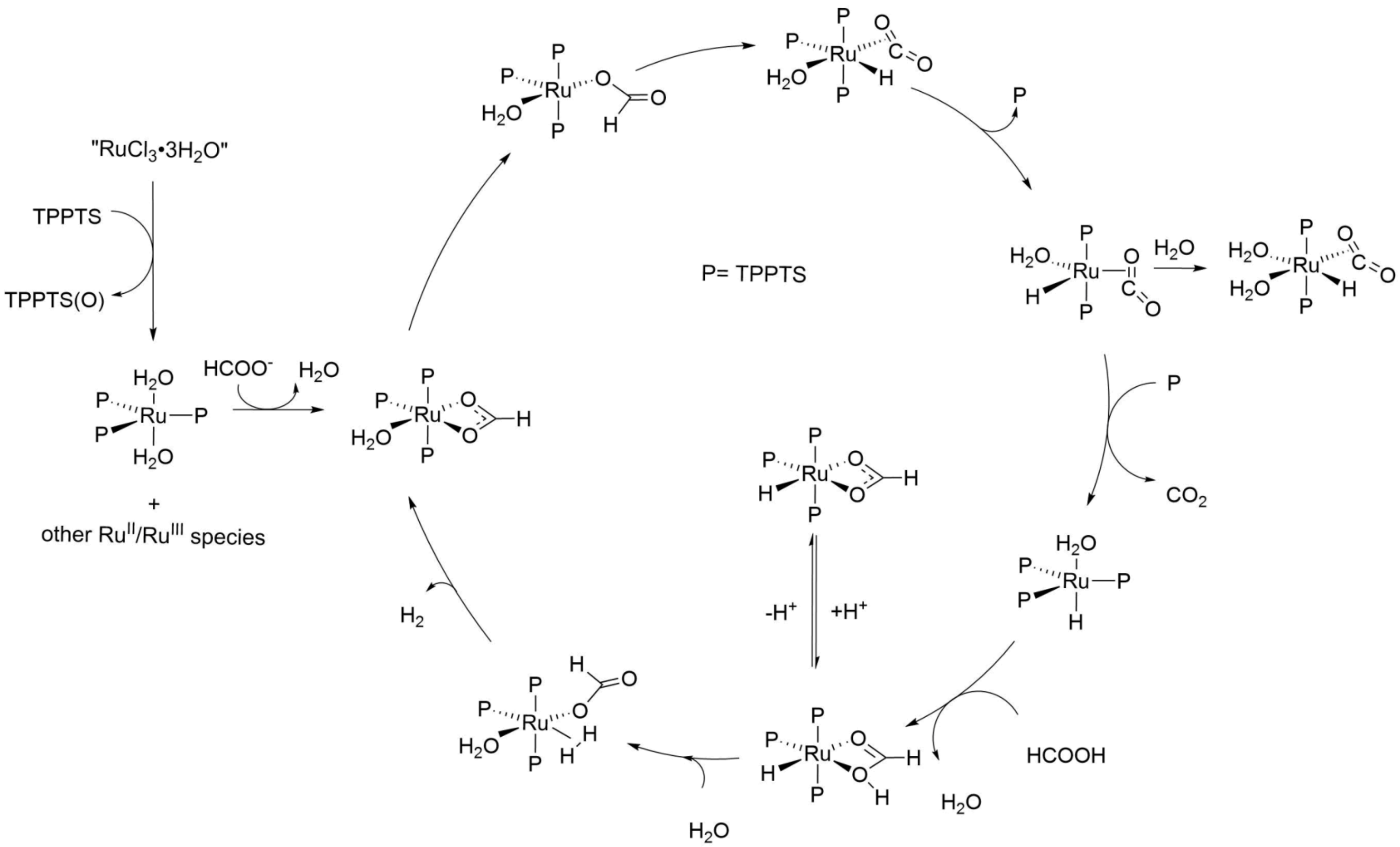






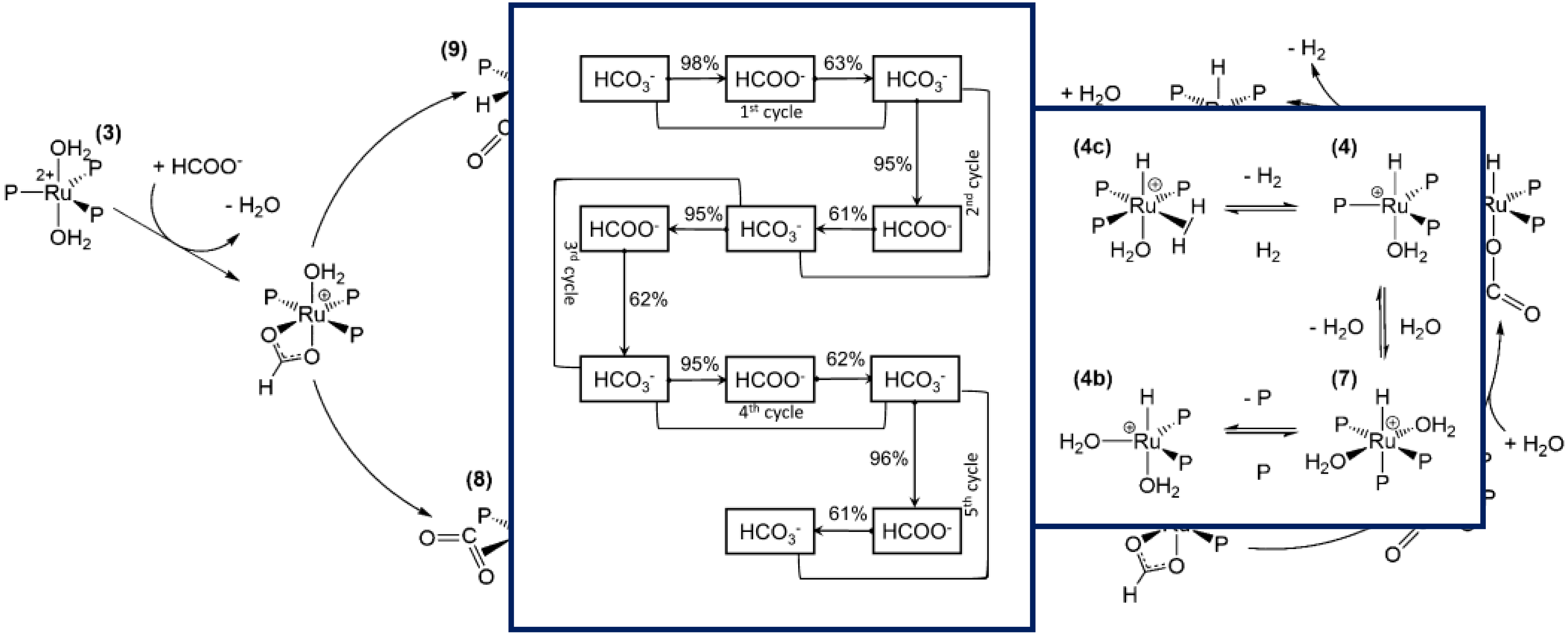
P.J.R.J. Sven Hida , Jim D. Atwood, J Coord Chem **1998**, 43, 345-348.
C. Fellay, P.J. Dyson, G. Laurenczy, Angew Chem Int Ed **2008**, 47, 3966-3968.
C. Fellay, N. Yan, P.J. Dyson, G. Laurenczy, Chemistry – A European Journal **2009**, 15, 3752-3760.
A. Thevenon, G. Weijia, A.F. Dalebrook, ChemCatChem **2014**, 6, 3146-3152.

$[Ru^{II}(TPPTS)_3(H_2O)_2]$ – Fast Cycle



A. Thevenon, G. Weijia, A.F. Dalebrook, ChemCatChem **2014**, 6, 3146-3152.

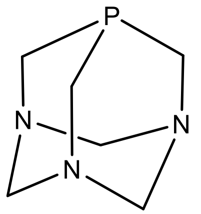
$[Ru^{II}(TPPTS)_3(H_2O)_2]$ – Fast+Slow Cycle



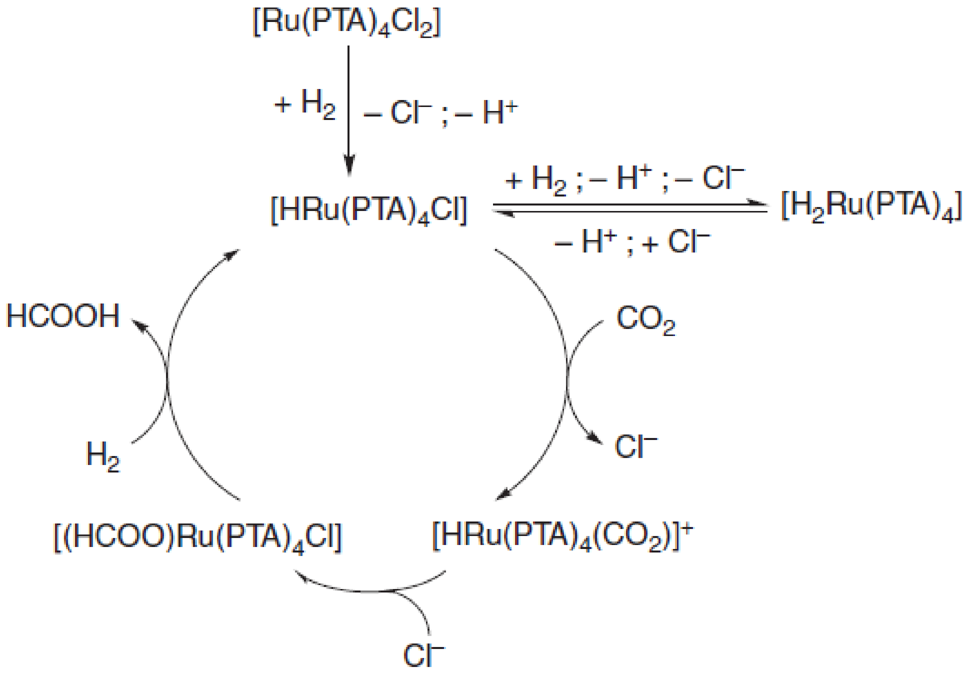
K. Sordakis, A. Tsurusaki, M. Iguchi, G. Laurenczy, Green Chemistry **2017**.

CO_2 Hydrogenation in DMSO: $[Ru(PTA)_4Cl_2]$

$$RuCl_3 \cdot 3H_2O + PTA \xrightarrow[\text{EtOH}]{\text{145°C, 3 min, µwave}} [Ru(PTA)_4Cl_2]$$

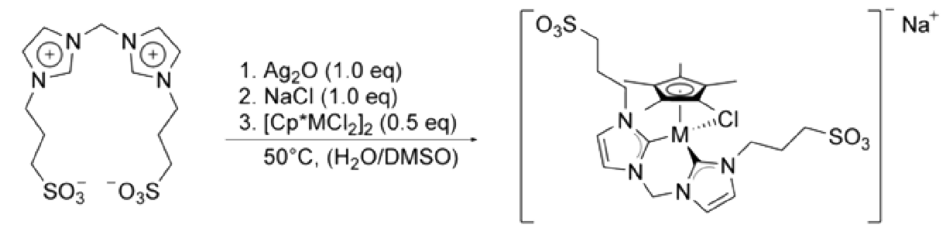


1,3,5-triaza-7-phosphaadamantane

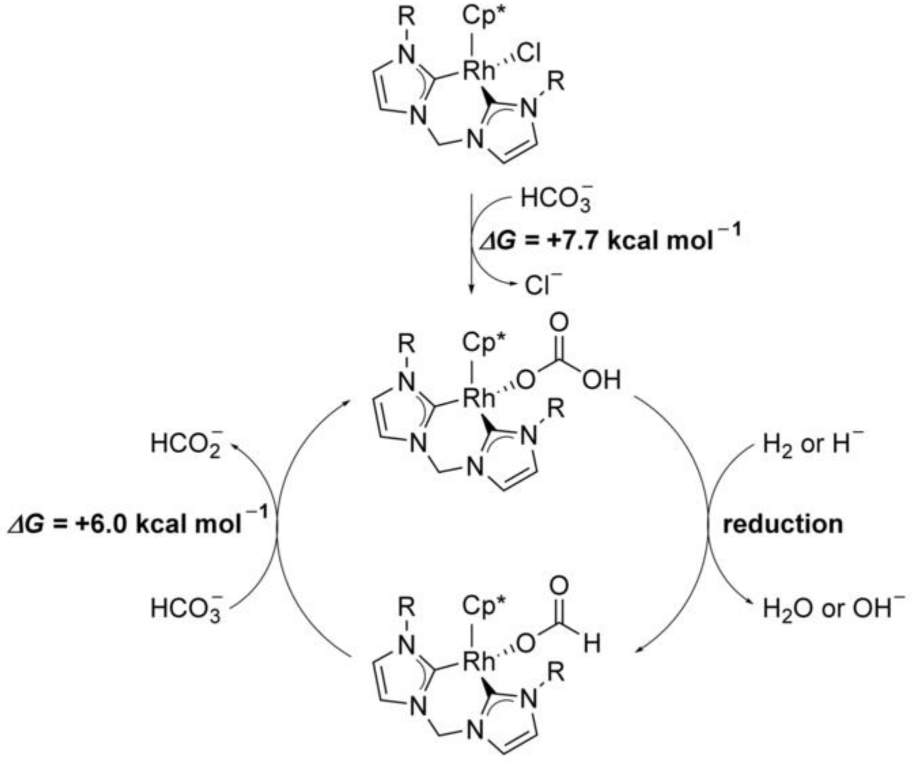


S. Moret, P.J. Dyson, G. Laurenczy, Nature Communications 2014, 5.

N-Heterocyclic Carbene Complex



1 (M = Rh, 93%)
2 (M = Ir, 90%)



D. Jantke, L. Pardatscher, M. Drees, M. Cokoja, ChemSusChem 2016, 9, 2849-2854.

N-Heterocyclic Carbene Complex

1 (M = Rh, 93%)
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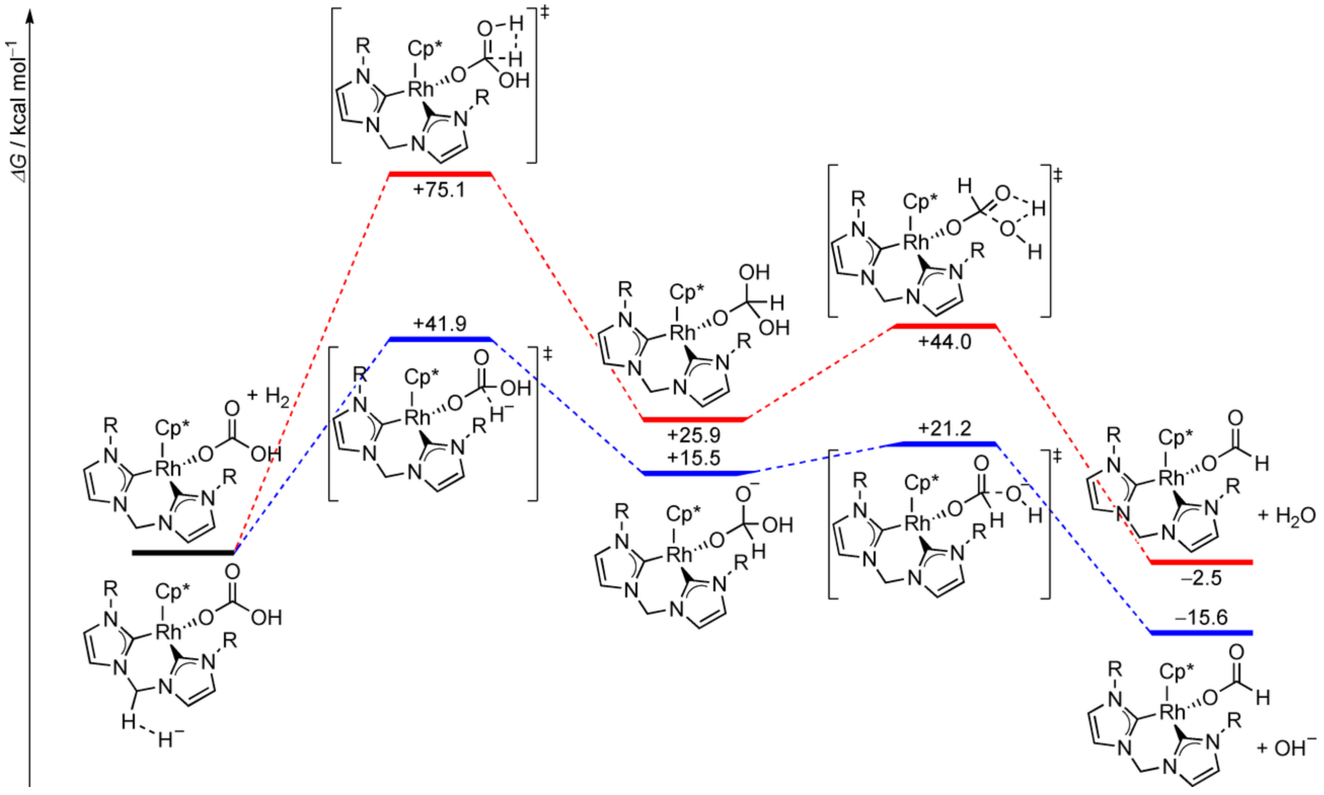
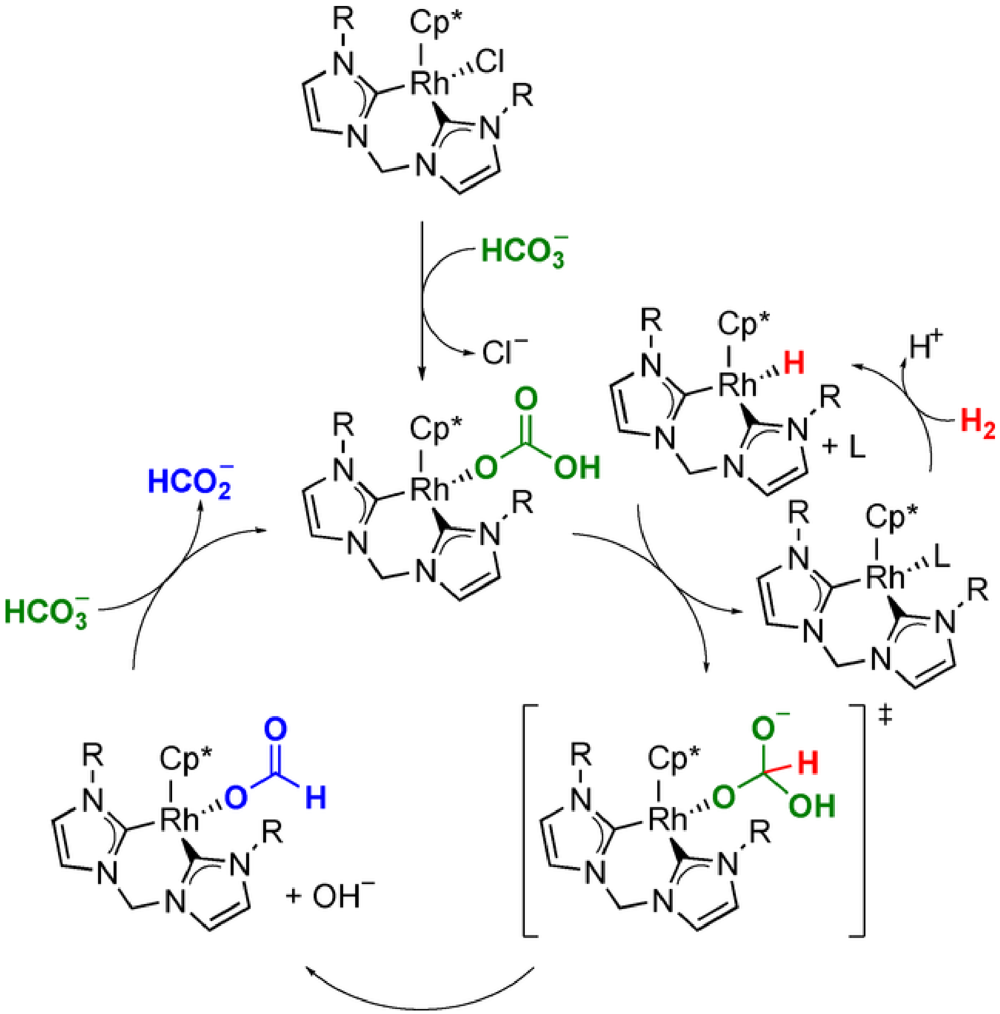


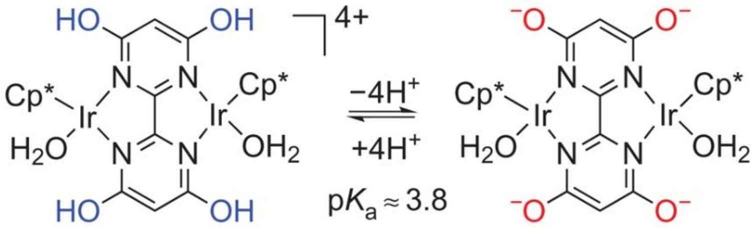
D. Jantke, L. Pardatscher, M. Drees, M. Cokoja, ChemSusChem **2016**, 9, 2849-2854.

N-Heterocyclic Carbene Complex



D. Jantke, L. Pardatscher, M. Drees, M. Cokoja, ChemSusChem **2016**, 9, 2849-2854.

Cp*Ir compounds with bidentate N,N' ligands



Protonated

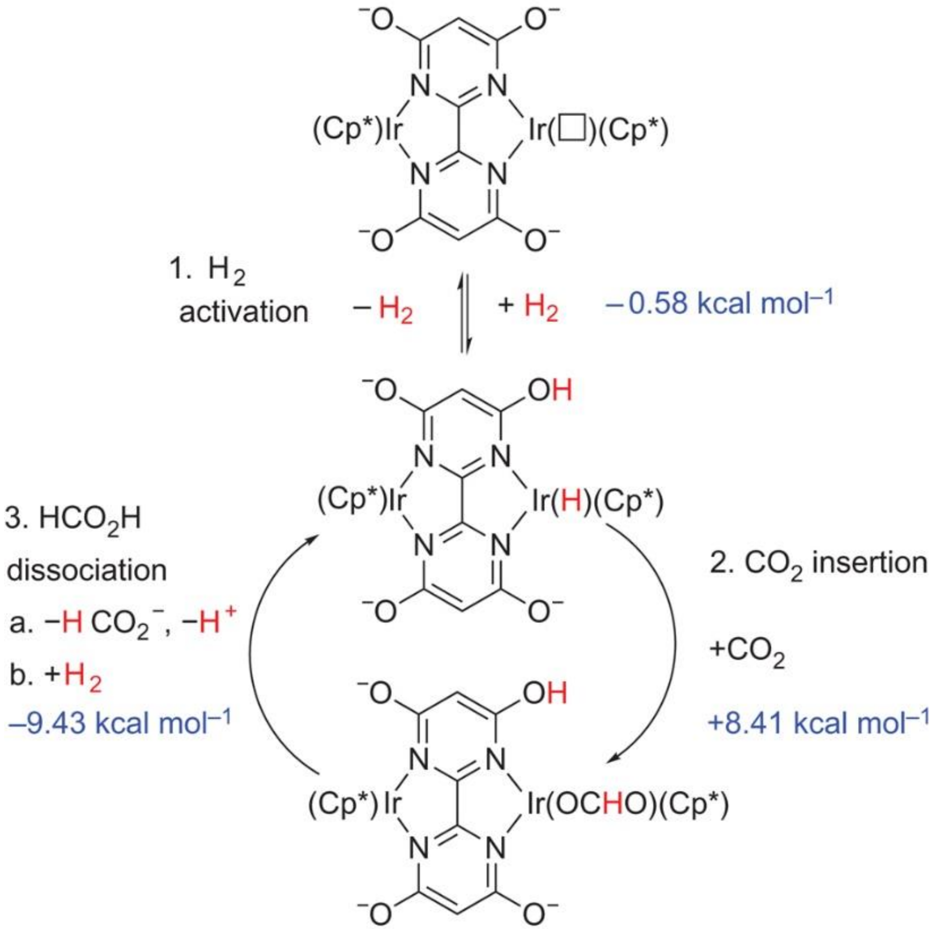
$\sigma_{p\,OH}^{+} = -0.91$

$[2(OH_2)_2]^{4+}$

Deprotonated

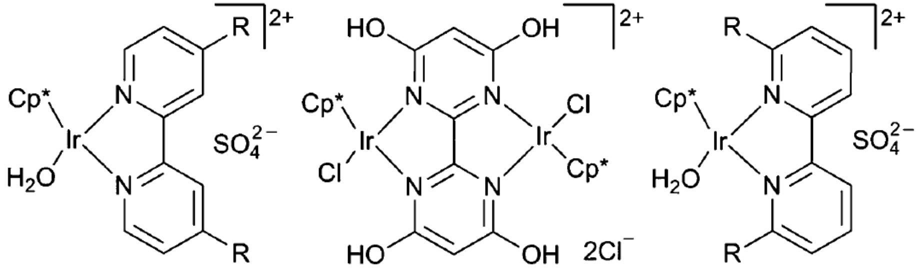
$\sigma_{p\,O^-}^{+} = -2.30$

$[2'(OH_2)_2]$



J.F. Hull, Y. Himeda, W.-H. Wang, B. Hashiguchi, Nature Chemistry **2012**, 4, 383-388.

Second-coordination-sphere Involvement



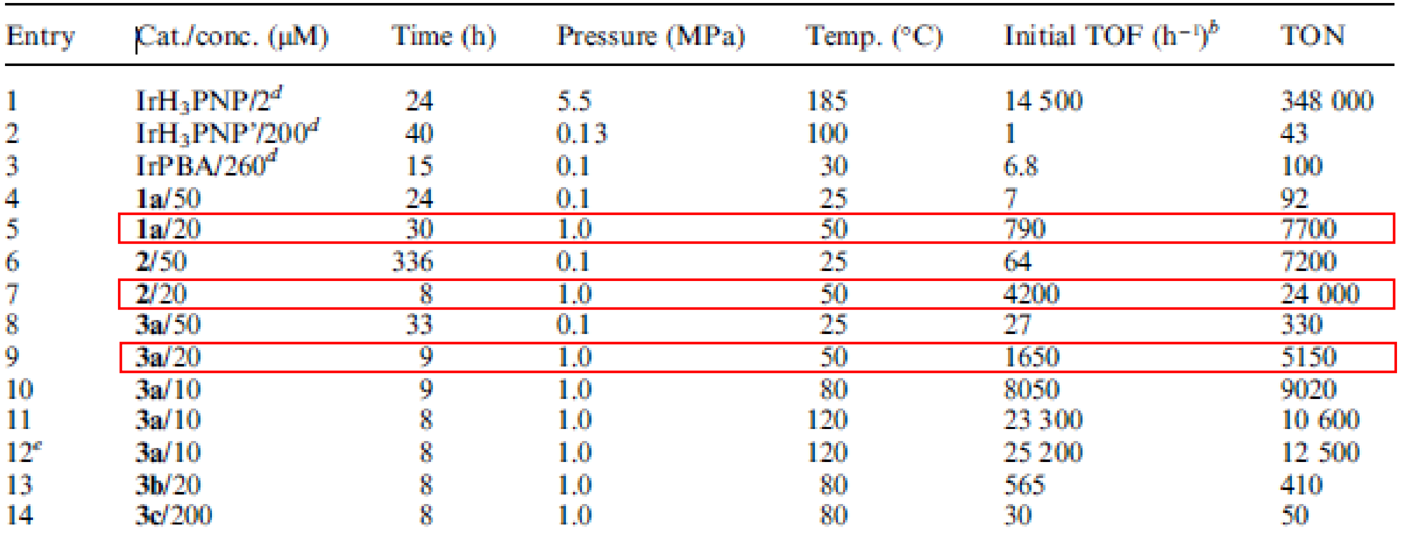
1a: R = OH
1b: R = OMe
1c: R = Me
1d: R = H

2

3a: R = OH
3b: R = OMe
3c: R = Me

Fig. 1 Catalysts **1**, **2**, and **3** for CO_2 hydrogenation.

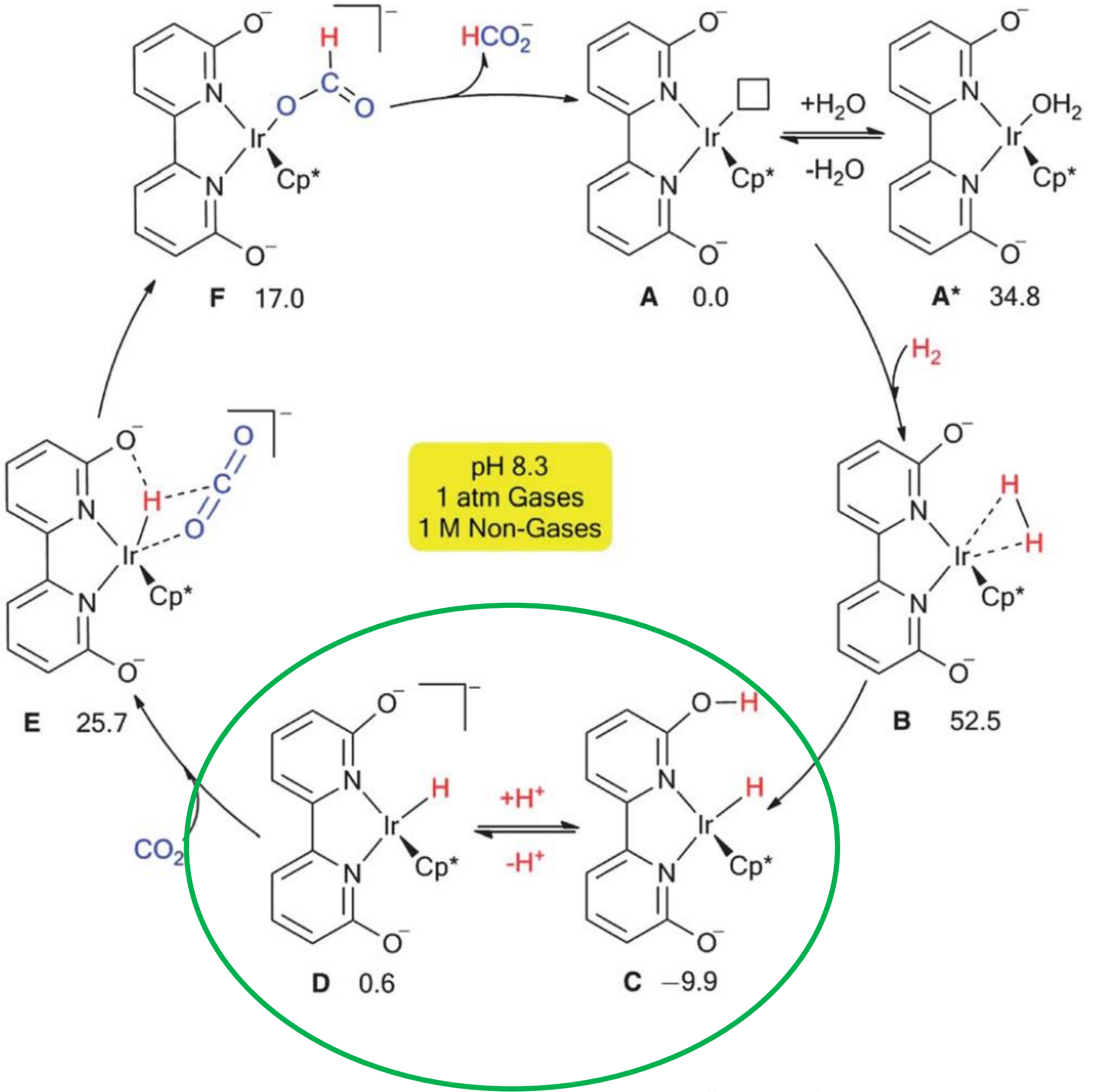
Mercury poising test to see if truly homogeneous system!



Entry	Cat./conc. (μM)	Time (h)	Pressure (MPa)	Temp. (°C)	Initial TOF (h^{-1})[b]	TON
1	IrH_3PNP/2[d]	24	5.5	185	14 500	348 000
2	IrH_3PNP'/200[d]	40	0.13	100	1	43
3	IrPBA/260[d]	15	0.1	30	6.8	100
4	**1a**/50	24	0.1	25	7	92
5	**1a**/20	30	1.0	50	790	7700
6	**2**/50	336	0.1	25	64	7200
7	**2**/20	8	1.0	50	4200	24 000
8	**3a**/50	33	0.1	25	27	330
9	**3a**/20	9	1.0	50	1650	5150
10	**3a**/10	9	1.0	80	8050	9020
11	**3a**/10	8	1.0	120	23 300	10 600
12[e]	**3a**/10	8	1.0	120	25 200	12 500
13	**3b**/20	8	1.0	80	565	410
14	**3c**/200	8	1.0	80	30	50

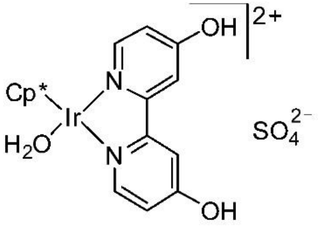
W.-H. Wang, J.F. Hull, J.T. Muckerman, E. Fujita, Energy & Environmental Science **2012**, 5, 7923-7926.

Proton relay mechanism

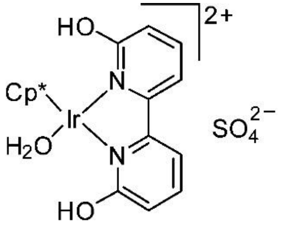


W.-H. Wang, J.F. Hull, J.T. Muckerman, E. Fujita, Energy & Environmental Science **2012**, 5, 7923-7926.

Water-bridged Proton Transfer: KIE



1



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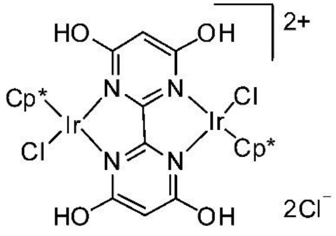

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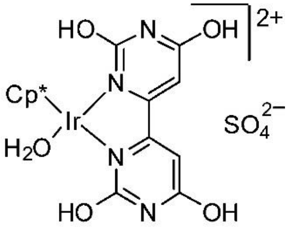

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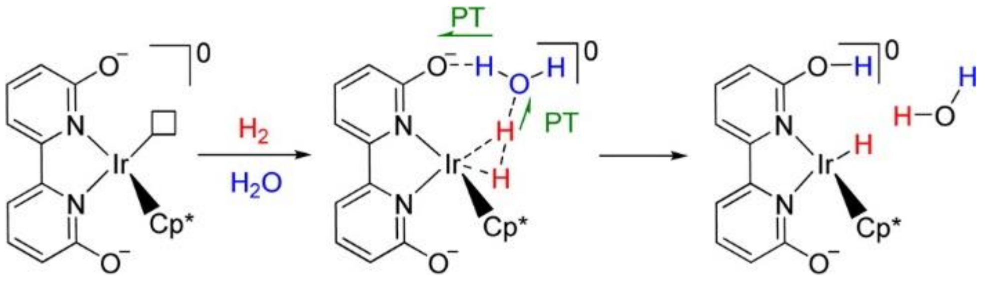
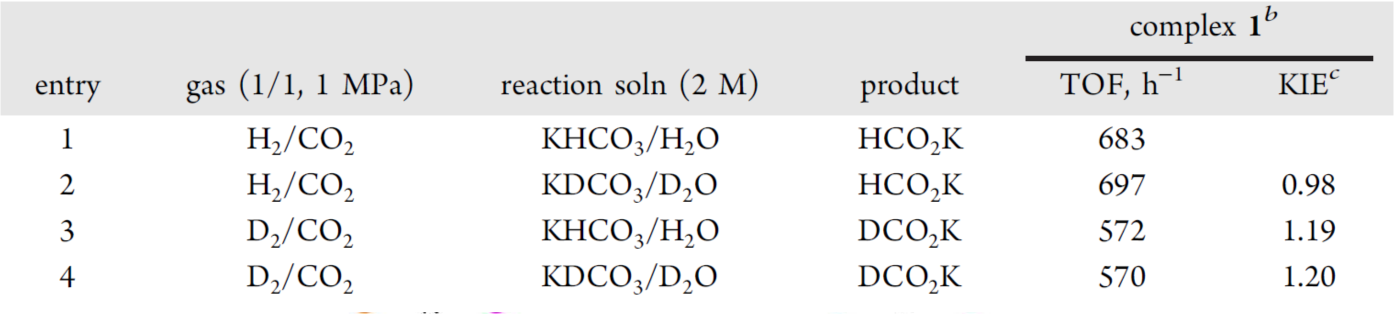
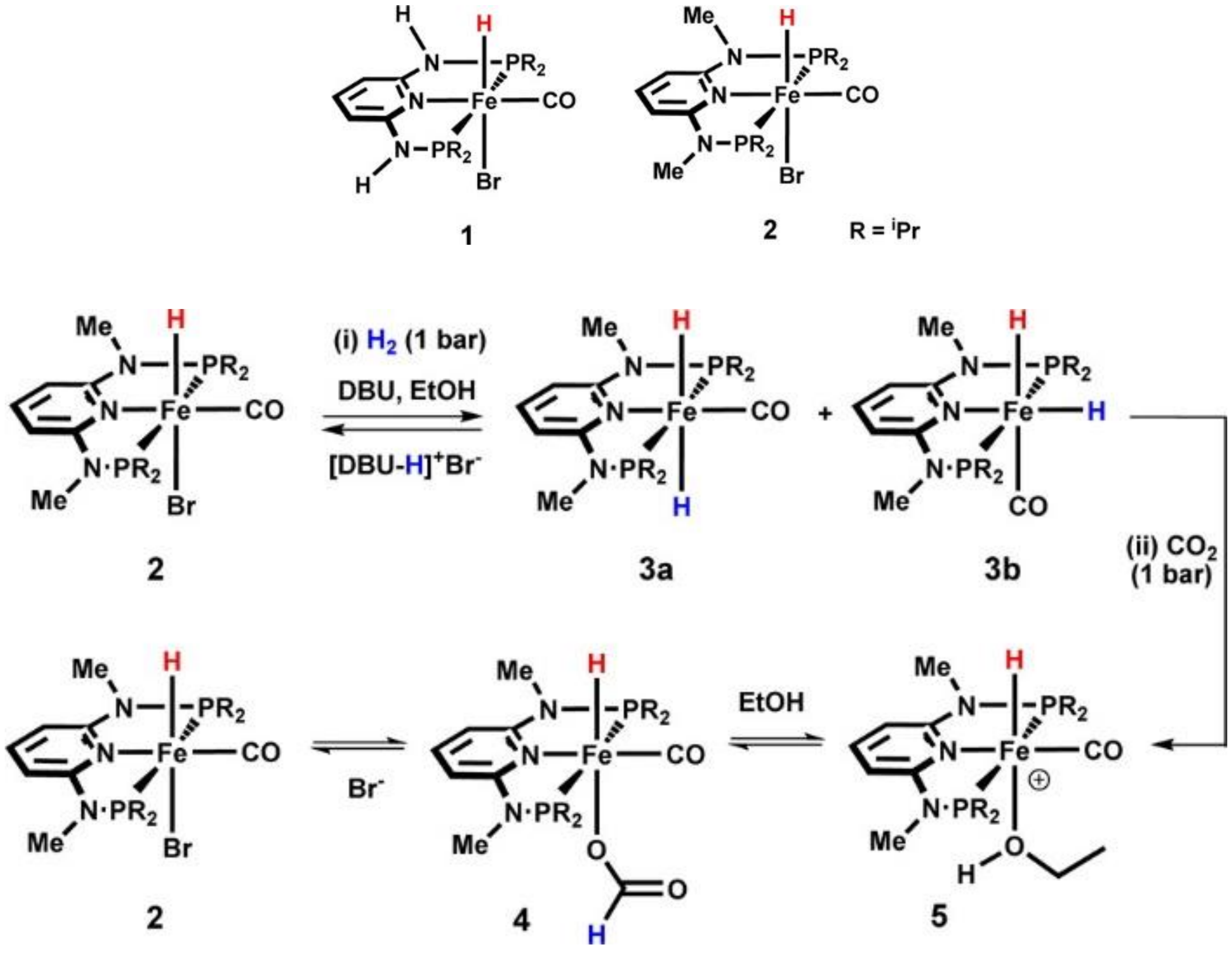




entry	gas (1/1, 1 MPa)	reaction soln (2 M)	product	complex **1**[b] TOF, h^{-1}	complex **1**[b] KIE[c]
1	H_2/CO_2	$KHCO_3/H_2O$	HCO_2K	683	
2	H_2/CO_2	$KDCO_3/D_2O$	HCO_2K	697	0.98
3	D_2/CO_2	$KHCO_3/H_2O$	DCO_2K	572	1.19
4	D_2/CO_2	$KDCO_3/D_2O$	DCO_2K	570	1.20

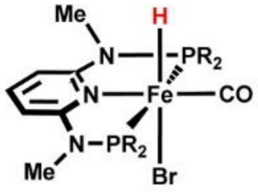
W.-H. Wang, J.T. Muckerman, E. Fujita, Y. Himeda, ACS Catalysis **2013**, 3, 856-860.

CO_2 Hydrogenation with Iron-Pincer Compounds

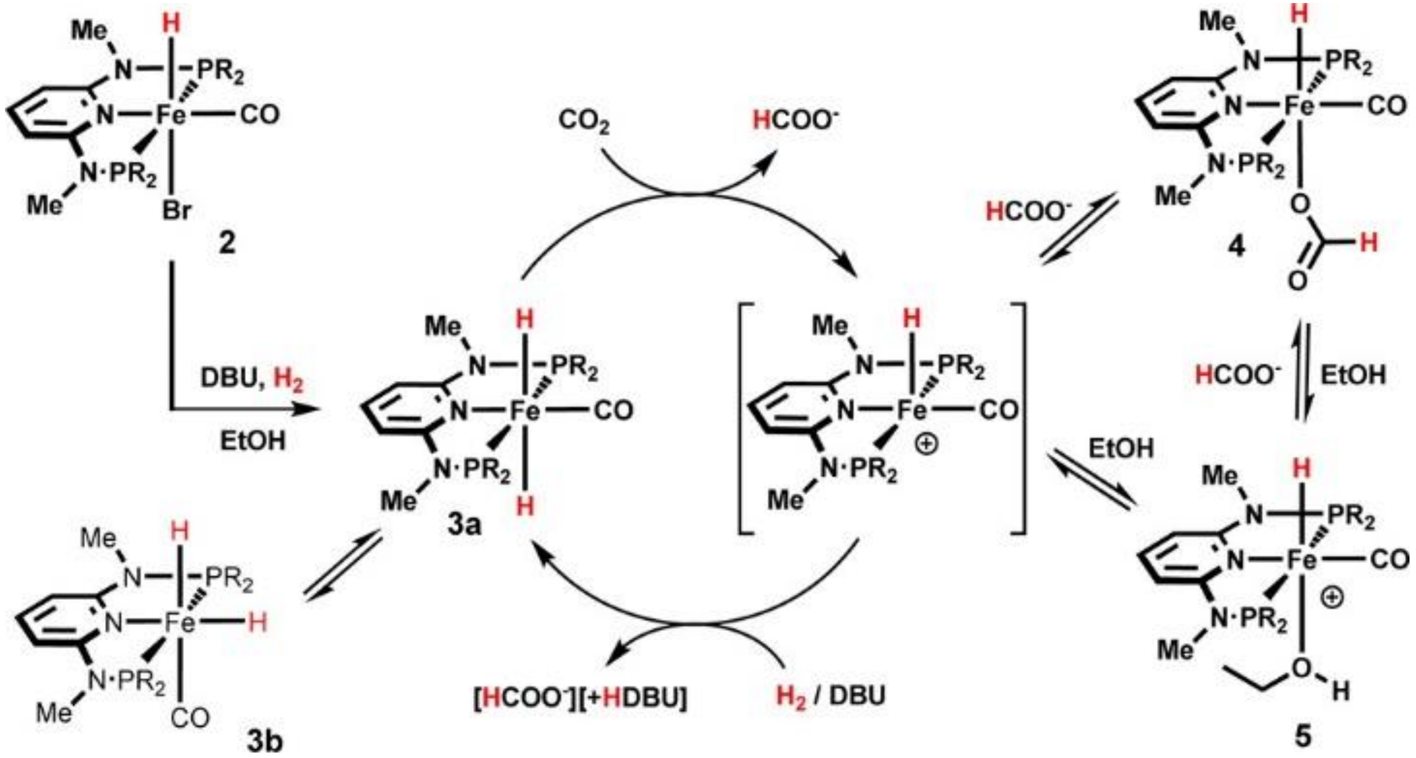


F. Bertini, N. Gorgas, B. Stöger, M. Peruzzini, ACS Catalysis 2016, 6, 2889-2893.

CO_2 Hydrogenation with Iron-Pincer Compounds

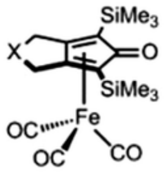


2 R = ^{i}Pr

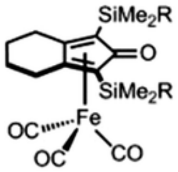


F. Bertini, N. Gorgas, B. Stöger, M. Peruzzini, ACS Catalysis 2016, 6, 2889-2893.

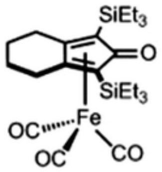
Photochemical Reduction: CO_2 to CO



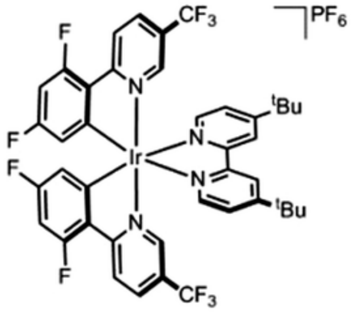
1 X = CH_2
2 X = O



3 R = Me
4 R = Et
5 R = ^{i}Pr
6 R = ^{t}Bu
7 R = Cy

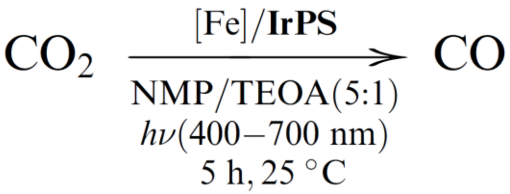


8

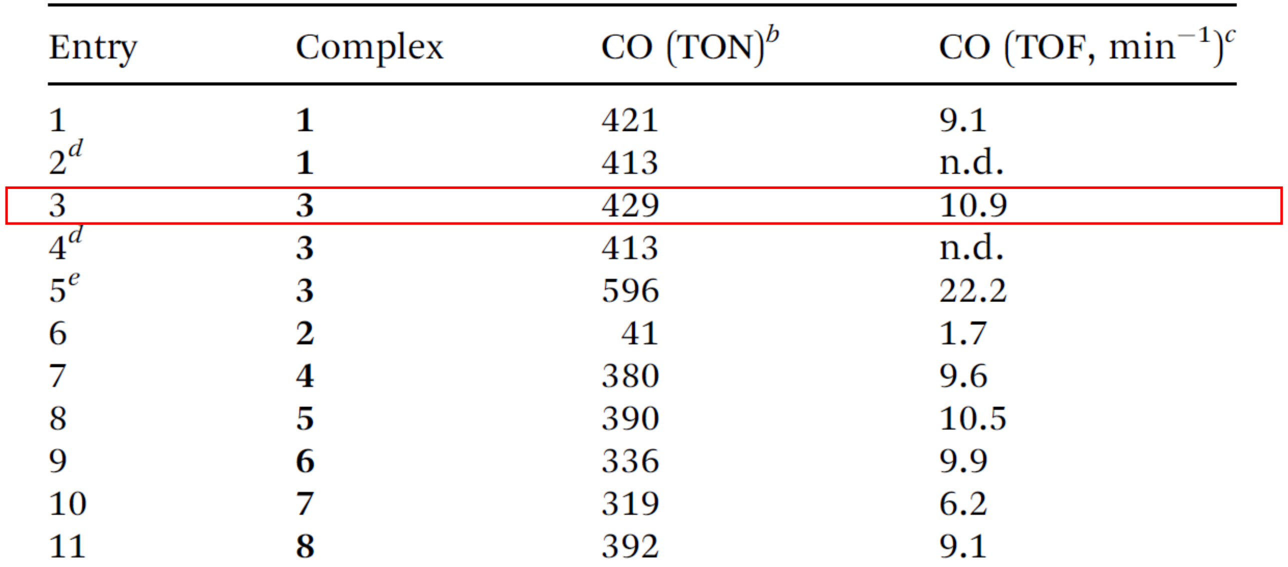


IrPS

Protic functional moiety in second coordination sphere leads to acceleration: kinetically favored intramolecular proton transfer



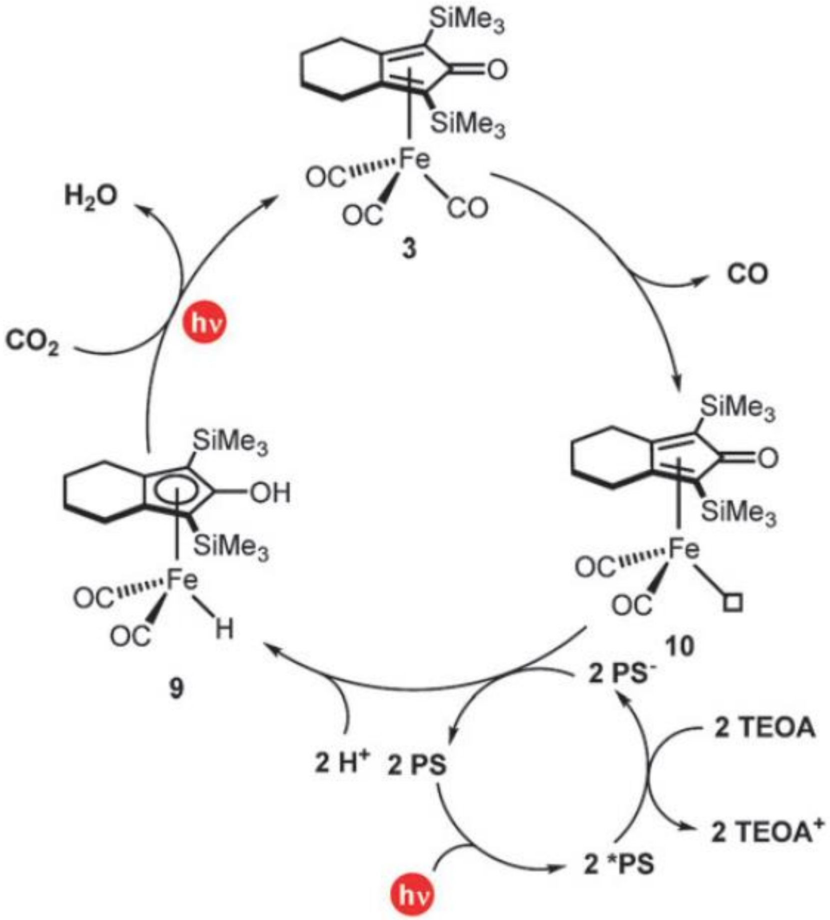
$$CO_2 \xrightarrow[\substack{\text{NMP/TEOA(5:1)} \\ h\nu(400\text{–}700\ \text{nm}) \\ 5\ \text{h},\ 25\ ^\circ\text{C}}]{[\text{Fe}]/\textbf{IrPS}} CO$$



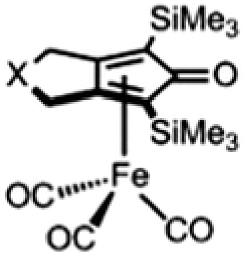
Entry	Complex	CO (TON)^{b}	CO (TOF, min^{-1})^{c}
1	**1**	421	9.1
2^{d}	**1**	413	n.d.
3	**3**	429	10.9
4^{d}	**3**	413	n.d.
5^{e}	**3**	596	22.2
6	**2**	41	1.7
7	**4**	380	9.6
8	**5**	390	10.5
9	**6**	336	9.9
10	**7**	319	6.2
11	**8**	392	9.1

A. Rosas-Hernandez, P.G. Alsabeh, E. Barsch, M. Beller, Chem Commun **2016**, 52, 8393-8396.

Photochemical Reduction: Catalytic Cycle



40 TONs of FA for catalyst 1 (~10%)



1 X = CH_2

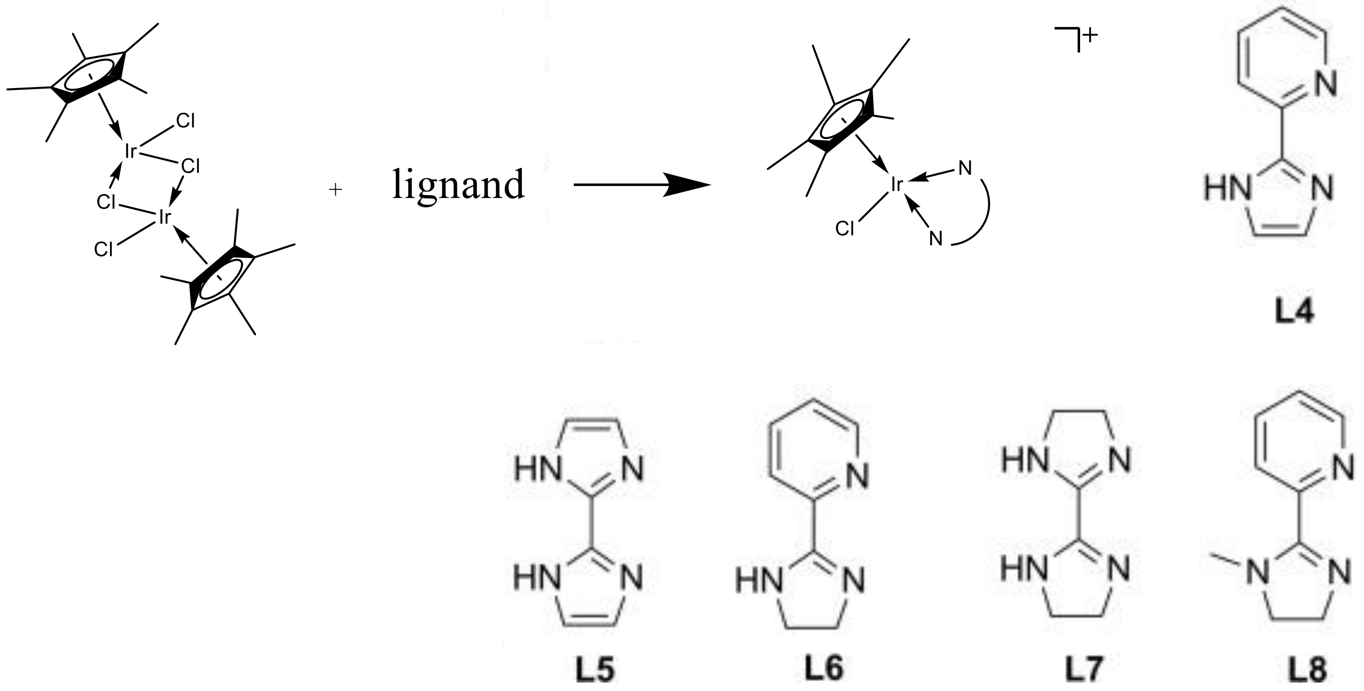
Conclusion & Perspective

- Relevant examples for CO_2 hydrogenation and formic acid dehydrogenation were presented
- A photocatalyst capable for reducing CO_2 to formic acid

- Advances in the development of non-precious metal catalysts are necessary (price)
- stable and fast catalysts are needed for industrial application

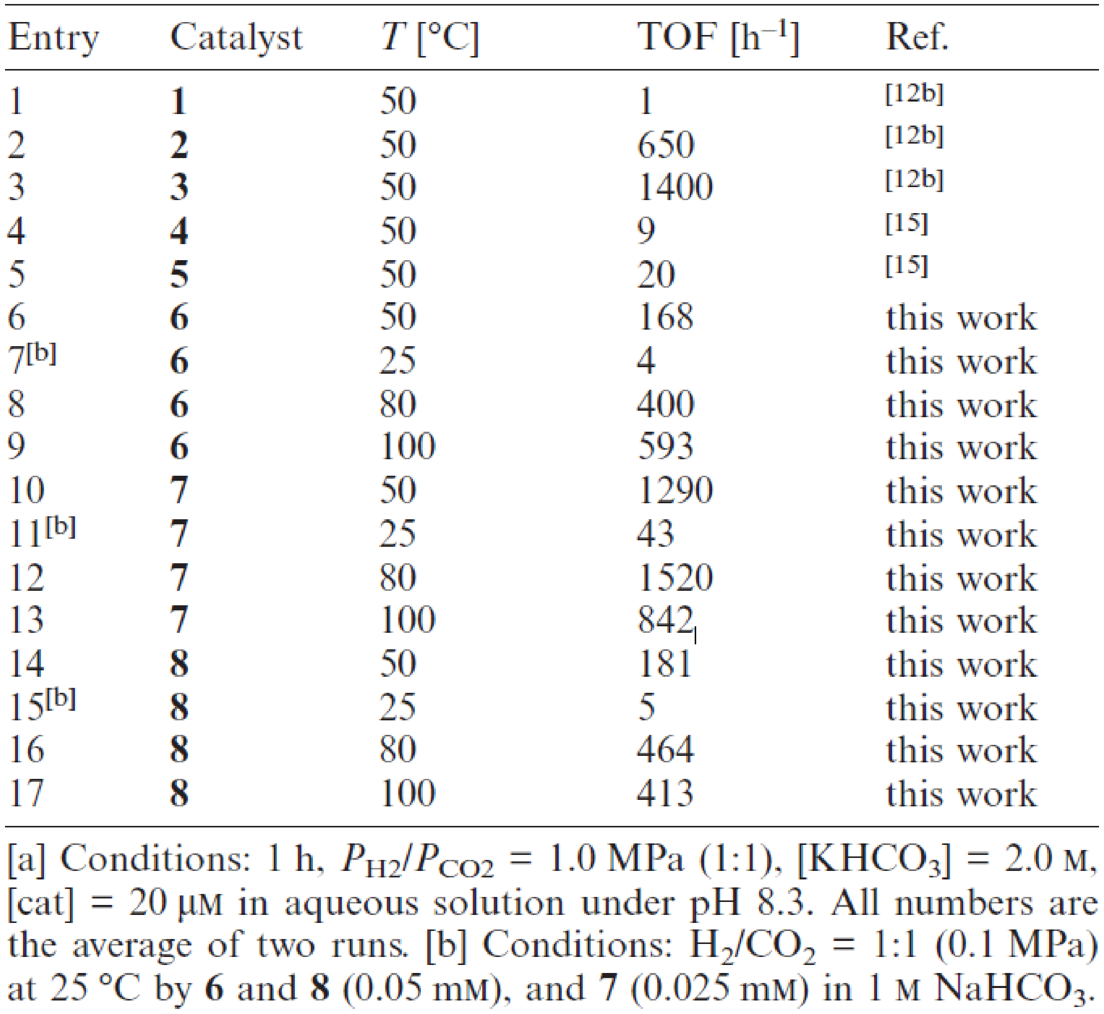
Question 1

$$CO_2 + H_2 + OH^- \xrightarrow{\text{Ir Cat. 1-8}} HCOO^- + H_2O$$



S. Xu, N. Onishi, A. Tsurusaki, Y. Himeda, Eur J Inorg Chem **2015**, 2015, 5591-5594.

Question 1

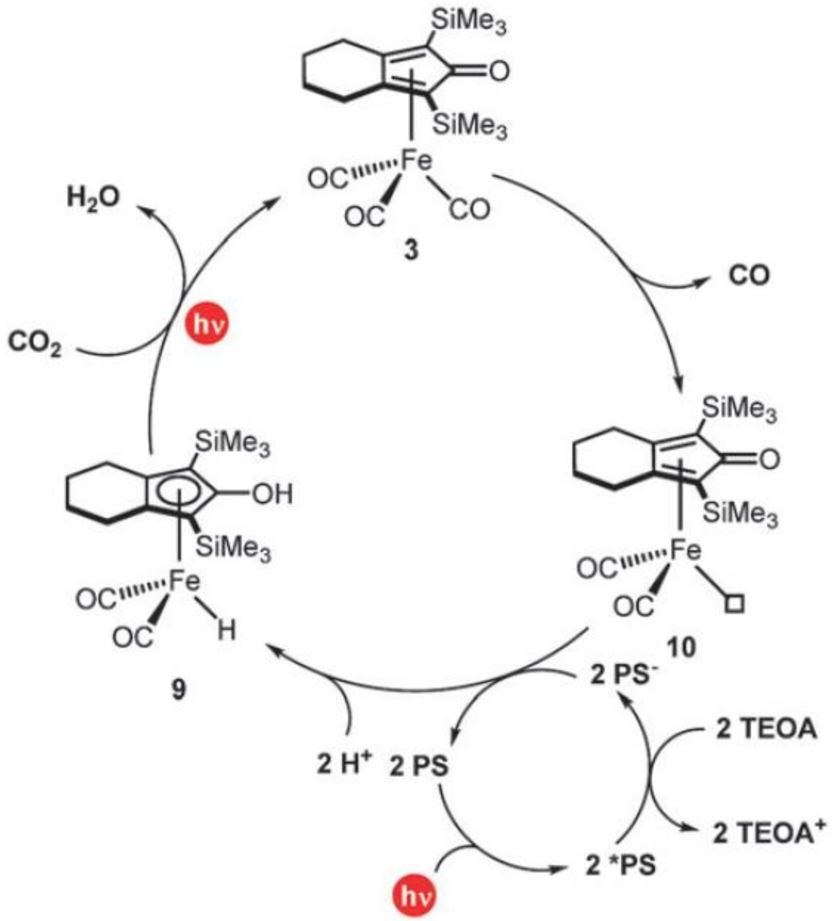


Entry	Catalyst	T [°C]	TOF [h^{-1}]	Ref.
1	**1**	50	1	[12b]
2	**2**	50	650	[12b]
3	**3**	50	1400	[12b]
4	**4**	50	9	[15]
5	**5**	50	20	[15]
6	**6**	50	168	this work
7[b]	**6**	25	4	this work
8	**6**	80	400	this work
9	**6**	100	593	this work
10	**7**	50	1290	this work
11[b]	**7**	25	43	this work
12	**7**	80	1520	this work
13	**7**	100	842	this work
14	**8**	50	181	this work
15[b]	**8**	25	5	this work
16	**8**	80	464	this work
17	**8**	100	413	this work

[a] Conditions: 1 h, P_{H2}/P_{CO2} = 1.0 MPa (1:1), [$KHCO_3$] = 2.0 M, [cat] = 20 μM in aqueous solution under pH 8.3. All numbers are the average of two runs. [b] Conditions: H_2/CO_2 = 1:1 (0.1 MPa) at 25 °C by **6** and **8** (0.05 mM), and **7** (0.025 mM) in 1 M $NaHCO_3$.

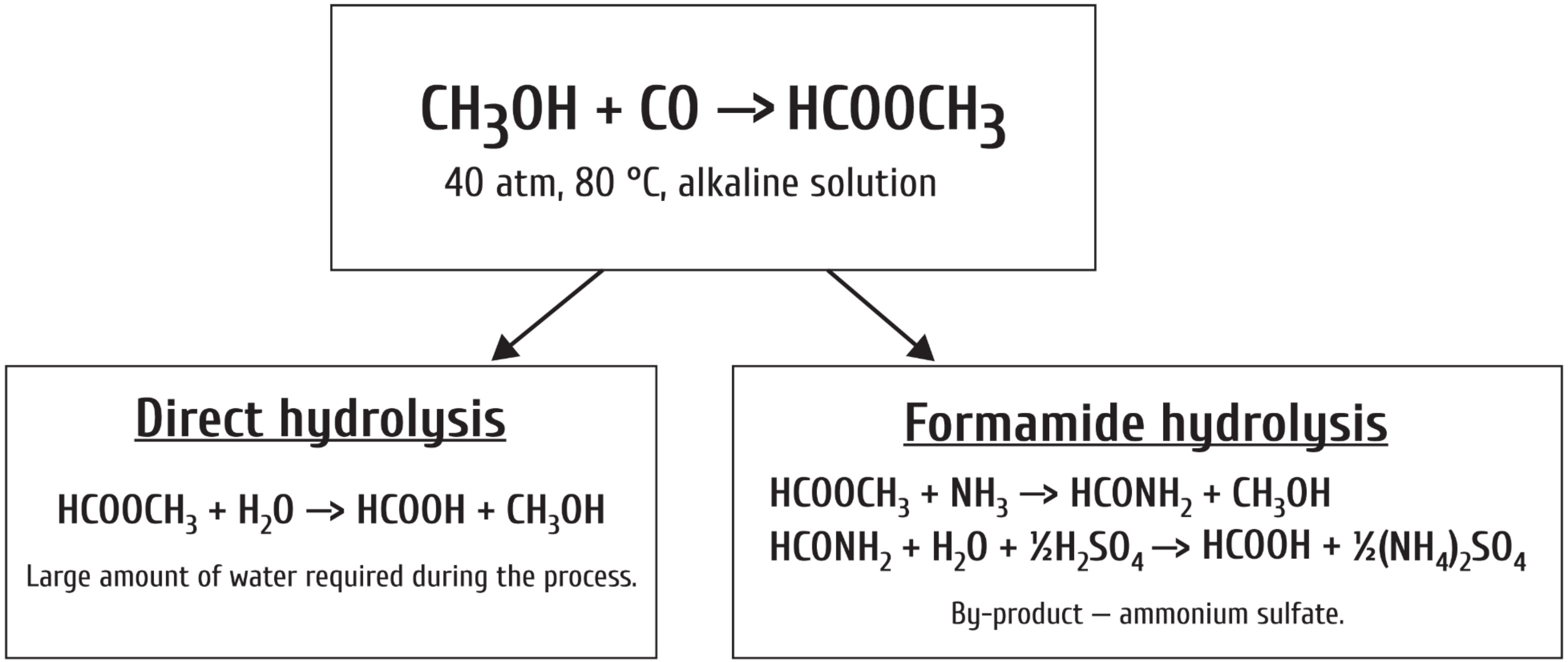
- Despite without proton-responsive group
- Powerful electron-donation of the imidazoline moiety

Question 2


SiMe$_3$
O
SiMe$_3$
Fe
OC
OC
CO
3
CO
SiMe$_3$
O
SiMe$_3$
Fe
OC
OC
□
10
2 PS$^-$
2 TEOA
2 TEOA$^+$
2 *PS
hν
2 H$^+$
2 PS
9
SiMe$_3$
OH
SiMe$_3$
Fe
OC
OC
H
CO$_2$
hν
H$_2$O

Question 2

Industrial methods of formic acid production



$CH_3OH + CO \rightarrow HCOOCH_3$

40 atm, 80 °C, alkaline solution

Direct hydrolysis

$HCOOCH_3 + H_2O \rightarrow HCOOH + CH_3OH$

Large amount of water required during the process.

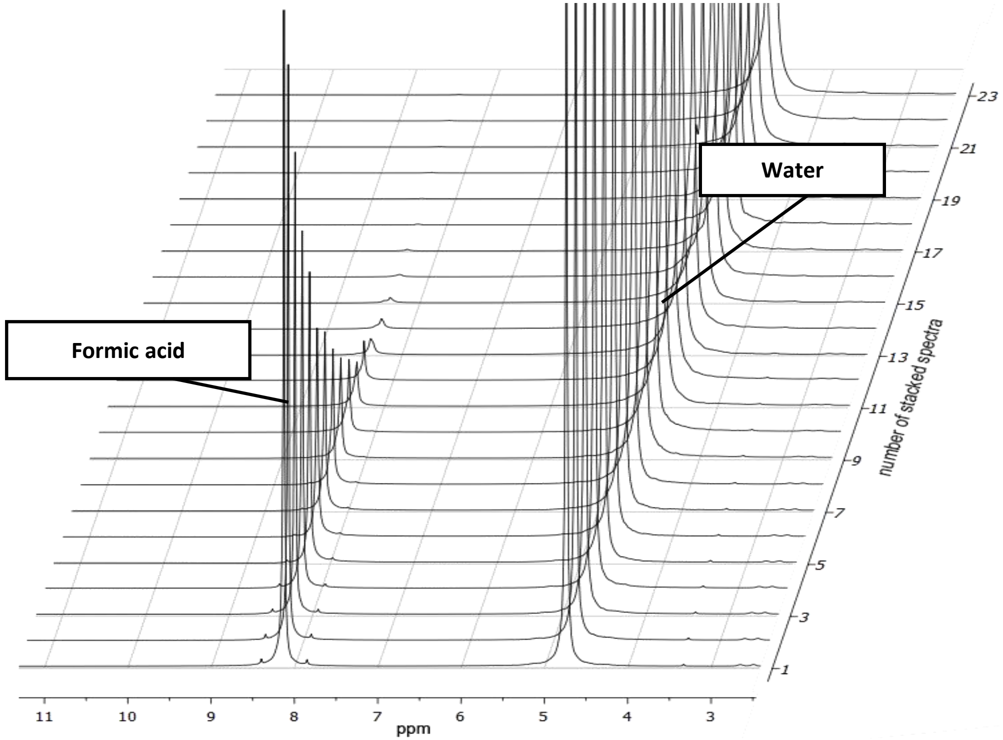
Formamide hydrolysis

$HCOOCH_3 + NH_3 \rightarrow HCONH_2 + CH_3OH$

$HCONH_2 + H_2O + \frac{1}{2}H_2SO_4 \rightarrow HCOOH + \frac{1}{2}(NH_4)_2SO_4$

By-product — ammonium sulfate.

^{1}H-NMR: Formic Acid Dehydrogenation



C. Fink, G. Laurenczy, Dalton Trans, **2017**, 46, 1670-1676.

Supporting Information

	ΔH° (kJ mol^{-1})	ΔS° (J mol^{-1} K^{-1})	ΔG° (kJ mol^{-1})	Eq.
$HCOOH_{(l)} \rightarrow H_{2(g)} + CO_{2(g)}$	+31.2	+215	−32.9	(1)
$HCOOH_{(l)} \rightarrow H_2O_{(l)} + CO_{(g)}$	+28.7	+138	−12.4	(2)
$CO_{2(g)} + H_{2(g)} \rightarrow HCOOH_{(l)}$	−31.2	−215	+32.9	(3)
$CO_{2(g)} + H_{2(g)} + NH_{3(aq)} \rightarrow HCO^{-}_{2(aq)} + NH^{+}_{4(aq)}$	−84.3	−250	−9.5	(4)
$CO_{2(aq)} + H_{2(aq)} + NH_{3(aq)} \rightarrow HCO^{-}_{2(aq)} + NH^{+}_{4(aq)}$	−59.8	−81	−35.4	(5)
$MHCO_{3(aq)} + H_{2(aq)} \rightarrow MHCO_{2(aq)} + H_2O_{(l)}$	−20.5	−66.4	−0.72	(6)