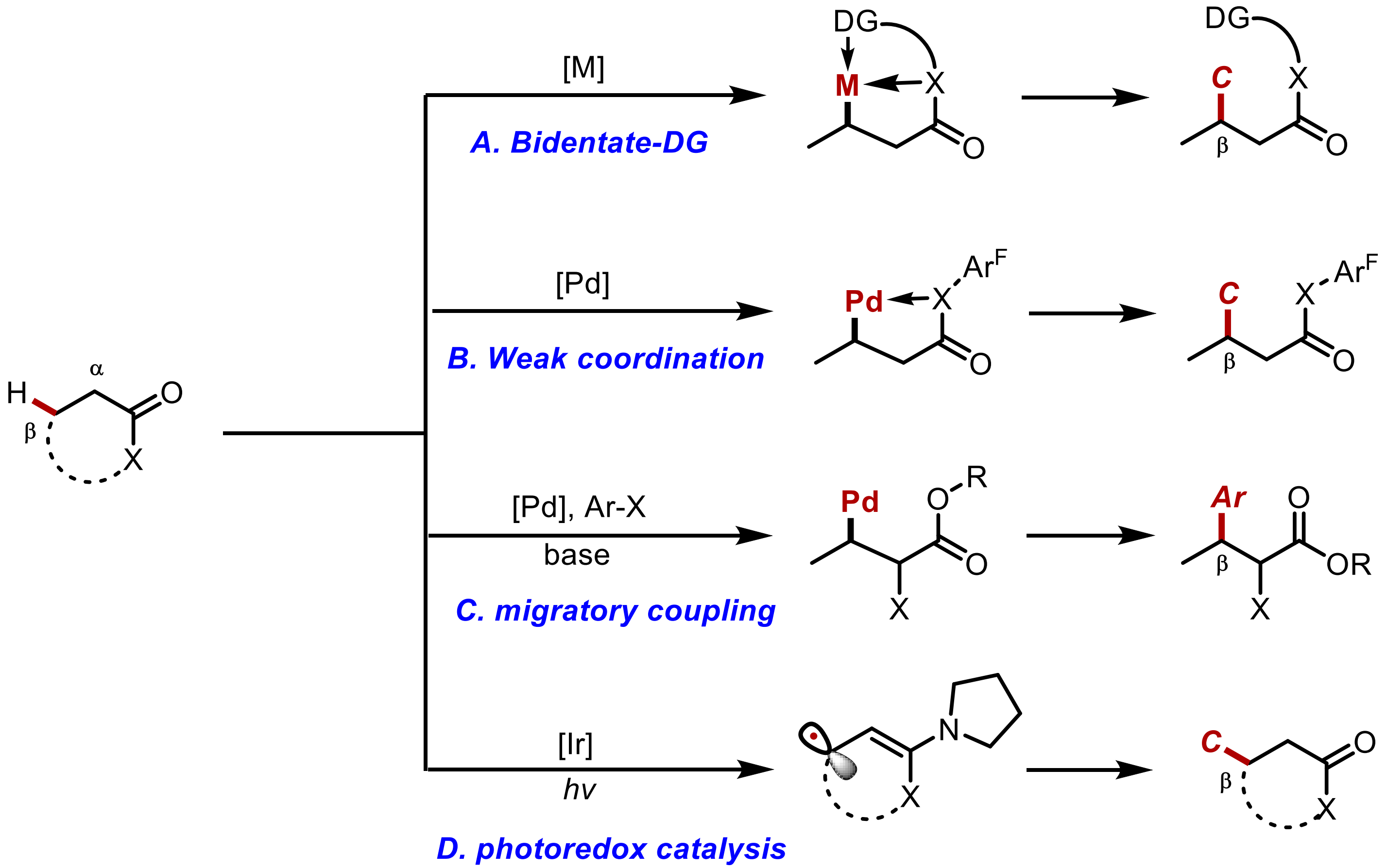
Catalytic C-C Bond Forming Transformations via β-C-H Functionalization of Carbonyl Compounds

Zhongxing Huang
May 7st, 2014

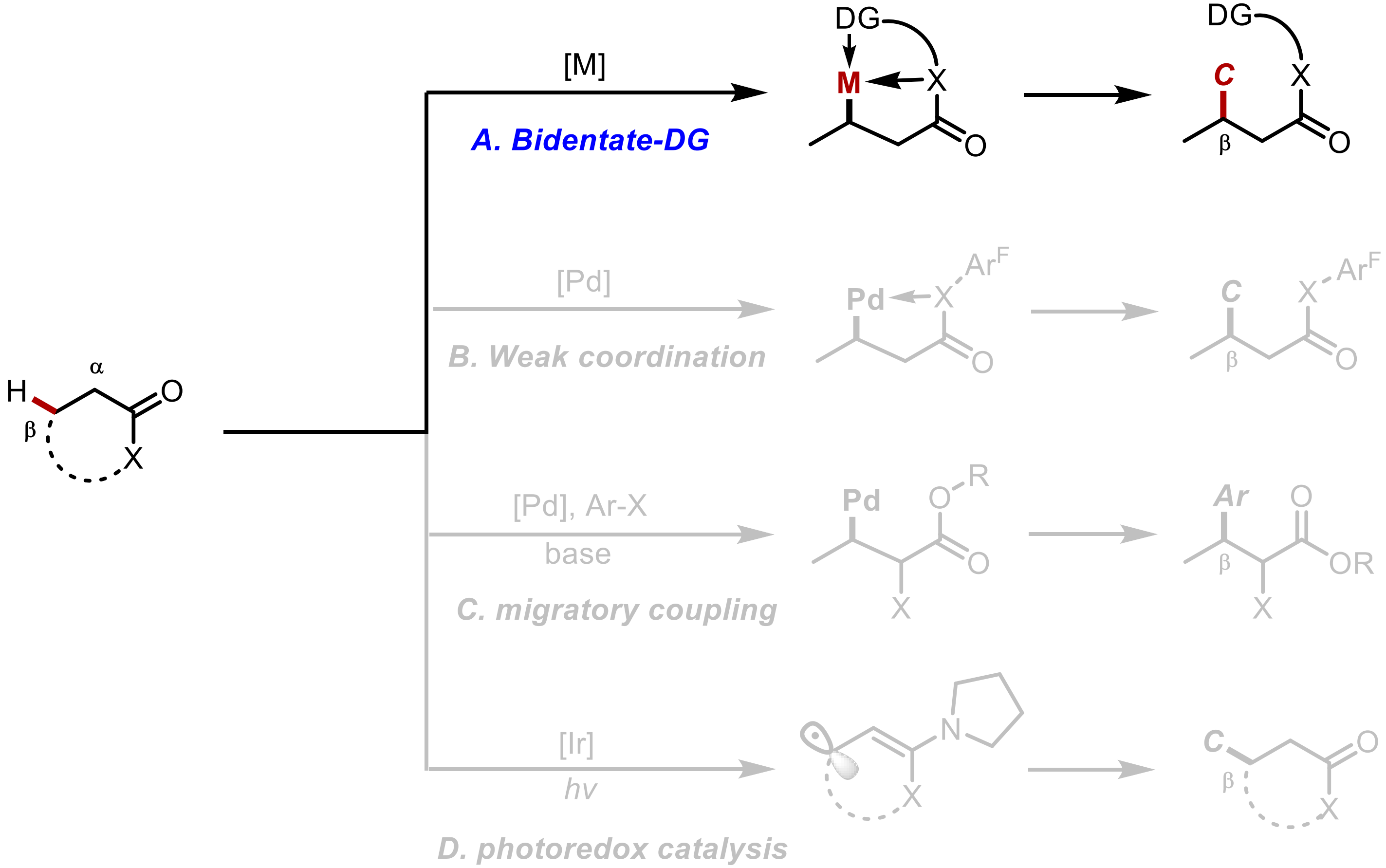
Content



Not covered today:

- NHC catalysis
- Dehydrogenative C-C coupling
- Enamine catalysis

Content



A. Bidentate-DG

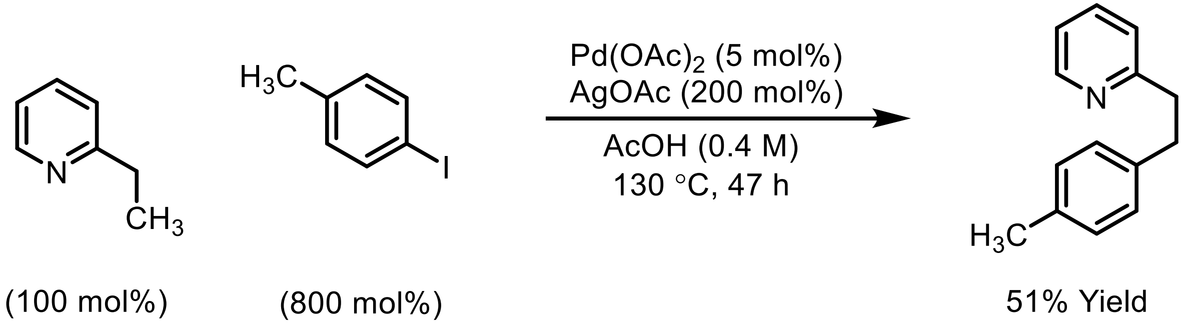
B. Weak coordination

C. migratory coupling

D. photoredox catalysis

Directing-Group Strategy-Bidentate

- **Daugulis's Novel Discovery**



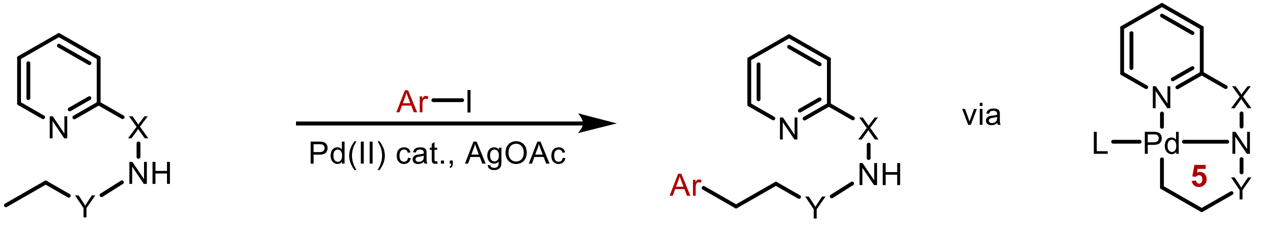
Features:

- Aryl iodide/silver salt combination (Sanford: diaryliodonium salt)
- Unactivated sp^3 C-H bonds
- Methylene C-H bonds cannot be arylated
- Electron-rich aryl iodide >> electron-poor ones

Daugulis, OL, 2005, 7, 3657

DG Strategy-Bidentate-Arylation

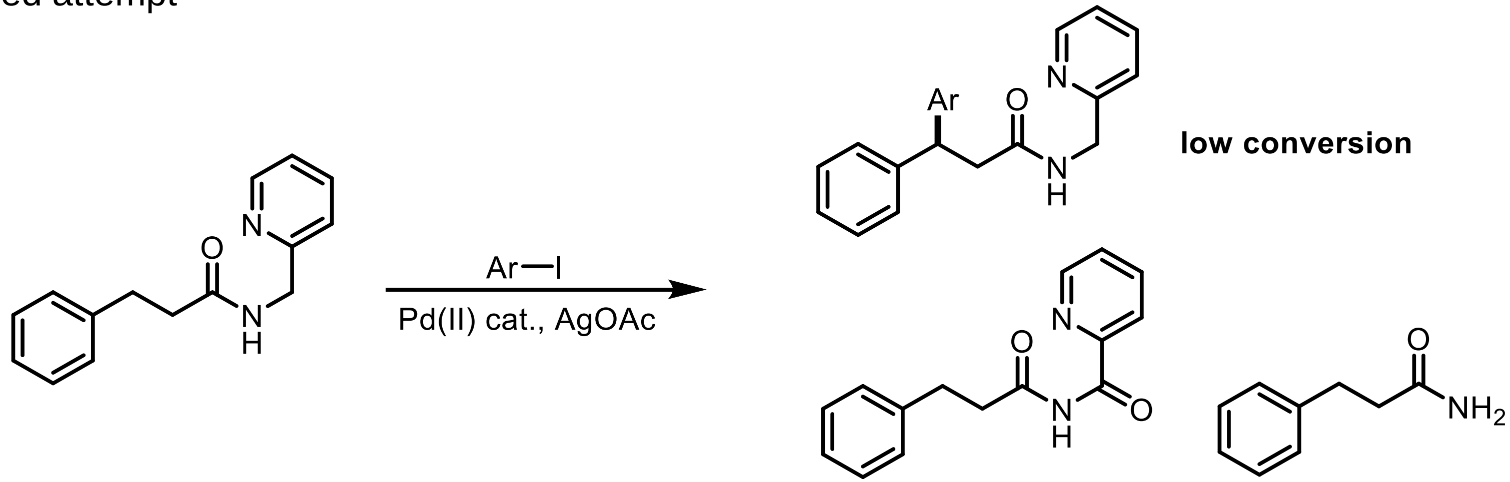
- **Design of detachable auxiliary**
  - Design



Y = C=O, carboxylic acid β-arylation

Y = CH_2, amine γ-arylation

  - Failed attempt

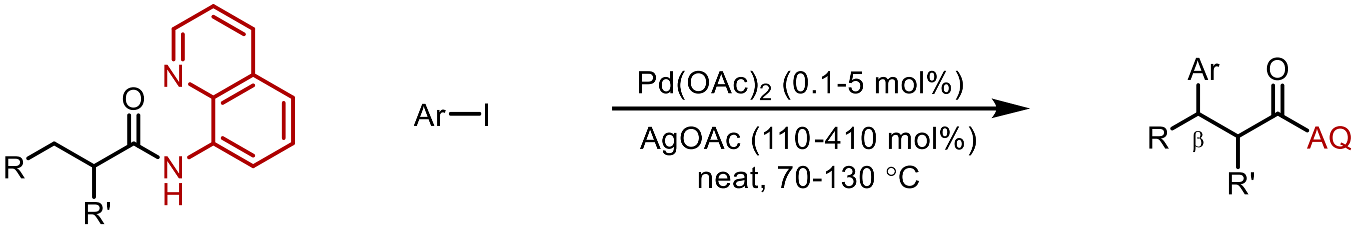


Byproducts

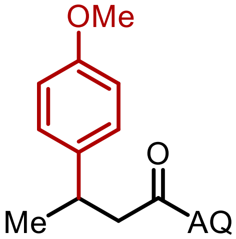
Daugulis, JACS, 2005, 127, 13154

DG Strategy-Bidentate-Arylation

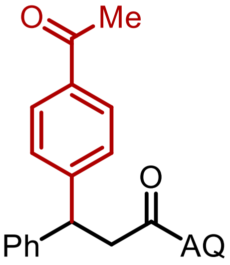
- **Design of detachable auxiliary**
  - 8-aminoquinoline (AQ)



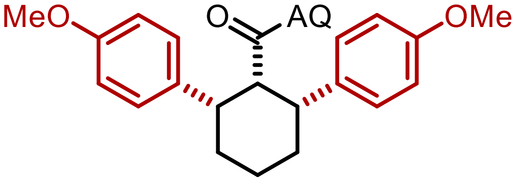
(100 mol%) (400-600 mol%)



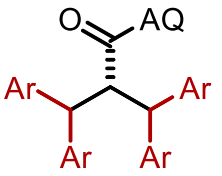
5 min, 110 °C
92% Yield



20 min, 120 °C
60% Yield



5 h, 70 °C
61% Yield



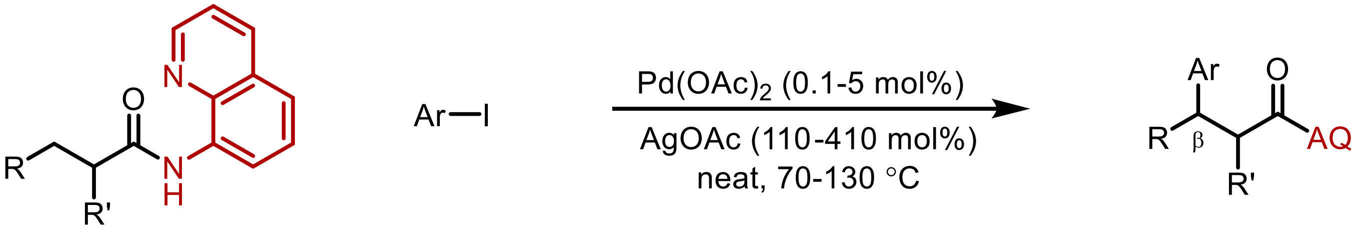
Ar = p-C_6H_4Me

30 min, 120 °C
60% Yield

Daugulis, JACS, 2005, 127, 13154

DG Strategy-Bidentate-Arylation

- **Design of detachable auxiliary**
  - 8-aminoquinoline (AQ)



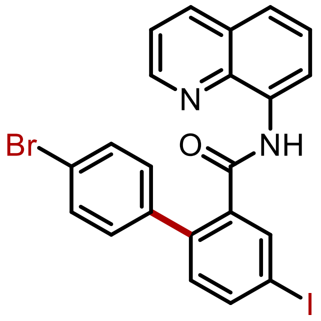
$Pd(OAc)_2$ (0.1-5 mol%)

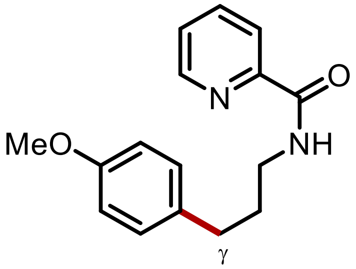
AgOAc (110-410 mol%)
neat, 70-130 °C

(100 mol%)   (400-600 mol%)

Features:

- Aryl iodide/silver salt combination
- Methylene C-H activation enabled
- Rate: secondary>primary C-H bonds
- Free NH required
- Neat condition

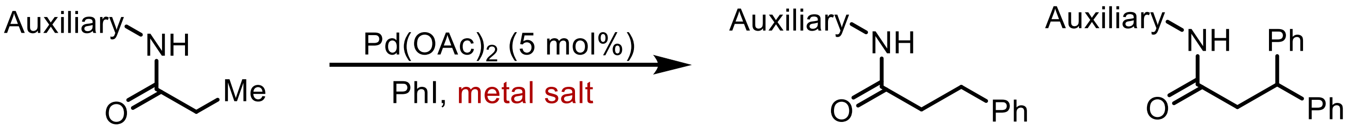




Daugulis, JACS, 2005, 127, 13154

DG Strategy-Bidentate-Arylation

- **‘Silver-free’ conditions**

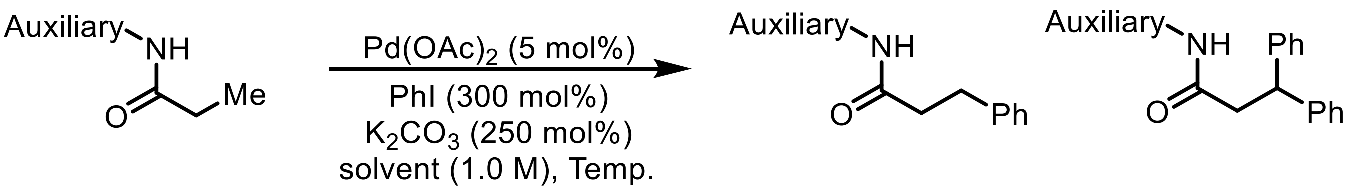


metal salt:
K_2CO_3
K_3PO_4
CsOAc
Cs_3PO_4

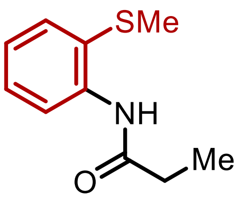
Daugulis, JACS, 2010, 132, 3965

DG Strategy-Bidentate-Arylation

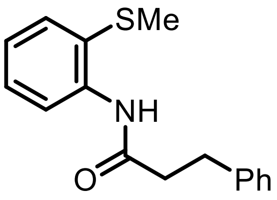
▪ Optimization of Auxiliary



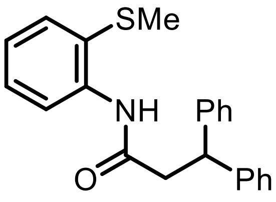
$Pd(OAc)_2$ (5 mol%)
PhI (300 mol%)
K_2CO_3 (250 mol%)
solvent (1.0 M), Temp.



t-Amy-OH:H_2O 4:1
90 °C

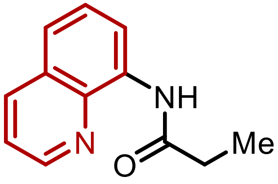


1a
84% Yield

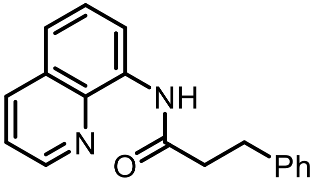


1b
13% Yield

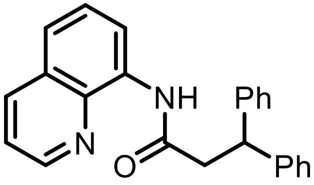
selective mono-arylation



t-Amy-OH:H_2O 4:1
110 °C



2a
66% Yield



2b
17% Yield

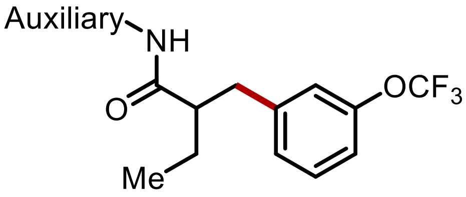
Daugulis, JACS, 2010, 132, 3965

DG Strategy-Bidentate-Arylation

- **Primary *vs* secondary C-H activation**

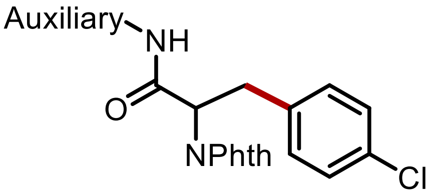
Auxiliary =

t-Amy-OH:H_2O
90 °C, K_2CO_3



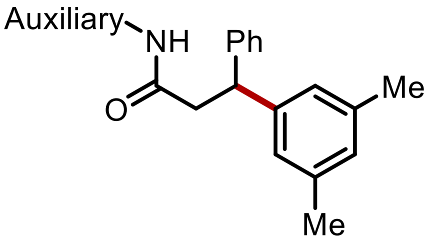
60% Yield

Toluene
110 °C, CsOAc



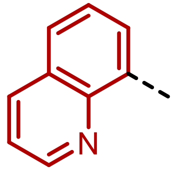
79% Yield

t-Amy-OH
90 °C, K_2CO_3
20 mol% PivOH

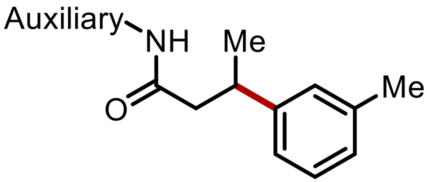


47% Yield

Auxiliary =

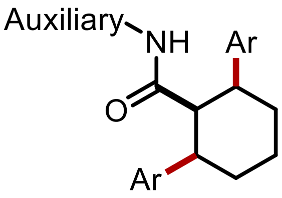


t-Amy-OH
90 °C, Cs_3PO_4



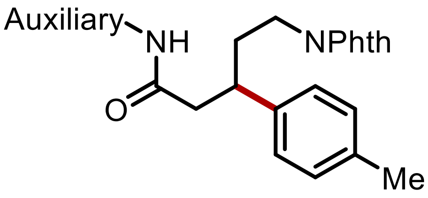
79% Yield

t-Amy-OH
90 °C, Cs_3PO_4
Ar = m-C_6H_4Br



52% Yield

t-Amy-OH
90 °C, Cs_3PO_4

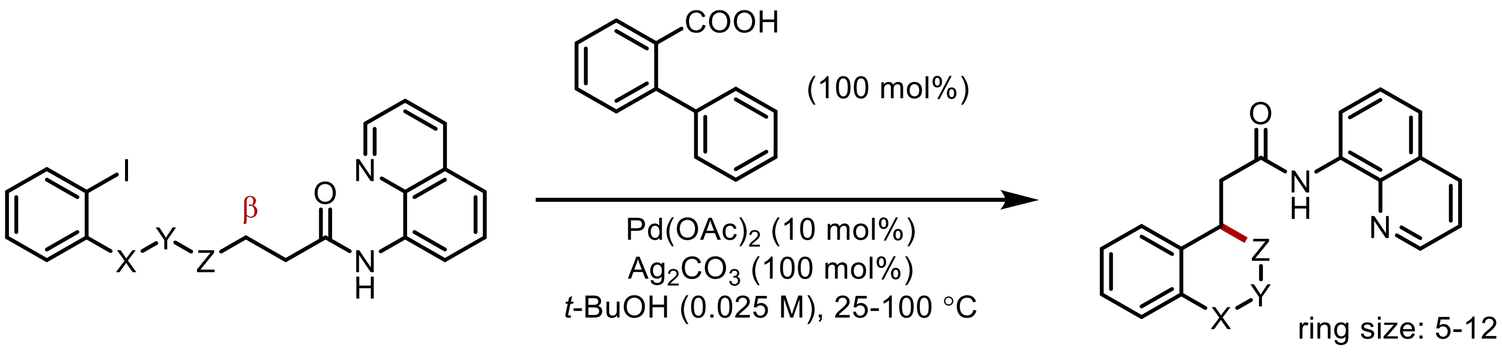


76% Yield

Daugulis, JACS, 2010, 132, 3965

Directing-Bidentate-Group Strategy

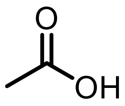
- **Intramolecular arylation**



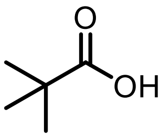
$Pd(OAc)_2$ (10 mol%)
Ag_2CO_3 (100 mol%)
t-BuOH (0.025 M), 25-100 °C

ring size: 5-12

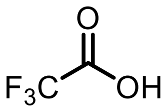
- Acid screen (50 ^{0}C, X=Y=Z=CH_2)



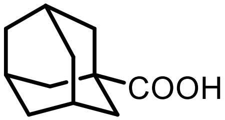
Yield: 15%



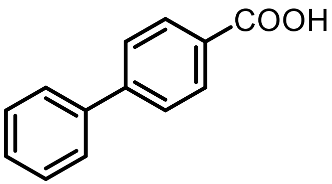
70%



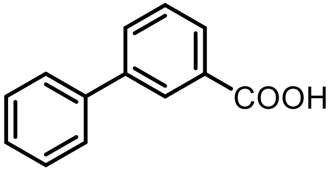
0%



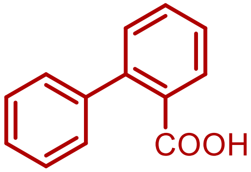
75%



10%



30%

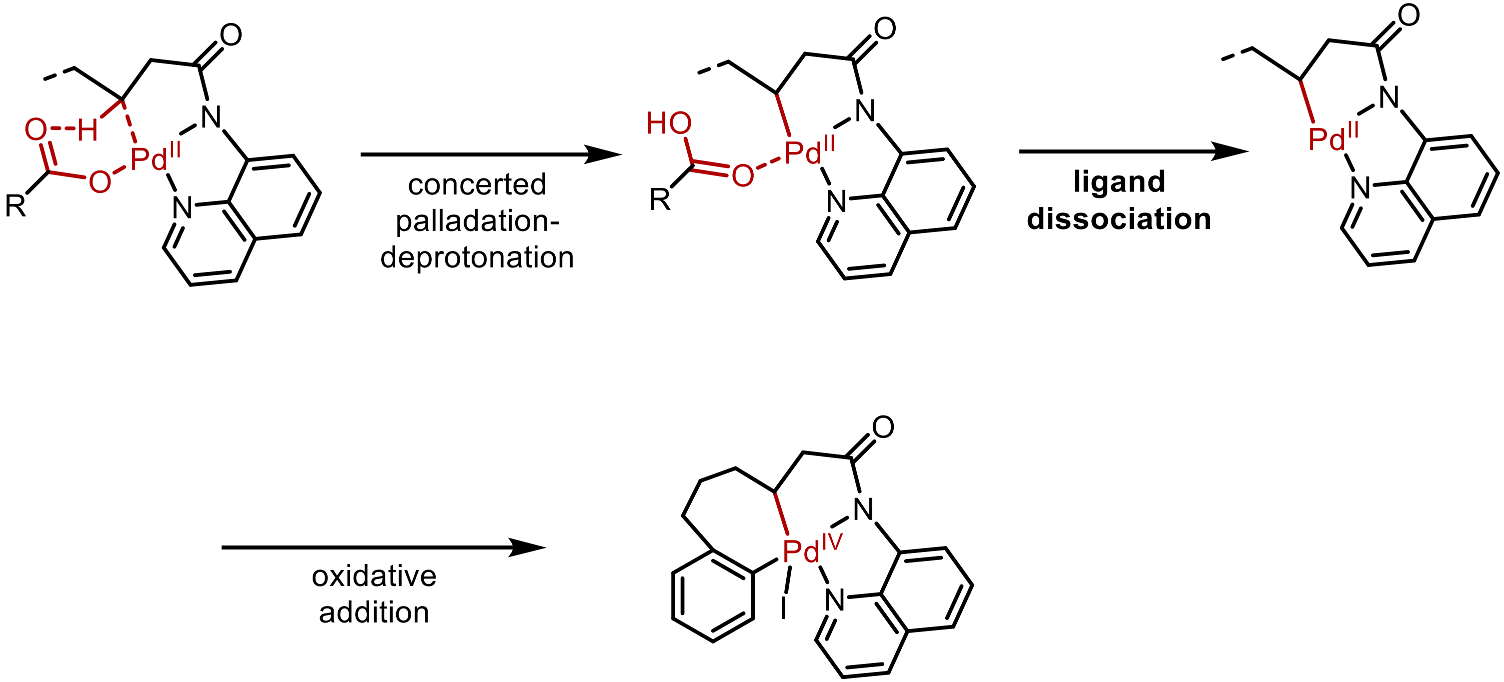


85%

Chen, OL, 2010, 12, 3414

DG Strategy-Bidentate-Arylation

- Reasoning

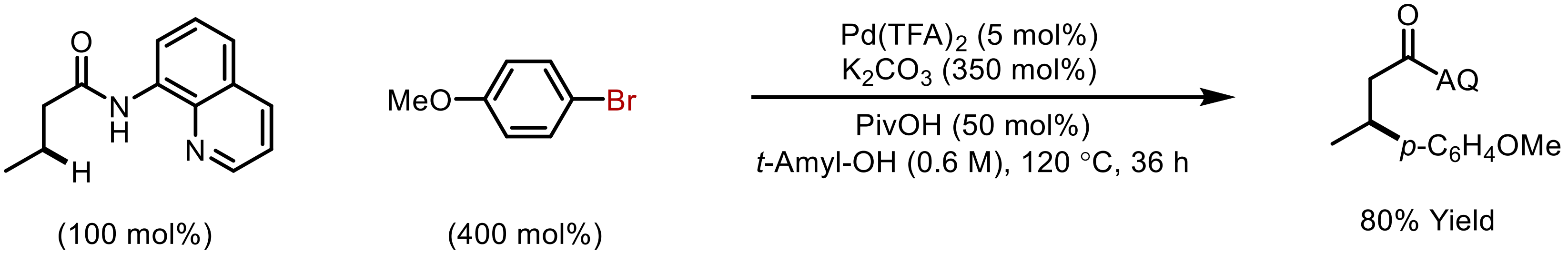


Chen, OL, 2010, 12, 3414

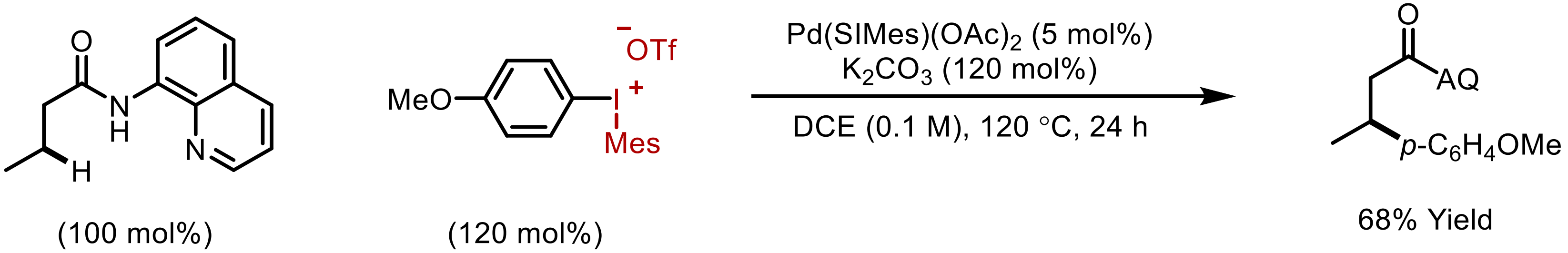
DG Strategy-Bidentate-Arylation

- **Other aryl source**

Zeng



Shi



Zeng's work

- OA as rate-determining step
- Na_2CO_3 and K_3PO_4 gave lower yield
- Cs_2CO_3 and AgOAc inhibit the reaction

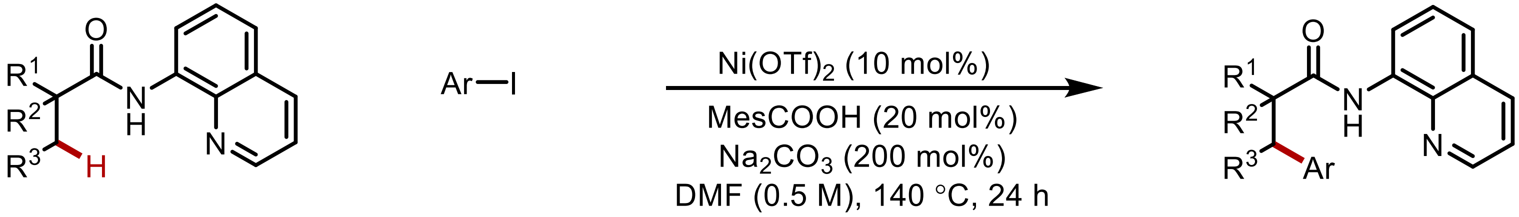
Shi's work

- ArI gave diminished yield
- Largely lowered Ar equivalence
- Lowered reactivity of catalyst

Zeng, OL, 2014, 16, 2248
Shi, OL, 2013, 15, 4758

DG Strategy-Bidentate-Arylation

- **Nickel Catalysis**



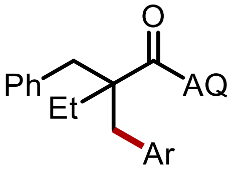
$Ni(OTf)_2$ (10 mol%)

MesCOOH (20 mol%)

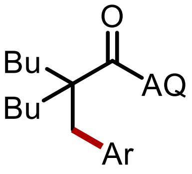
Na_2CO_3 (200 mol%)

DMF (0.5 M), 140 °C, 24 h

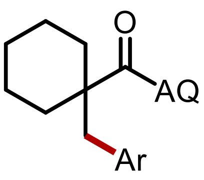
(100 mol%) (200 mol%)



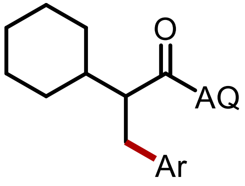
56%



50%

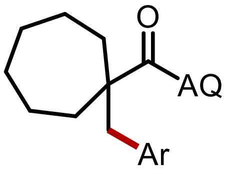


61%



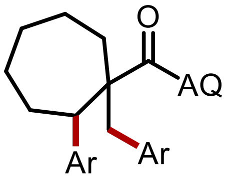
30% (40% recovered)

Ar = p-C_6H_4OMe

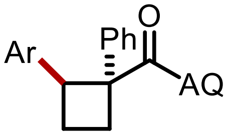


41%

and

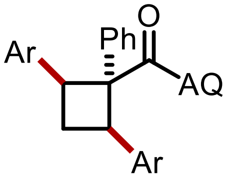


33%



50%

and



33%

Features:

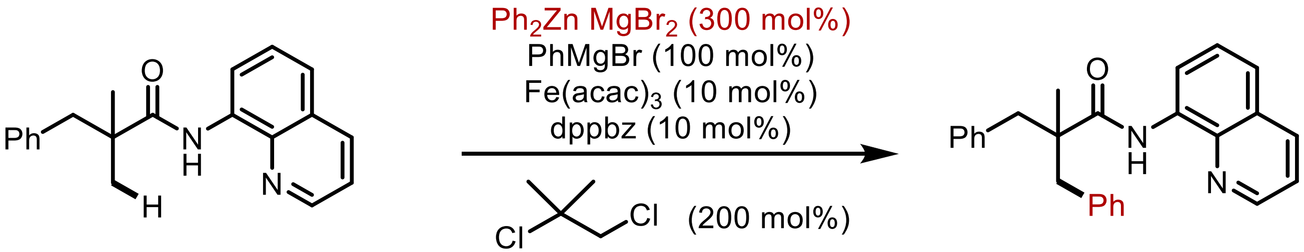
- Primary>secondary C-H bonds
- No second arylation
- α-C-H bond not tolerated
- Thio DG doesn’t work
- radical pathway not supported

Chatani, JACS, 2014, 136, 898

You, Chem Comm, 2014, 50, 3944

DG Strategy-Bidentate-Arylation

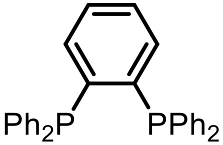
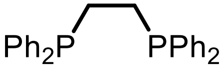
- **Iron Catalysis**



$Ph_2Zn\ MgBr_2$ (300 mol%)
PhMgBr (100 mol%)
$Fe(acac)_3$ (10 mol%)
dppbz (10 mol%)
(200 mol%)
THF, 50 °C

(100 mol%)

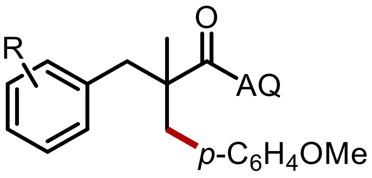
85% Yield

no ligand	 **dppbz**	 **dppe**	 **dppe**
0%	80%	9%	0%

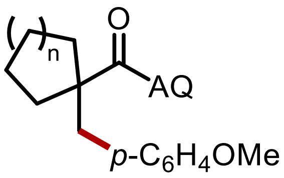
Features:
- 7 equiv. Grignard mixed with 3 equiv. zinc
- 1 equiv. Grignard for deprotonation
- Sensitive to ligand structure

Nakamura, JACS, 2013, 135, 6030

DG Strategy-Bidentate-Arylation



R = H	79%
p-F	74%
p-Cl	71%
p-Br	73%
m-OMe	71%

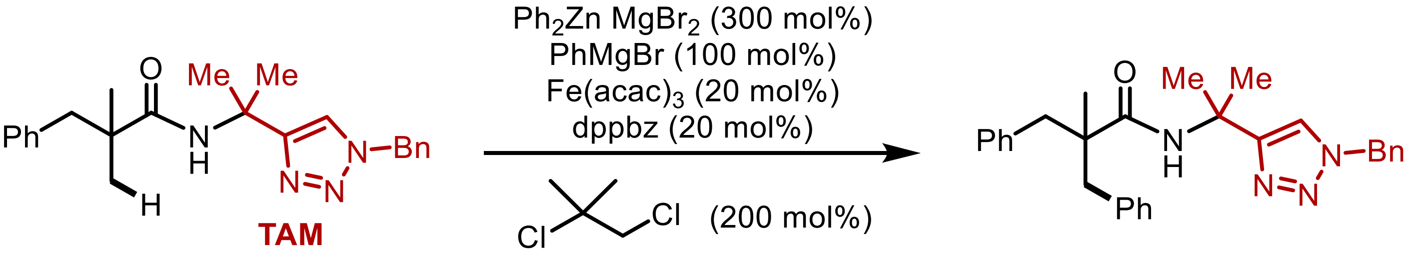


n = 1, 69%
n = 2, 75%

Features:

- α-C-H bond not tolerated
- Primary>secondary (benzylic) C-H bonds
- No second arylation

- **TAM as directing group**



Ph_2Zn $MgBr_2$ (300 mol%)
PhMgBr (100 mol%)
$Fe(acac)_3$ (20 mol%)
dppbz (20 mol%)

(200 mol%)

Toluene, 80 °C, 48 h

68% Yield

Nakamura, JACS, 2013, 135, 6030
Ackermann, ACIE, 2014, 53, 3868

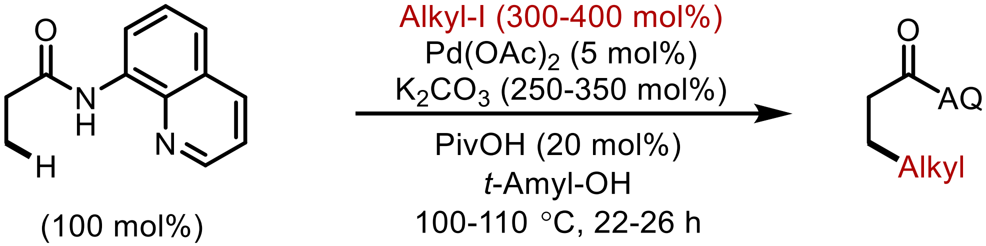
DG Strategy-Bidentate-Alkylation

- **Pd catalysis**

Challenges:

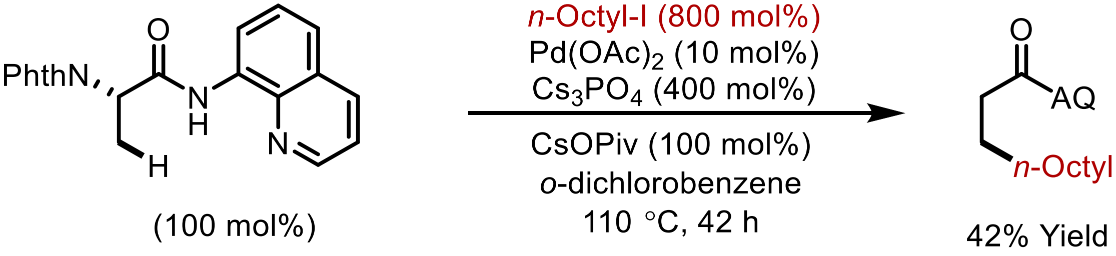
- Difficult C-H insertion
- Difficult oxidative addition
- Difficult alkyl-alkyl reductive elimination

- **Three examples from Daugulis**



Alkyl-I (300-400 mol%)
$Pd(OAc)_2$ (5 mol%)
K_2CO_3 (250-350 mol%)
PivOH (20 mol%)
t-Amyl-OH
100-110 °C, 22-26 h

Alkyl = *i*-butyl	58% Yield
Alkyl = *n*-octyl	47% Yield



n-Octyl-I (800 mol%)
$Pd(OAc)_2$ (10 mol%)
Cs_3PO_4 (400 mol%)
CsOPiv (100 mol%)
o-dichlorobenzene
110 °C, 42 h

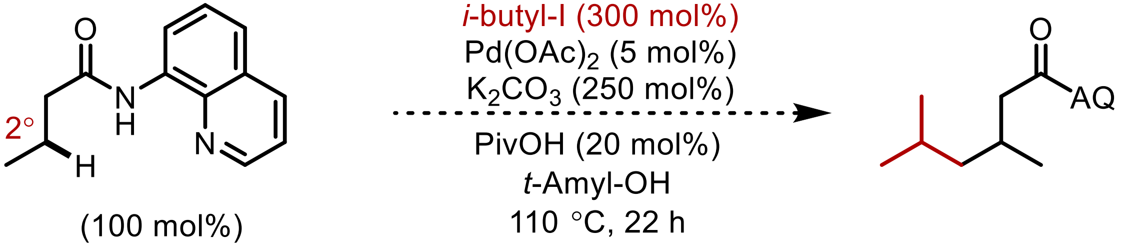
- Primary C-H bond only
- Low efficiency
- Ag considered bad

Daugulis, JACS, 2010, 132, 3965
Daugulis, ACIE, 2012, 51, 5188

DG Strategy-Bidentate-Alkylation

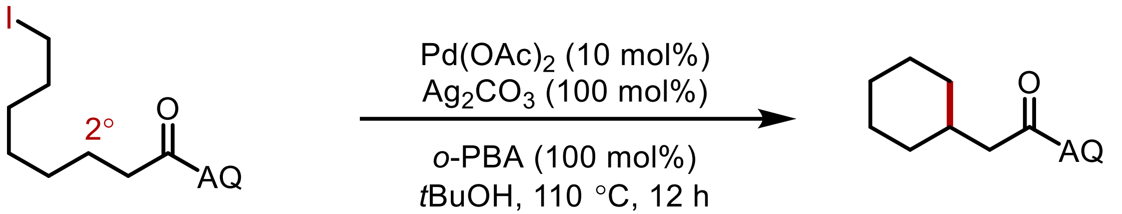
Chen

Same conditions as Daugulis'



(100 mol%)

i-butyl-I (300 mol%)
$Pd(OAc)_2$ (5 mol%)
K_2CO_3 (250 mol%)
PivOH (20 mol%)
t-Amyl-OH
110 °C, 22 h



(100 mol%)

$Pd(OAc)_2$ (10 mol%)
Ag_2CO_3 (100 mol%)
o-PBA (100 mol%)
*t*BuOH, 110 °C, 12 h

13% Yield

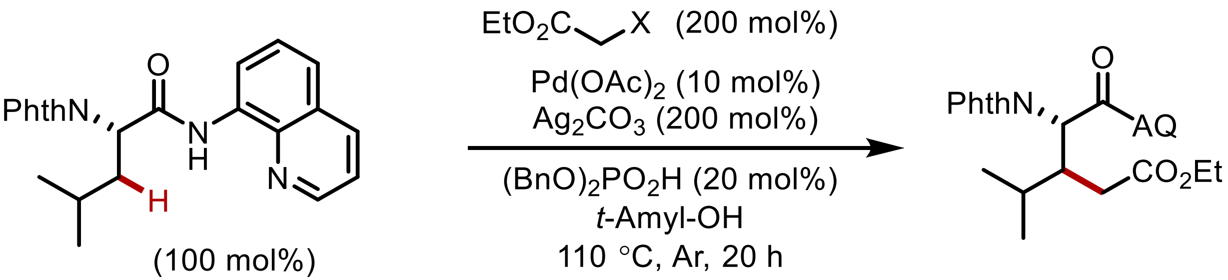
- Secondary C-H palladation should not be a problem
- Difficulty of OA and RE **(RI's problem)**
- Side reactions: esterification, E2…**(RI's problem)**

Better electrophile required

Chen, OL, 2010, 12, 3414
Chen, JACS, 2013, 135, 12135

DG Strategy-Bidentate-Alkylation

Chen



(100 mol%)

EtO_2C⌄X (200 mol%)

$Pd(OAc)_2$ (10 mol%)

Ag_2CO_3 (200 mol%)

$(BnO)_2PO_2H$ (20 mol%)

t-Amyl-OH

110 °C, Ar, 20 h

X = I, 59% Yield

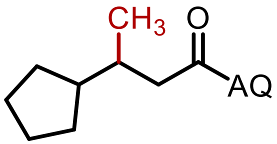
X = Br, 78% Yield

Ag+:

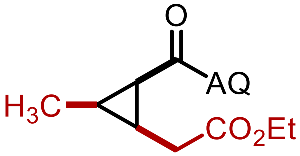
- Promotes OA via SN2
- Halide scavenger

$(BnO)_2PO_2H$:

- 1.0 equiv. gave lower yield
- Form soluble complex with Ag salt

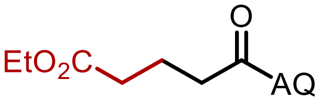


92%

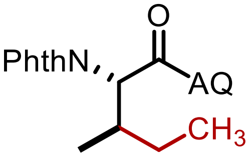


First w/ ester: 80%

second w/ MeI: 66%



90%



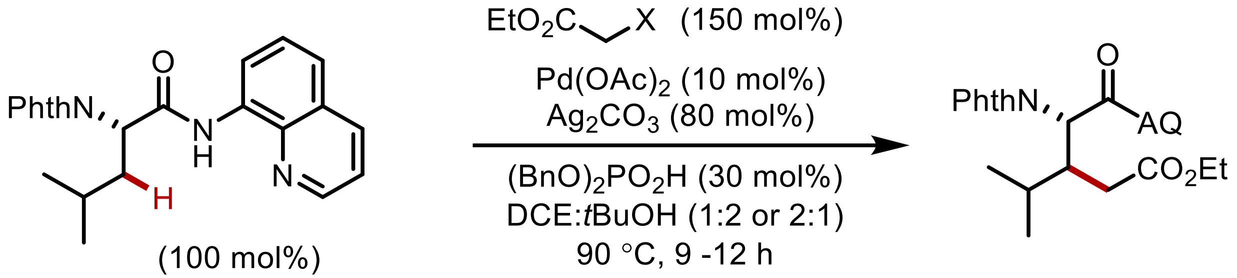
62%, dr ~8:1

Secondary alkyl halide didn’t work

Chen, JACS, 2013, 135, 12135

DG Strategy-Bidentate-Alkylation

Shi



EtO_2C X (150 mol%)

$Pd(OAc)_2$ (10 mol%)

Ag_2CO_3 (80 mol%)

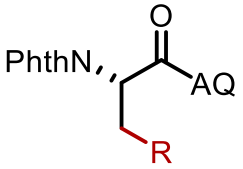
$(BnO)_2PO_2H$ (30 mol%)

DCE:*t*BuOH (1:2 or 2:1)

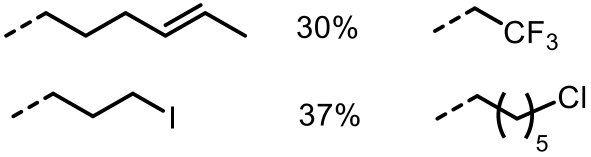
90 °C, 9 -12 h

X = I, 77% Yield
X = Br, 44% Yield

w/ alkyl iodide

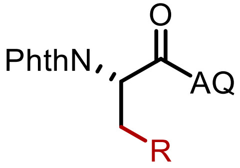


R =	
Me	55%
Et	79%
*n*Pr	84%
i$PrCH_2CH_2$	85%

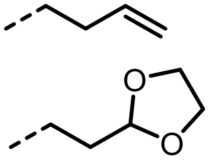


30%
54%
37%
84%

w/ alkyl bromide



R =	
Me	79%
Et	78%
*n*Pr	54%
i$PrCH_2CH_2$	43%



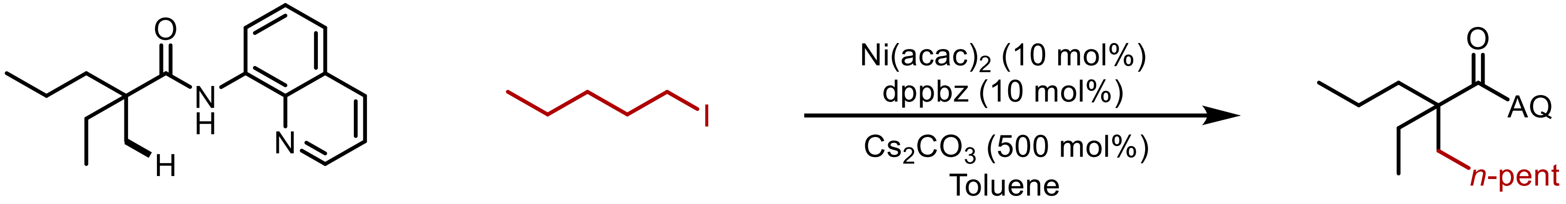
16%
54%

Secondary alkyl halide didn't work

Shi, Chem Sci, 2013, 4, 3906

DG Strategy-Bidentate-Alkylation

- **Ni catalysis**



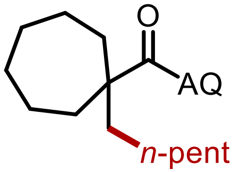
Ni(acac)$_2$ (10 mol%)
dppbz (10 mol%)
Cs_2CO_3 (500 mol%)
Toluene
150 °C, N_2, 24 h

(100 mol%)

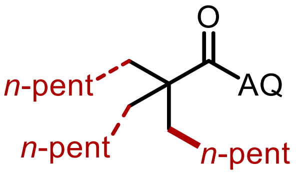
(500 mol%)

86% Yield

Amide scope



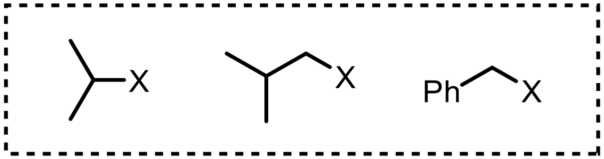
76%



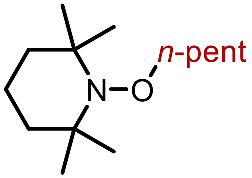
92% (mono:di:tri = 39:44:8)

- Quaternary α-carbon required
- No alkylation for secondary C-H

Alkyl halide scope



- Alkene, cyano tolerated
- Alkyl-Br and –Cl worked with CsI

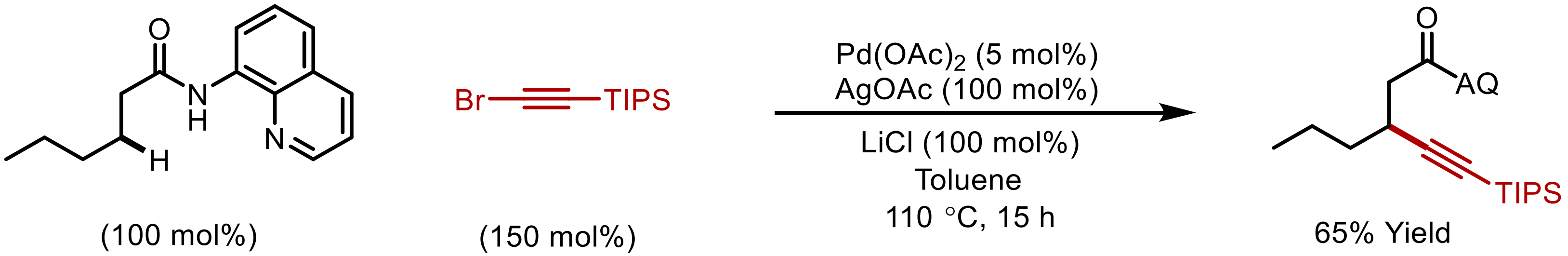


isolated

- TEMPO inhibit the reaction
- C-H activation as rds

Ge, JACS, 2014, 136, 1789

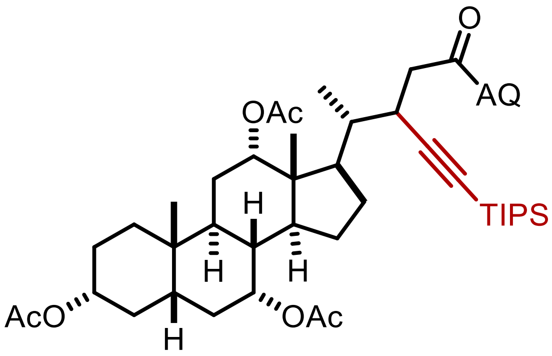
DG Strategy-Bidentate-Alkynylation



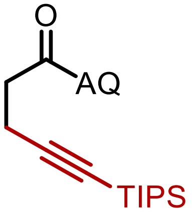
(100 mol%)

(150 mol%)

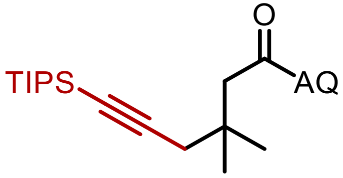
65% Yield



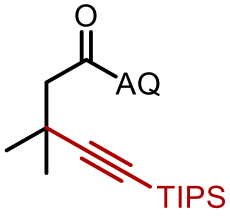
67%



7%



33%



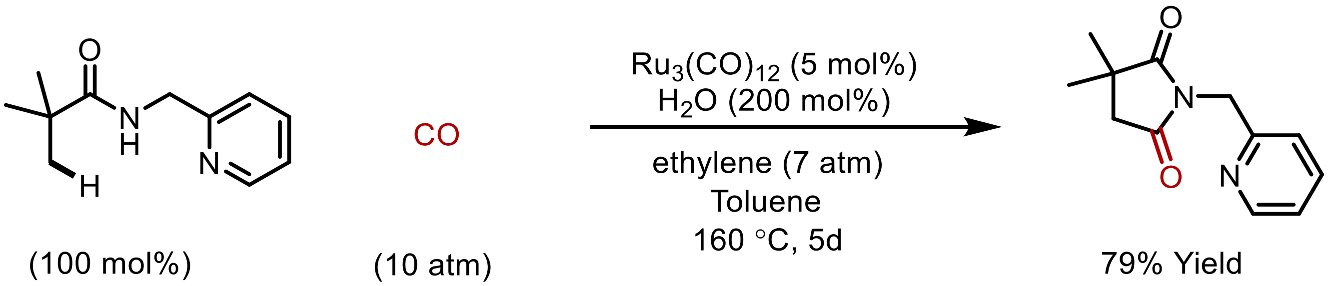
17%
(γ-product observed)

- -NHC_6F_5 not working as directing group
- Only TIPS acetylene bromide as electrophile
- Selective for secondary C-H bonds

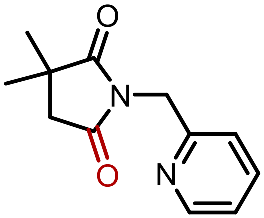
Chatani, JACS, 2011, 133, 12984

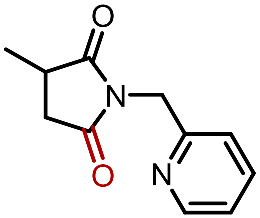
DG Strategy-Bidentate-Carbonylation

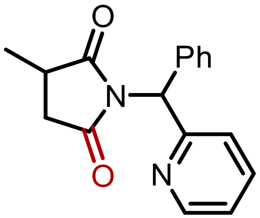
- **Ru catalysis**

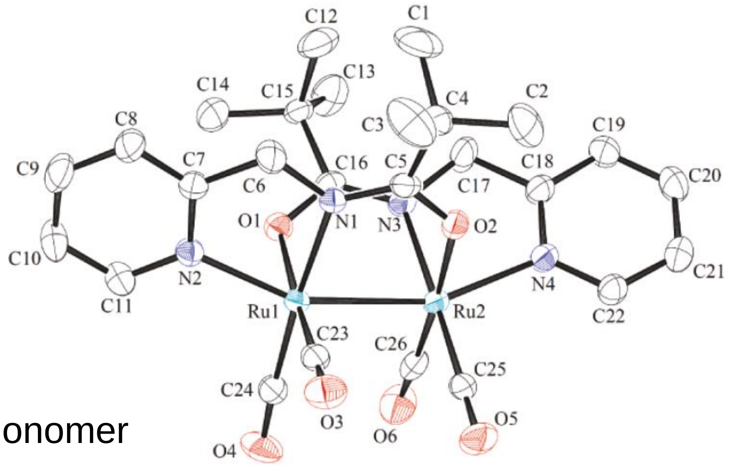


- No ethylene, no carbonylation
- Water increases the efficiency of the carbonylation
- Methyl C-H bond > methylene C-H bond


79%


14%


59%



Ru(I) dimer

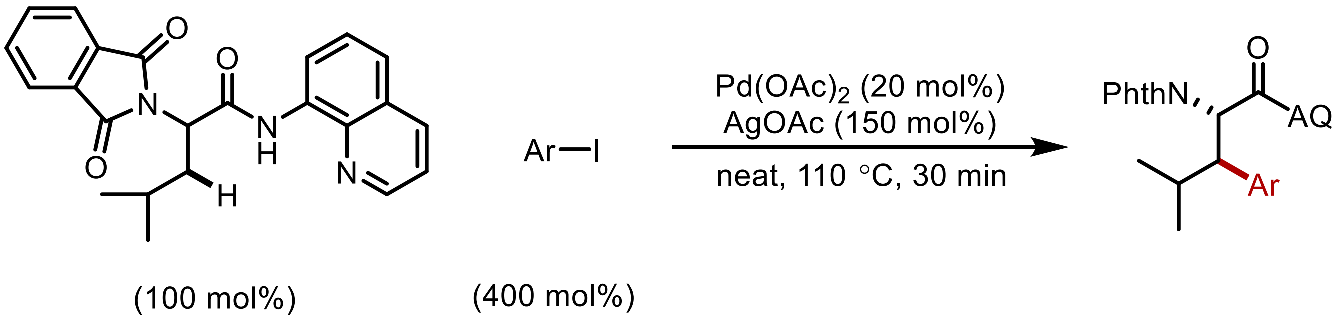
- Ru(I) dimer as catalyst resting state
- React with water to release CO_2 and Ru(II)-hydride monomer
- Ru(II)-hydride is in the catalytic cycle

Chatani, JACS, 2011, 133, 8070

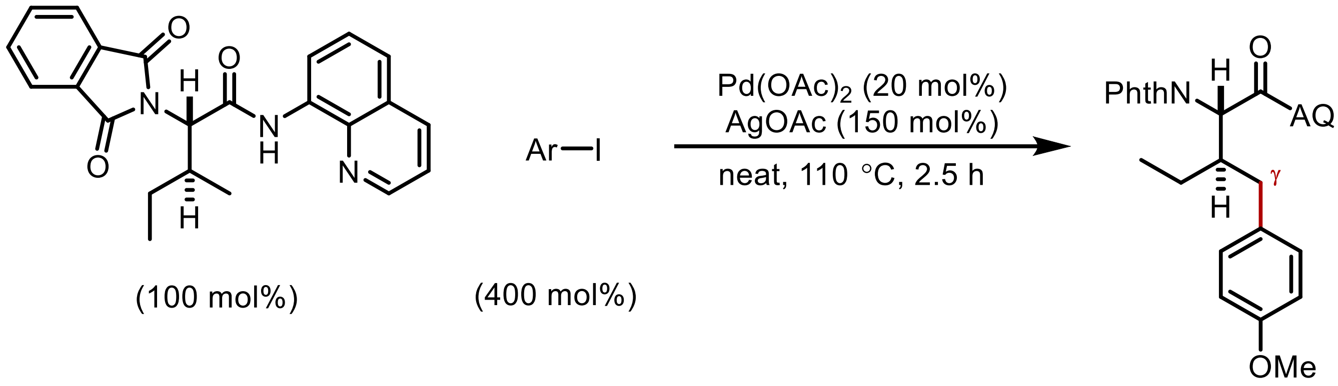
DG Strategy-Bidentate-Application

- **Unnatural amino acid**

Corey



Ar = C_6H_5, 86%
Ar = *p*-MeC_6H_4, 93%
Ar = *p*-$NO_2C_6H_4$, 79%
Ar = *m*-$CF_3C_6H_4$, 91%



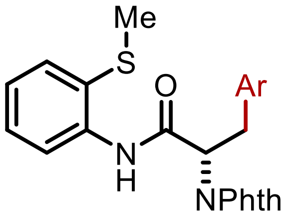
87% Yield

Corey, OL, 2006, 8, 3391

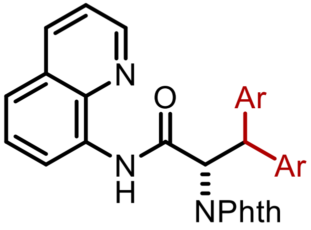
DG Strategy-Bidentate-Application

- **Unnatural amino acid**

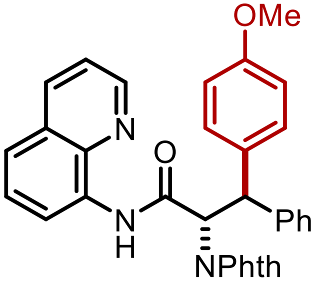
Daugulis



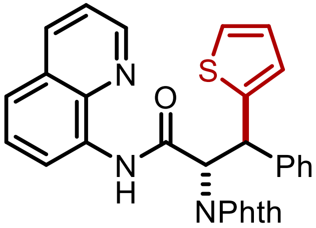
Ar = Ph	78%
Ar = p-OMeC$_6$H$_4$	68%
Ar = 2-naphthyl	60%
Ar = 2-benzothiophenyl	74%
Ar = 3-(1-methylindolyl)	61%
Ar = 3-azidophenyl	81%



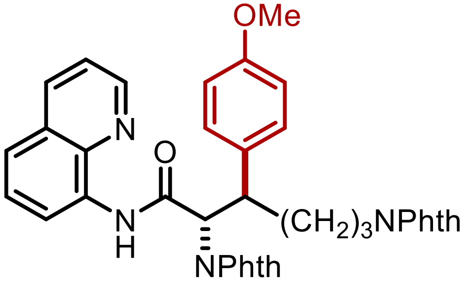
Ar = 3,4-(CH$_3$)$_2$C$_6$H$_3$	92%
Ar = 4-EtO$_2$CC$_6$H$_4$	84%



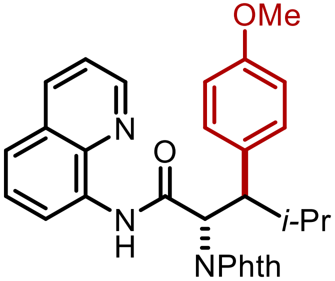
91%, dr 24:1



95%, dr >50:1



85%, dr 16:1



77%, dr >50:1

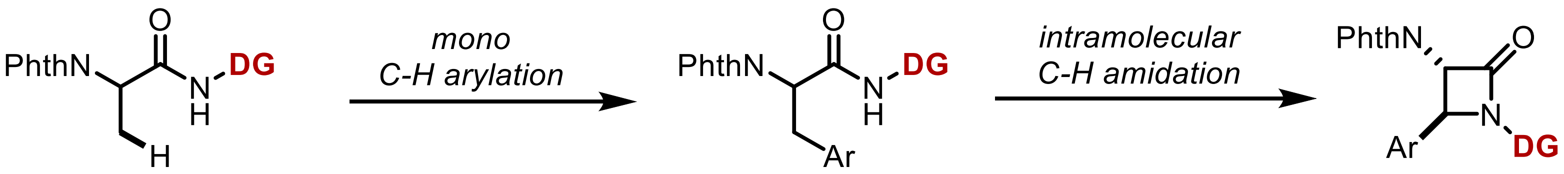
- *ee* eroded by less than 10%

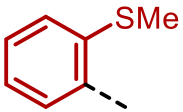
Daugulis, ACIE, 2012, 51, 5188

DG Strategy-Bidentate-Application

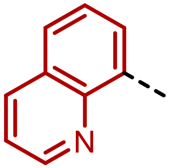
- **α-amino-β-lactams**

Designed Strategy



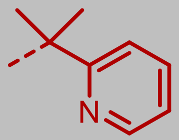
Auxiliary = 

- selective mono-arylation
- fragile in oxidative amidation

Auxiliary = 

- problematic mono-selectivity

New DG employed



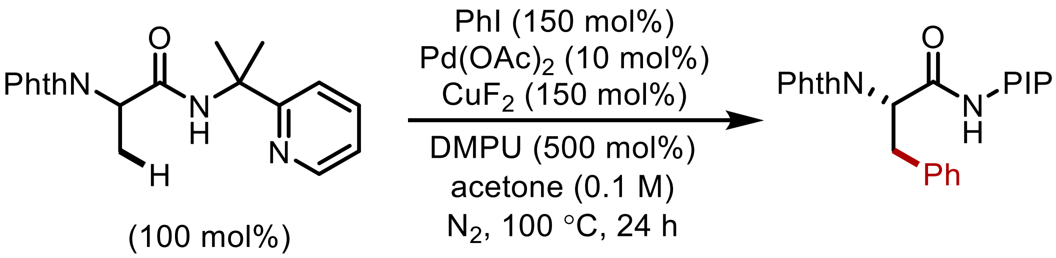
PIP

(pyridin-2-yl)isopropyl

Shi, ACIE, 2013, 52, 13588

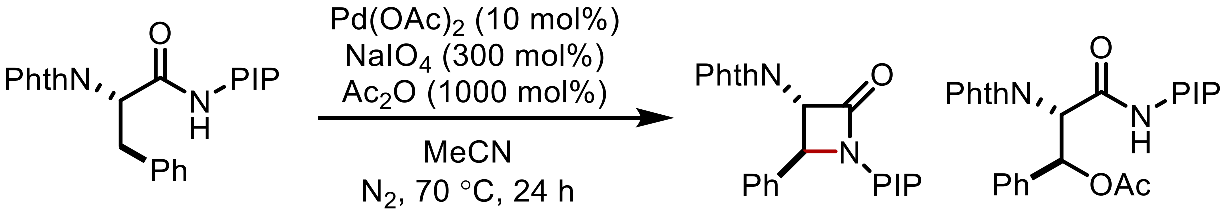
DG Strategy-Bidentate-Application

- **α-amino-β-lactams**



- CuF$_2$ as iodide scavenger
- Cu(OAc)$_2$ gave 43% yield
- DMPU improves selectivity

(81% Yield, 99% *ee*, mono:di 25:1)



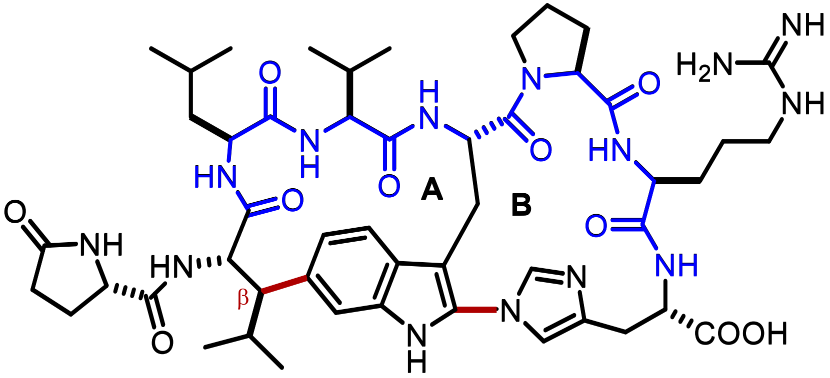
(74% Yield, amidation:acetoxylation 12.5:1)

- NaIO$_4$ good with FG, but not soluble
- NaIO$_4$/Ac$_2$O gives IO$_{4-n}$(OAc)$_{2n-1}$, soluble

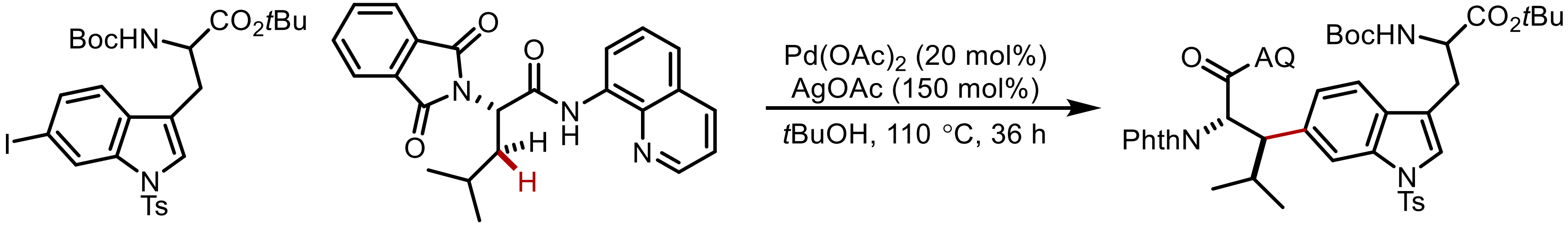
Shi, ACIE, 2013, 52, 13588

DG Strategy-Bidentate-Application

- **Total Synthesis of Celogentin C**



Celogentin C



Pd(OAc)$_2$ (20 mol%)
AgOAc (150 mol%)
*t*BuOH, 110 °C, 36 h

(100 mol%)

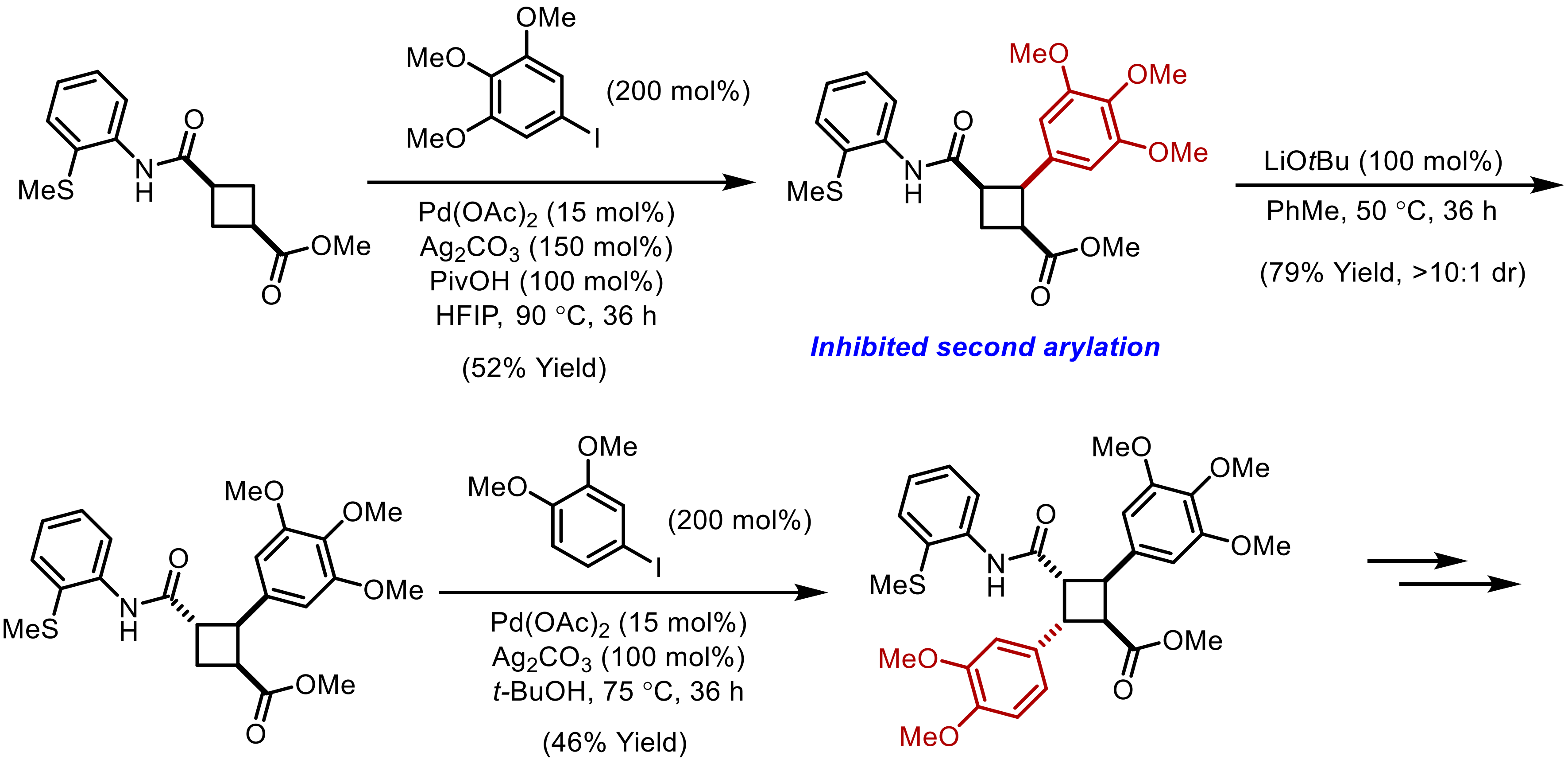
(200 mol%)

85% Yield, 4 gram scale
complete diastereoselectivity

Chen, ACIE, 2010, 49, 958

DG Strategy-Bidentate-Application

- **Total Synthesis of Piperarborenine B**



(200 mol%)

$Pd(OAc)_2$ (15 mol%)
Ag_2CO_3 (150 mol%)
PivOH (100 mol%)
HFIP, 90 °C, 36 h

(52% Yield)

Inhibited second arylation

LiO*t*Bu (100 mol%)

PhMe, 50 °C, 36 h

(79% Yield, >10:1 dr)

(200 mol%)

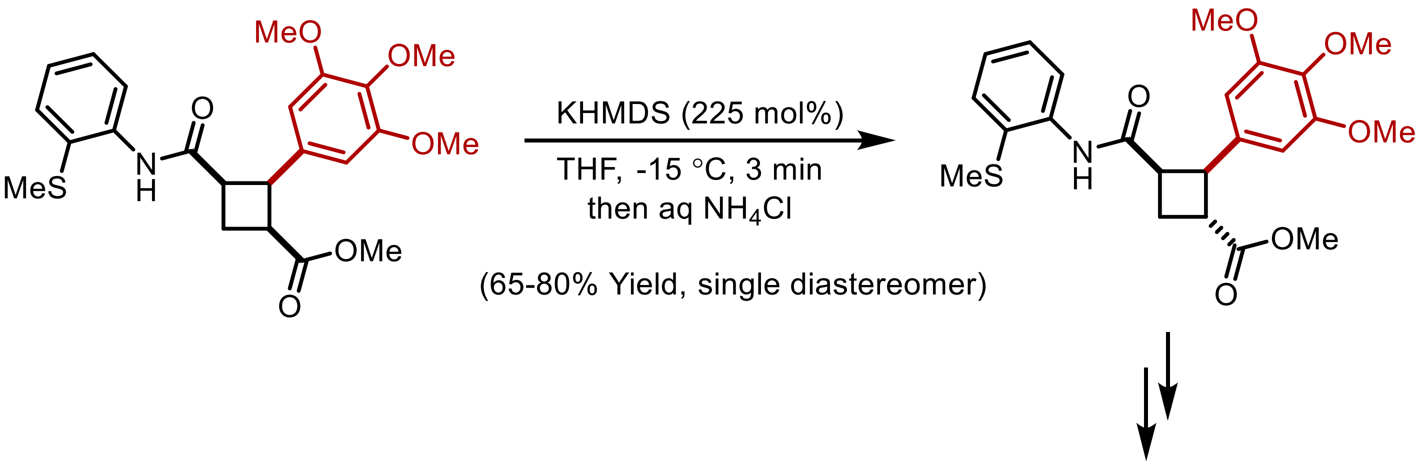
$Pd(OAc)_2$ (15 mol%)
Ag_2CO_3 (100 mol%)
t-BuOH, 75 °C, 36 h

(46% Yield)

Baran, JACS, 2011, 133, 19076

DG Strategy-Bidentate-Application

- **Total Synthesis of Piperarborenine B**

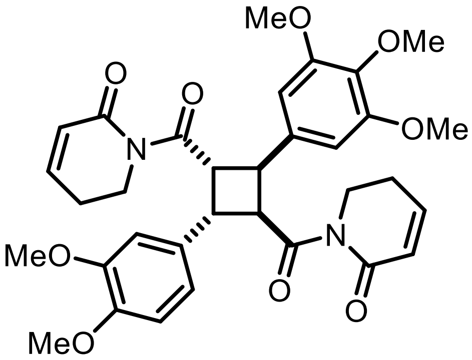


KHMDS (225 mol%)

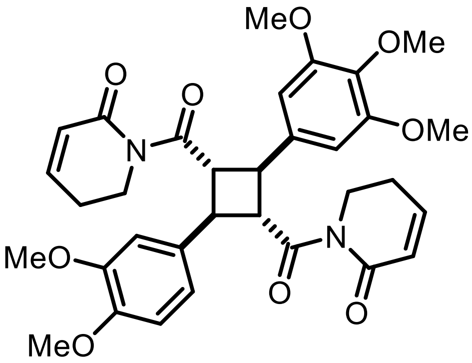
THF, -15 °C, 3 min

then aq NH_4Cl

(65-80% Yield, single diastereomer)



Piperarborenine B

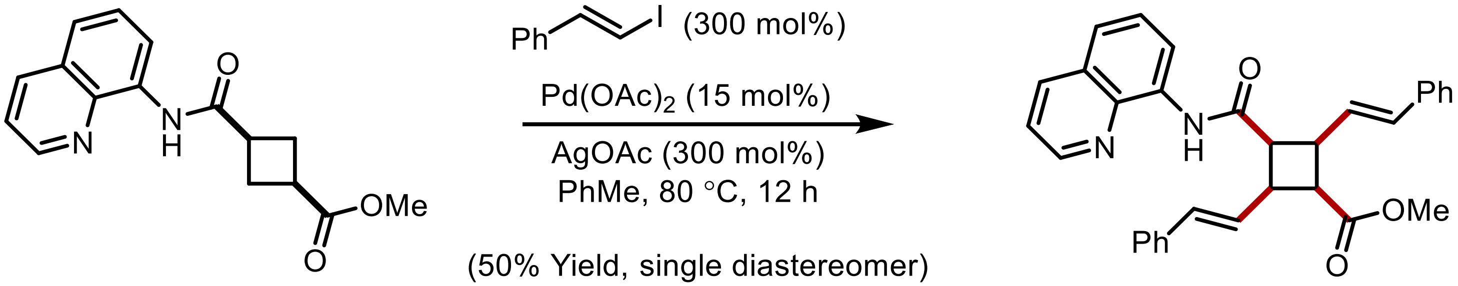


Piperarborenine D
(proposed structure)

Baran, JACS, 2011, 133, 19076

DG Strategy-Bidentate-Application

- **Pipercyclobutanamide A from sequential arylation and olefination**



(300 mol%)

Pd(OAc)$_2$ (15 mol%)

AgOAc (300 mol%)

PhMe, 80 °C, 12 h

(50% Yield, single diastereomer)

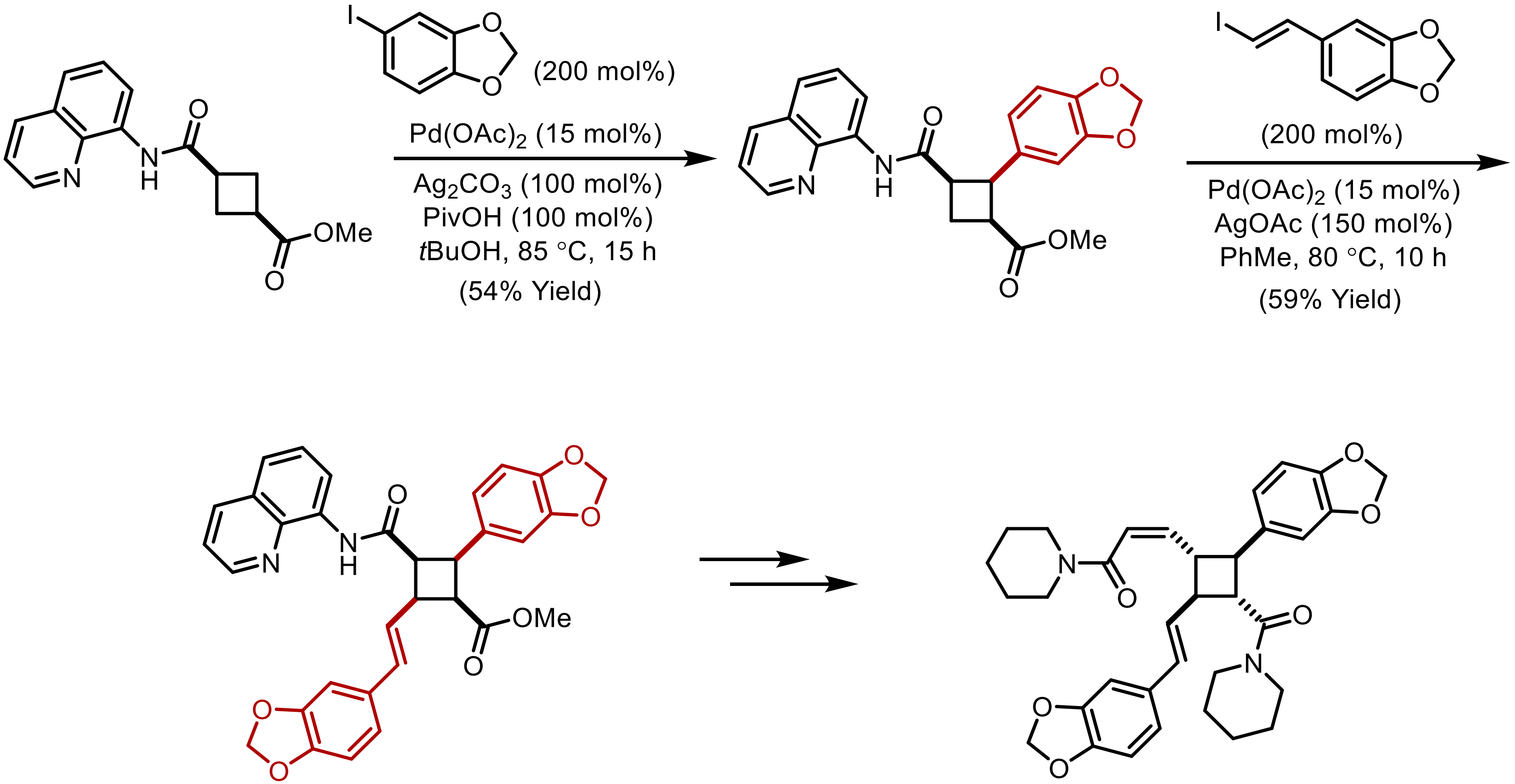
all-*cis*

second olefination not inhibited

Baran, ACIE, 2012, 51, 7507

DG Strategy-Bidentate-Application

- **Pipercyclobutanamide A from sequential arylation and olefination**



(200 mol%)

$Pd(OAc)_2$ (15 mol%)

Ag_2CO_3 (100 mol%)
PivOH (100 mol%)
*t*BuOH, 85 °C, 15 h

(54% Yield)

(200 mol%)

$Pd(OAc)_2$ (15 mol%)
AgOAc (150 mol%)
PhMe, 80 °C, 10 h

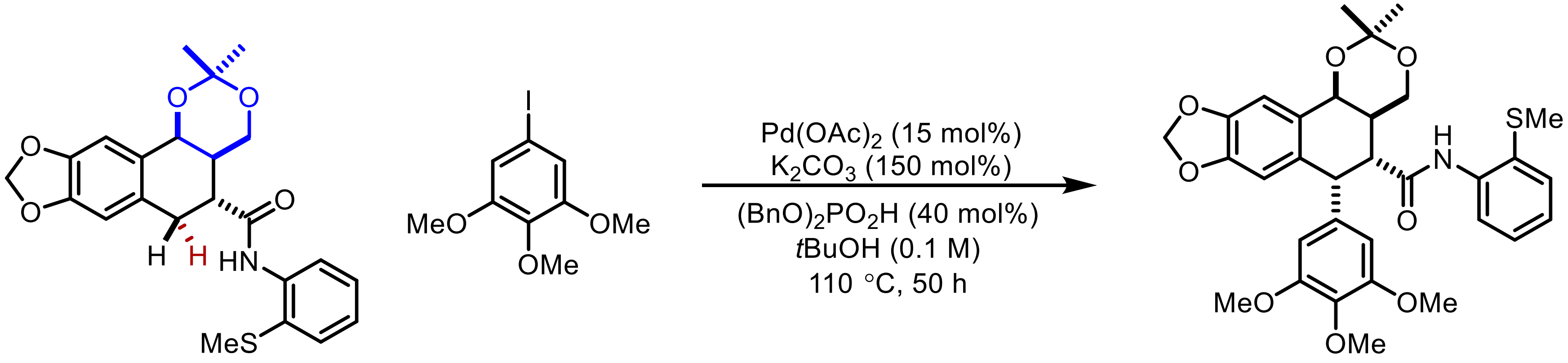
(59% Yield)

Pipercyclobutanamide A
(proposed structutre)

Baran, ACIE, 2012, 51, 7507

DG Strategy-Bidentate-Application

- **Total Synthesis of Podophyllotoxin**

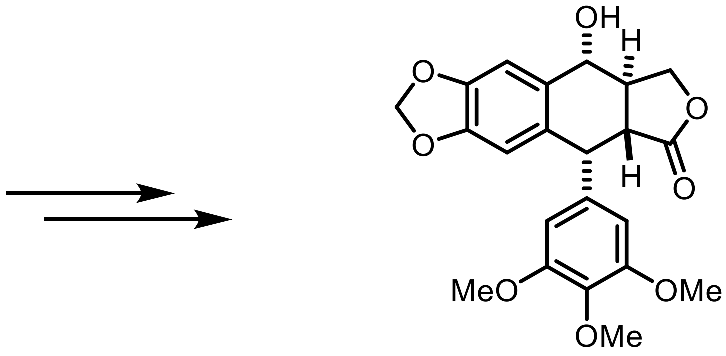


$Pd(OAc)_2$ (15 mol%)
K_2CO_3 (150 mol%)
$(BnO)_2PO_2H$ (40 mol%)
*t*BuOH (0.1 M)
110 °C, 50 h

(100 mol%)

(200 mol%)

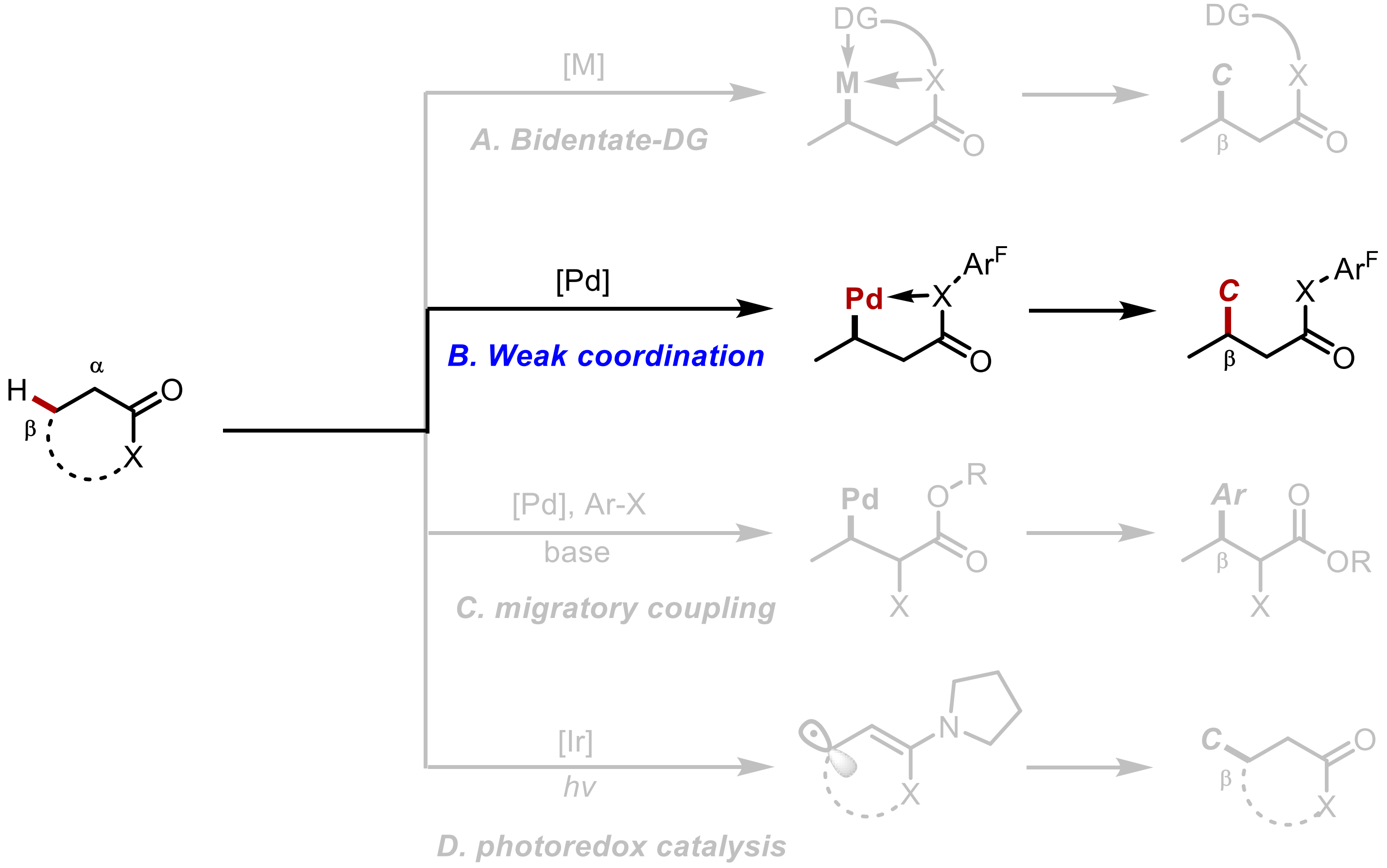
58% Yield



Podophyllotoxin

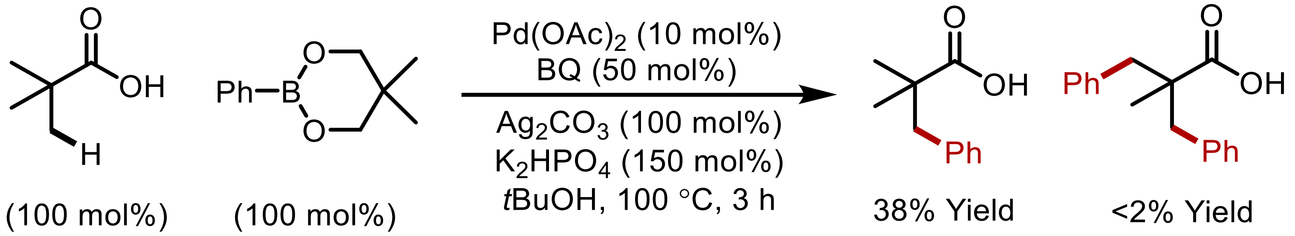
Maimone, ACIE, 2014, 53, 3115

Content


H
α
O
β
X
[M]
A. Bidentate-DG
DG
M
X
O
DG
C
X
β
O
[Pd]
B. Weak coordination
Pd
X
Ar^F
O
C
X
Ar^F
β
O
[Pd], Ar-X
base
C. migratory coupling
Pd
O
R
O
X
Ar
O
β
OR
X
[Ir]
hv
D. photoredox catalysis
N
X
C
β
O
X

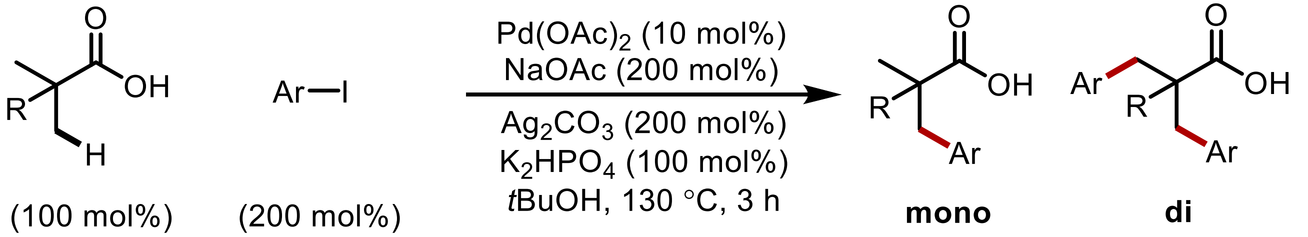
DG Strategy-Monodentate

- **Carboxylic acid as DG**

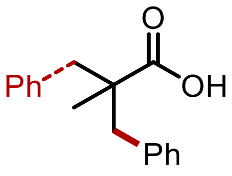


$Pd(OAc)_2$ (10 mol%)
BQ (50 mol%)
Ag_2CO_3 (100 mol%)
K_2HPO_4 (150 mol%)
*t*BuOH, 100 °C, 3 h

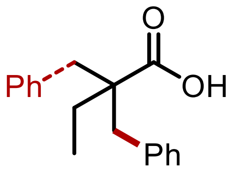
- In-situ generated K salt
- Low efficiency
- Pd(0)/Pd(II) proposed



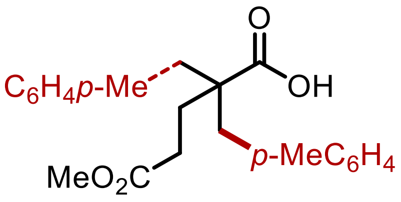
$Pd(OAc)_2$ (10 mol%)
NaOAc (200 mol%)
Ag_2CO_3 (200 mol%)
K_2HPO_4 (100 mol%)
*t*BuOH, 130 °C, 3 h



70%
(mono:di 5:2)



72%
(mono:di 4:2)



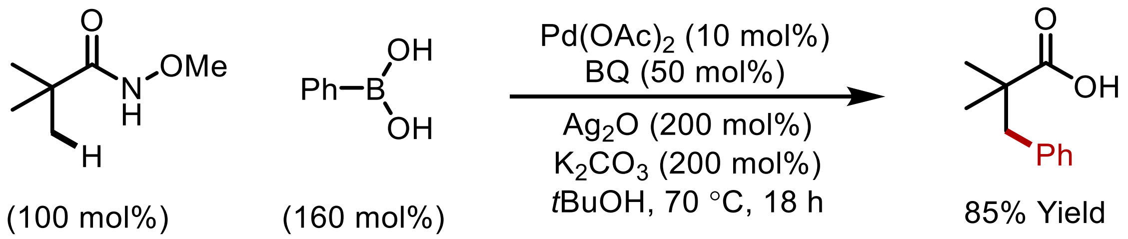
43%
(mono:di 5:1)

- Ag as iodide scavenger
- NaOAc also helps
- Pd(II)/Pd(IV) proposed
- Methyl C-H only
- α-proton not tolerated

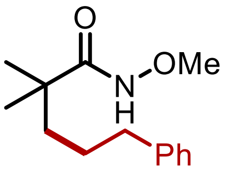
Yu, JACS, 2007, 129, 3510

DG Strategy-Monodentate

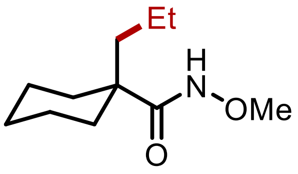
- **Stronger DG**



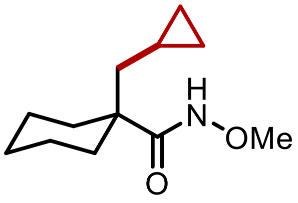
- 2,2,5,5-tetramethyl THF as solvent



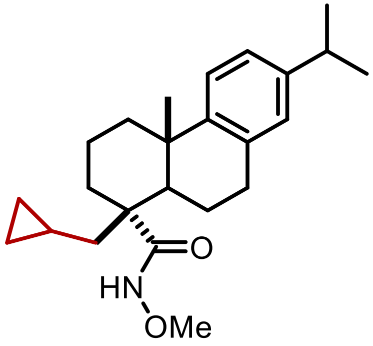
65%



60%



63%



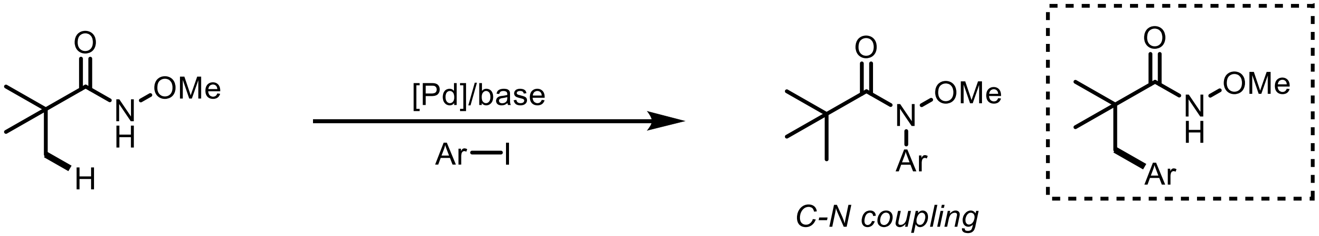
52%

- Pd(0)/Pd(II) proposed
- Air (20 atm) can be used as oxidant
- Methyl C-H only
- α-proton not tolerated

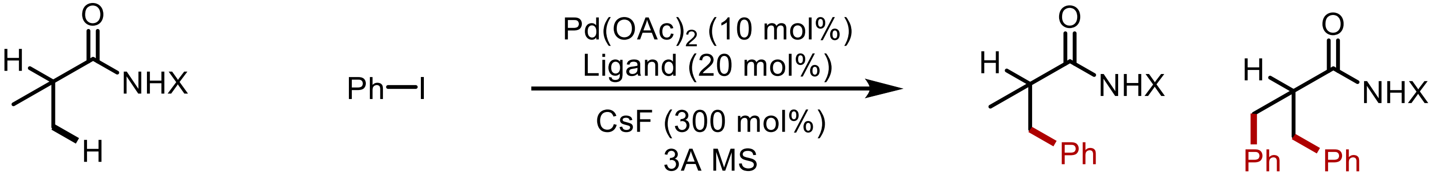
Yu, JACS, 2008, 130, 7190

DG Strategy-Monodentate

- **Acidic amide as DG**

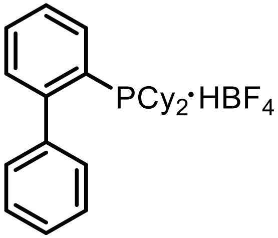


C-N coupling

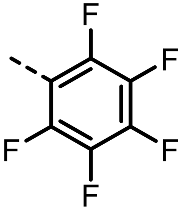
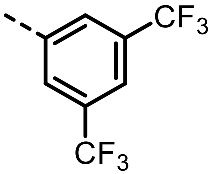


Pd($OAc)_2$ (10 mol%)
Ligand (20 mol%)
CsF (300 mol%)
3A MS
Toluene, 100 °C, 24 h

(100 mol%) (300 mol%)



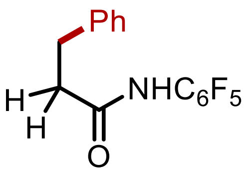
Cy-JohnPhos

X =		34%	54%
		18%	8%

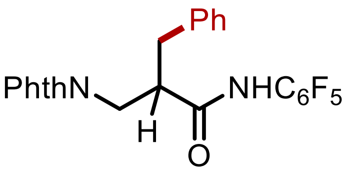
Yu, JACS, 2009, 131, 9886

DG Strategy-Monodentate

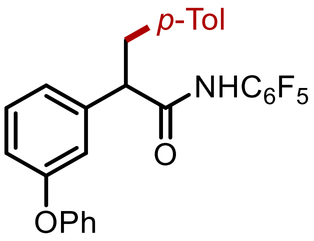
- **Acidic amide as DG**



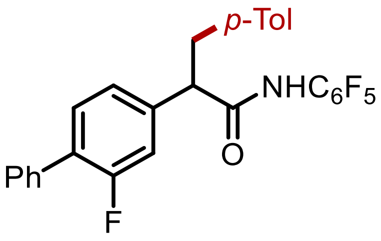
58%



64%

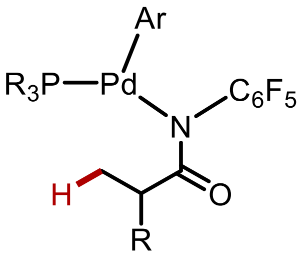


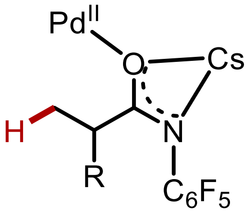
68%



72%

- α-proton tolerated under weaker CsF
- Methyl C-H only
- No C-N cross coupling found

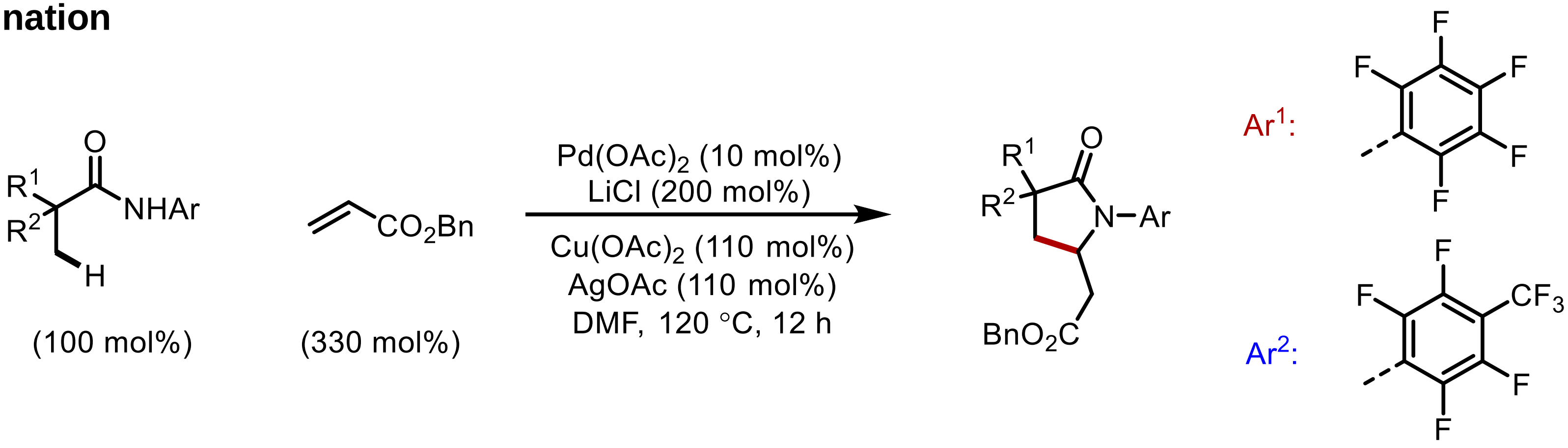


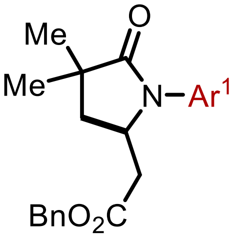


Yu, JACS, 2009, 131, 9886

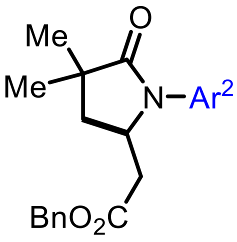
DG Strategy-Monodentate

- **Olefination**

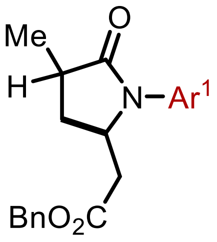




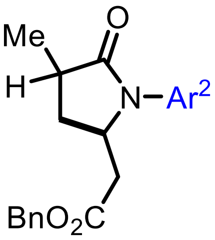
87%



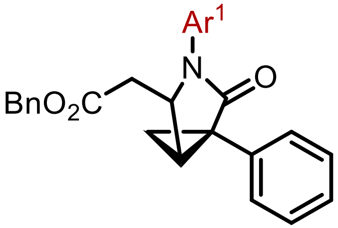
94%



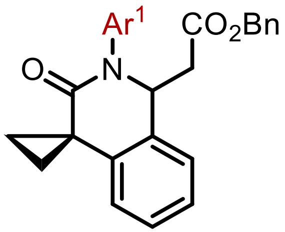
55%



91%

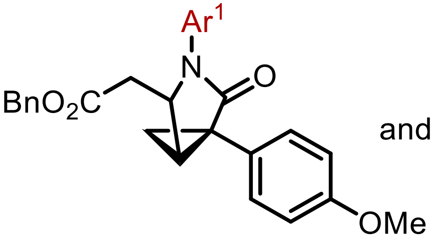


and

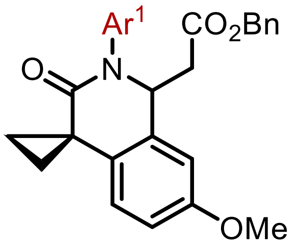


71%

18%



and



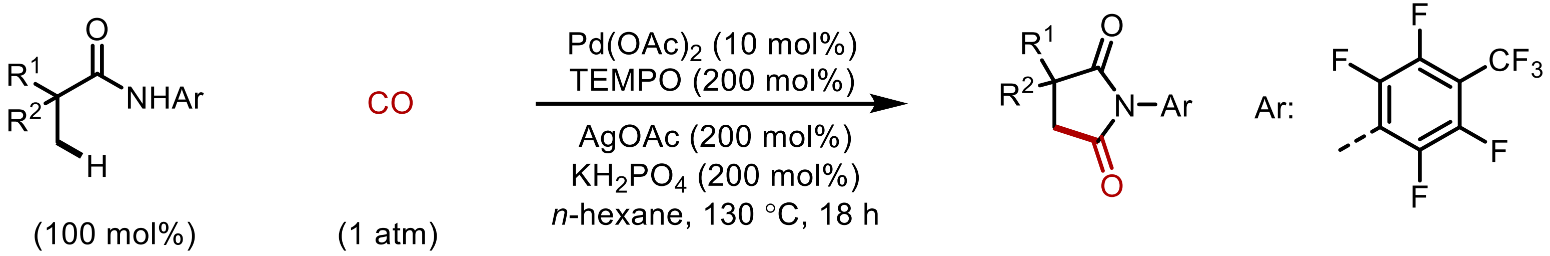
51%

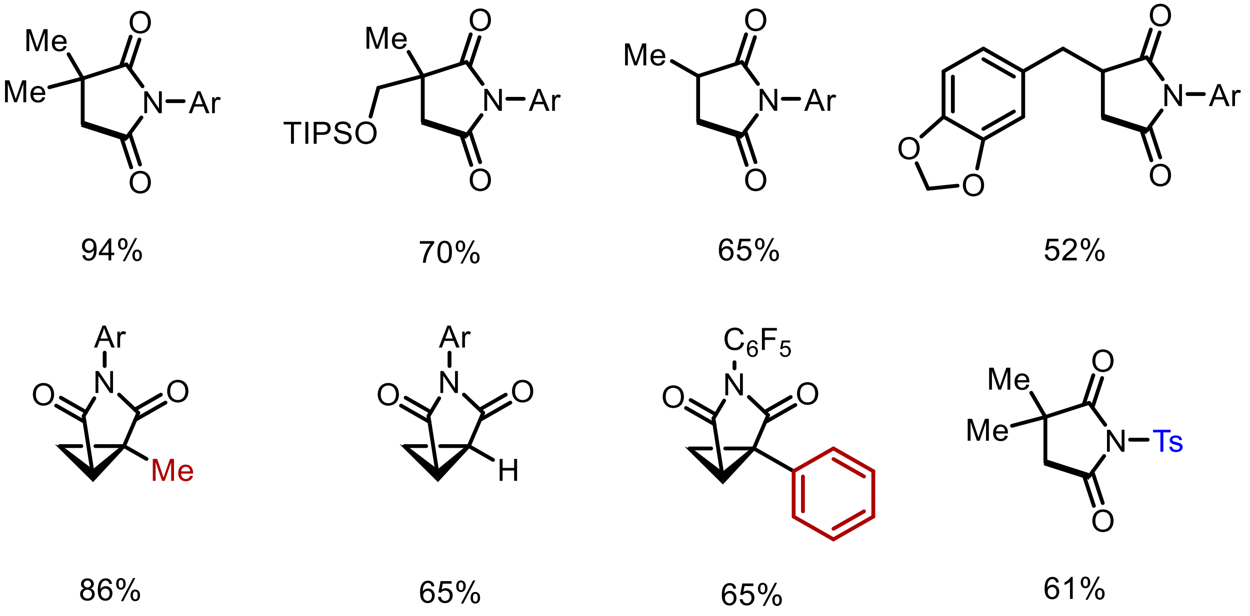
33%

Yu, JACS, 2010, 132, 3680

DG Strategy-Monodentate

- **Carbonylation**





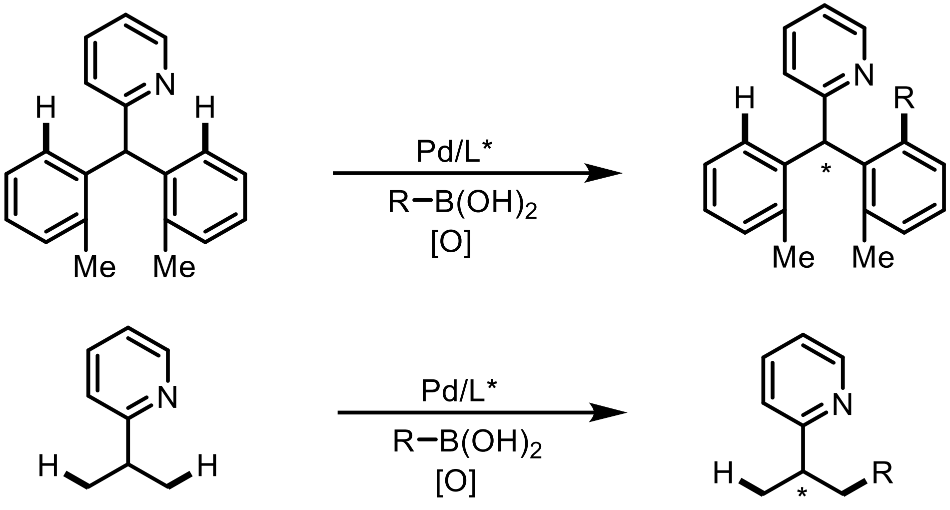
- In this case, cyclopropyl methylene C-H > methyl C-H and sp2 C-H

Yu, JACS, 2010, 132, 17378

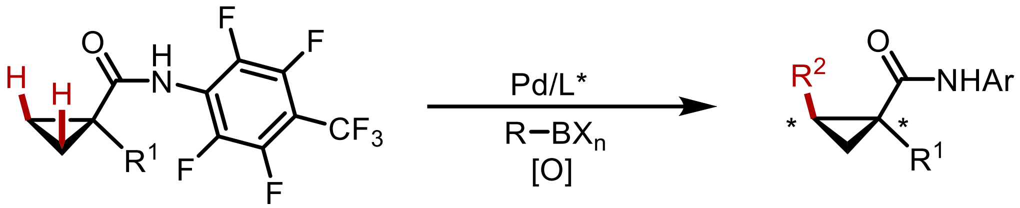
DG Strategy-Monodentate

- **Enantioselective C-H activation of cyclopropanes**

Previous work



This work

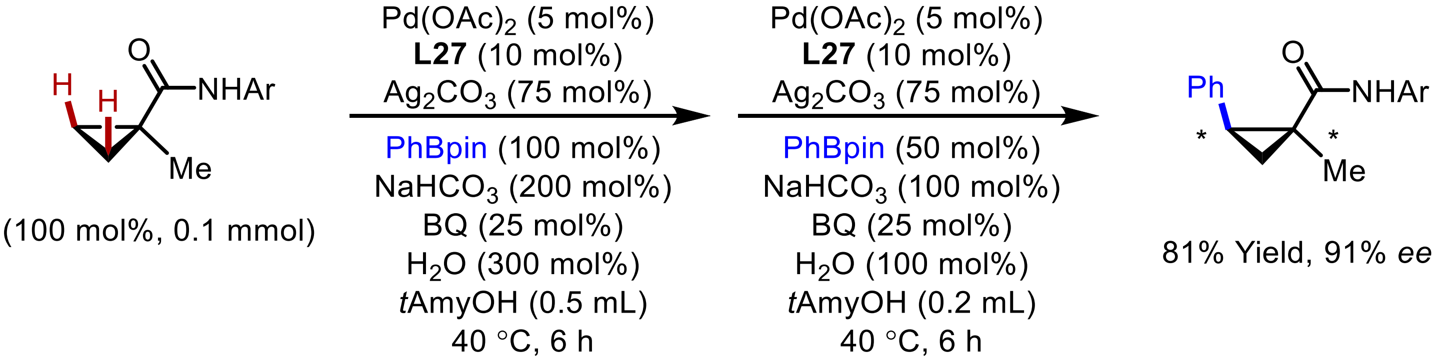


- special acidic methylene
- desymmetrization?

Yu, JACS, 2011, 133, 19598

DG Strategy-Monodentate

- **Enantioselective C-H activation of cyclopropanes**
  - First use of amino acid ligand in the area

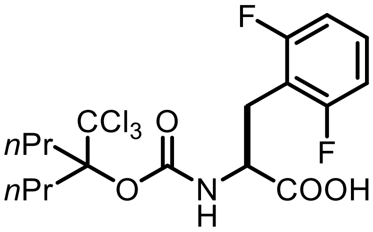


(100 mol%, 0.1 mmol)

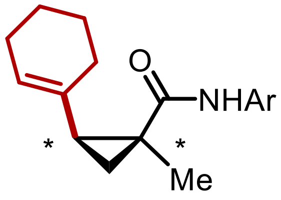
$Pd(OAc)_2$ (5 mol%)
L27 (10 mol%)
Ag_2CO_3 (75 mol%)
PhBpin (100 mol%)
$NaHCO_3$ (200 mol%)
BQ (25 mol%)
H_2O (300 mol%)
*t*AmyOH (0.5 mL)
40 °C, 6 h

$Pd(OAc)_2$ (5 mol%)
L27 (10 mol%)
Ag_2CO_3 (75 mol%)
PhBpin (50 mol%)
$NaHCO_3$ (100 mol%)
BQ (25 mol%)
H_2O (100 mol%)
*t*AmyOH (0.2 mL)
40 °C, 6 h

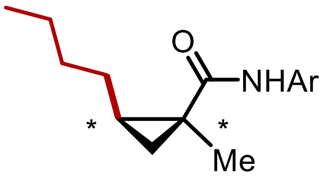
81% Yield, 91% *ee*



L27



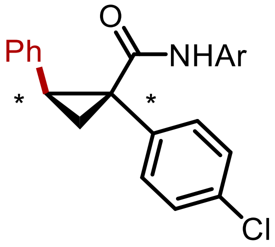
60% Yield, 82% *ee*



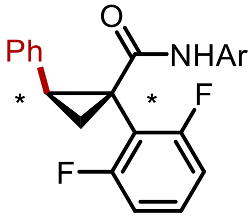
49% Yield, 62% *ee*

Take-home message

Don’t give up!



51% Yield, 89% *ee*

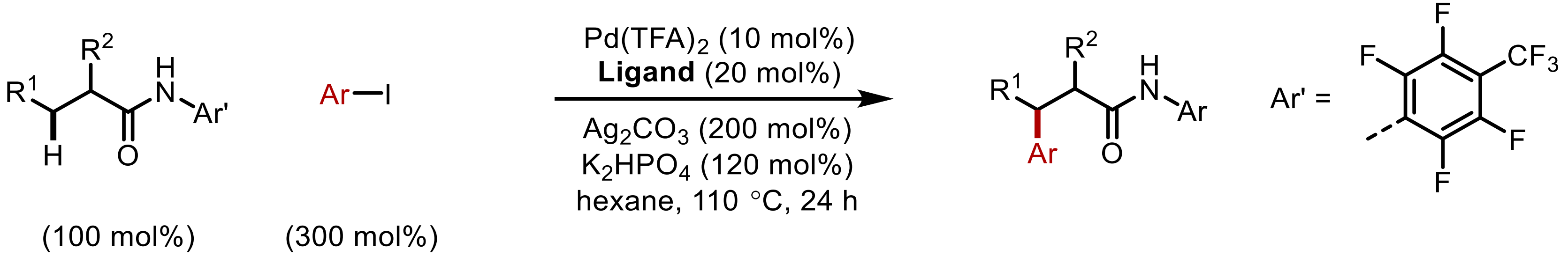


70% Yield, 91% *ee*

Yu, JACS, 2011, 133, 19598

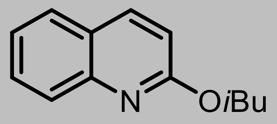
DG Strategy-Monodentate

- **Ligand-enabled 'real' methylene C-H activation**



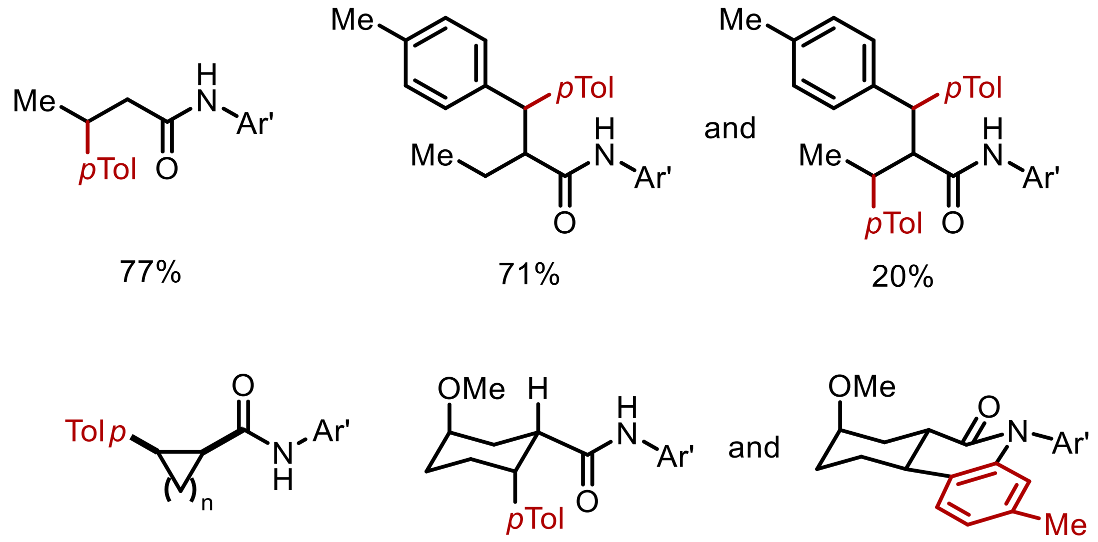
$Pd(TFA)_2$ (10 mol%)
Ligand (20 mol%)
Ag_2CO_3 (200 mol%)
K_2HPO_4 (120 mol%)
hexane, 110 °C, 24 h

(100 mol%) (300 mol%)



Ligand

- steric bulk (not too bulk)
- electron-donating
- singly bound fashion



77% 71% 20%

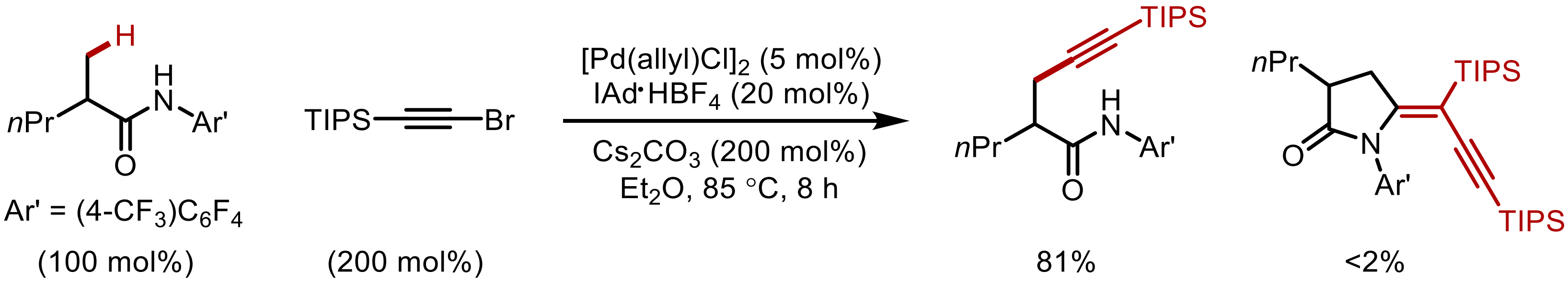
n = 1, 86%
n = 2, 92%, mono:di 1:8
n = 3, 71%, mono:di 7:1

72% 12%

Yu, JACS, 2012, 134, 18570

DG Strategy-Monodentate

- **Alkynylation**



$[Pd(allyl)Cl]_2$ (5 mol%)
IAd·HBF_4 (20 mol%)
Cs_2CO_3 (200 mol%)
Et_2O, 85 °C, 8 h

Ar' = (4-CF_3)C_6F_4

(100 mol%)

(200 mol%)

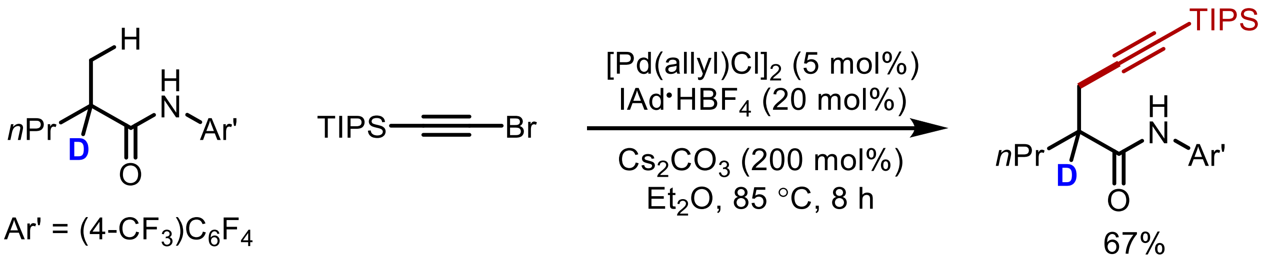
81%

<2%

Scope:

- α-proton required (pivalic acid gave low yield)
- Methyl C-H only

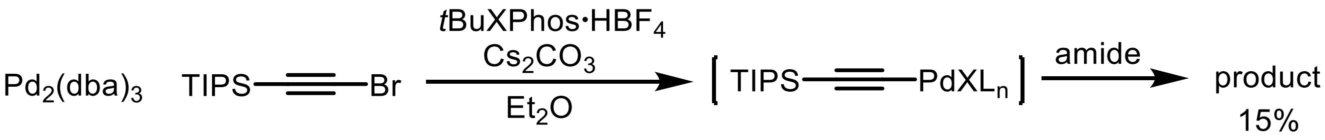
Bulkiness of Pd(II)-alkynyl species



$[Pd(allyl)Cl]_2$ (5 mol%)
IAd·HBF_4 (20 mol%)
Cs_2CO_3 (200 mol%)
Et_2O, 85 °C, 8 h

Ar' = (4-CF_3)C_6F_4

67%



$Pd_2(dba)_3$ TIPS—≡—Br $\xrightarrow[Et_2O]{tBuXPhos·HBF_4,\ Cs_2CO_3}$ [TIPS—≡—$PdXL_n$] $\xrightarrow{amide}$ product

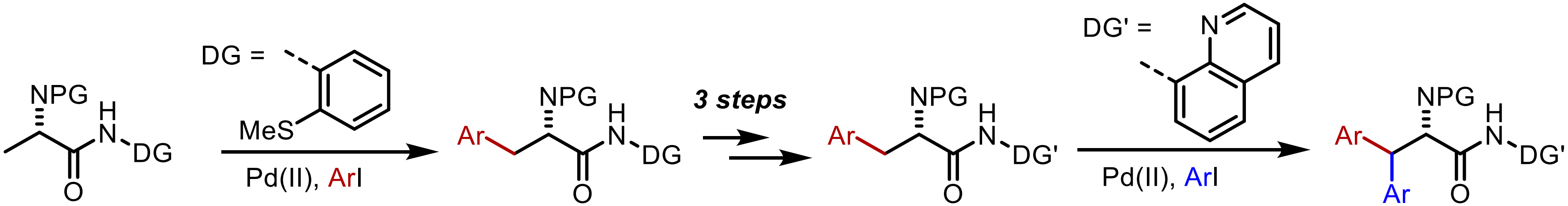
15%

Yu, JACS, 2013, 135, 3387

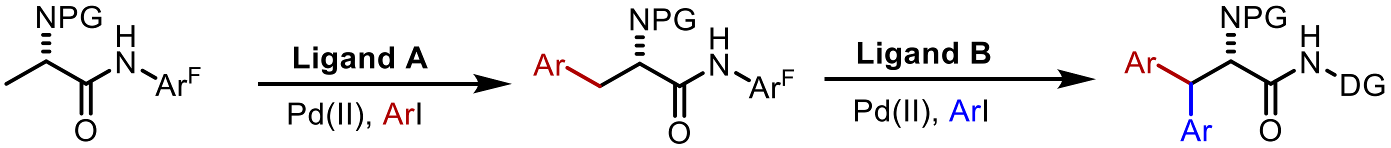
DG Strategy-Monodentate

- **β,β'-hetero-diarylation of amino acid**

DG-controlled route



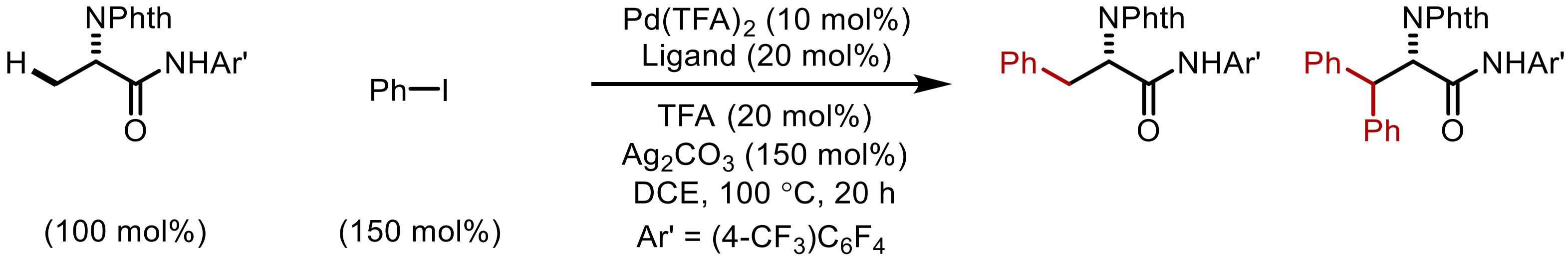
Ligand-controlled route

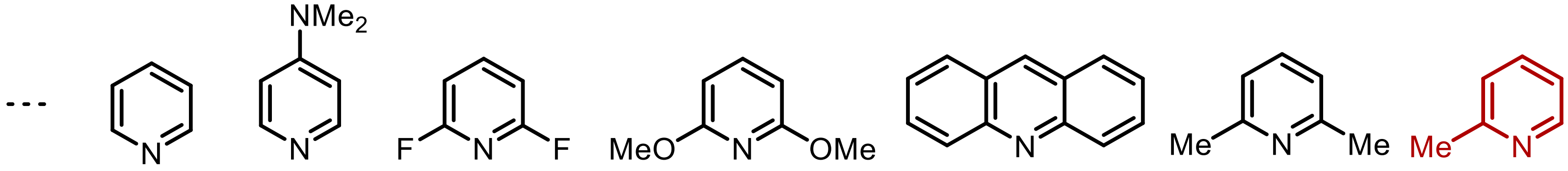


Yu, Science, 2014, 343, 1216

DG Strategy-Monodentate

- **β,β’-hetero-diarylation of amino acid**



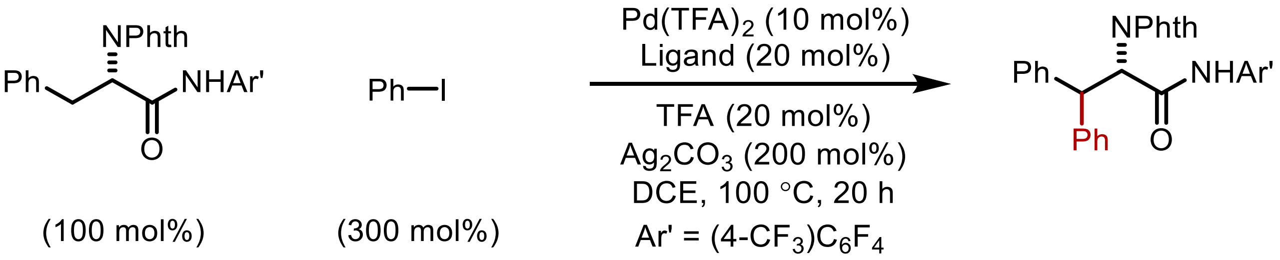


mono:	47%	29%	52%	65%	87%	88%	91%	94%
di:	1%	0%	0%	2%	13%	12%	9%	2%

Yu, Science, 2014, 343, 1216

DG Strategy-Monodentate

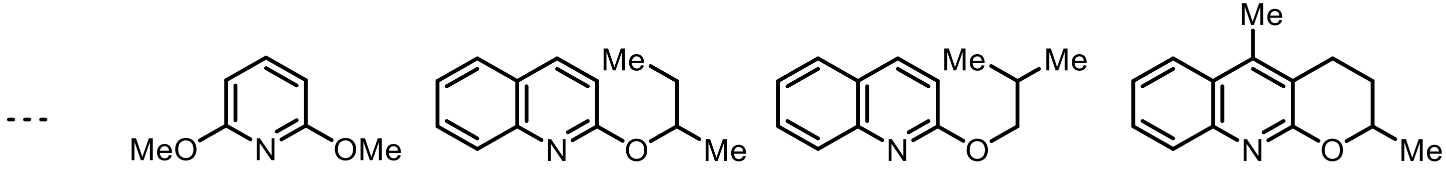
- **β,β'-hetero-diarylation of amino acid**



(100 mol%) (300 mol%)

Pd(TFA)$_2$ (10 mol%)
Ligand (20 mol%)

TFA (20 mol%)
Ag$_2$CO$_3$ (200 mol%)
DCE, 100 °C, 20 h
Ar' = (4-CF$_3$)C$_6$F$_4$



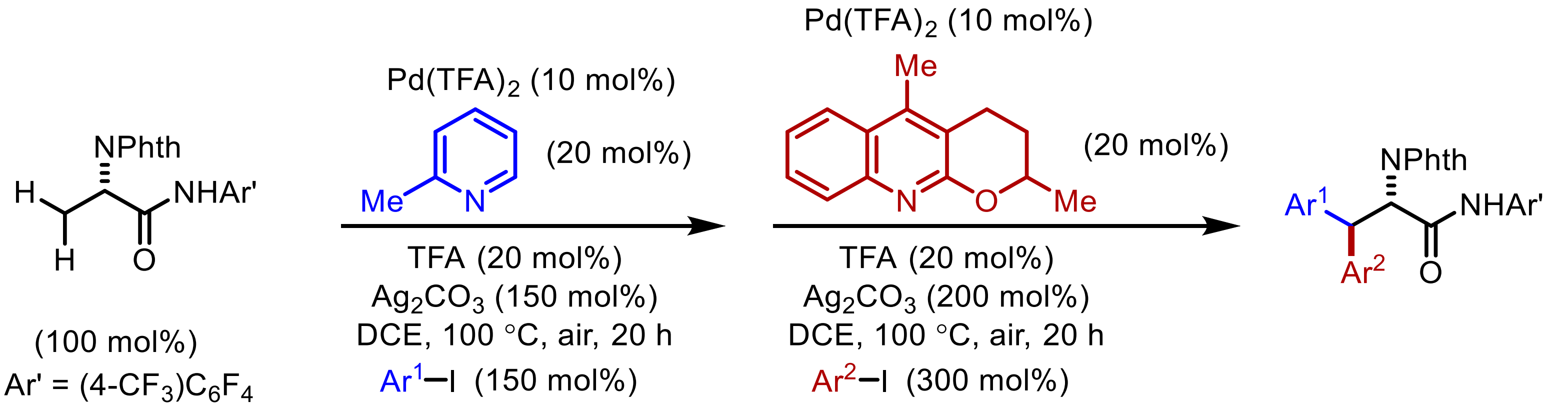
4% 47% 55% 67% 92%

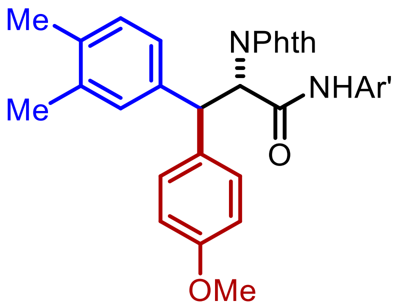
- More 'forcing' conditions than mono-arylation
- fixed conformation facilitates conjugation

Yu, Science, 2014, 343, 1216

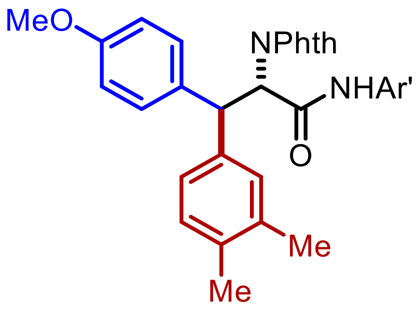
DG Strategy-Monodentate

- **β,β'-hetero-diarylation of amino acid**





59%, dr > 20:1



60%, dr 16:1

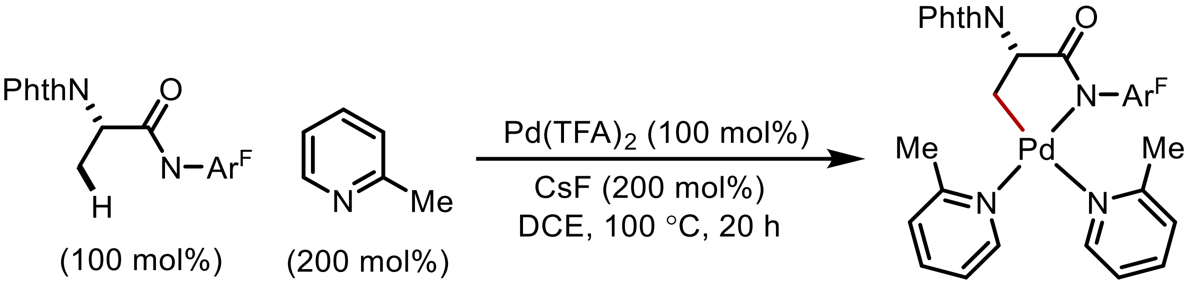
One pot reaction

- Biaryl formation detected
- Remaining Ar^1-I outcompeted by Ar^2-I
- no loss in ee

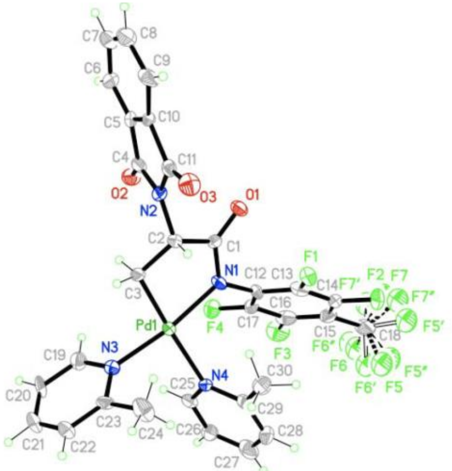
Yu, Science, 2014, 343, 1216

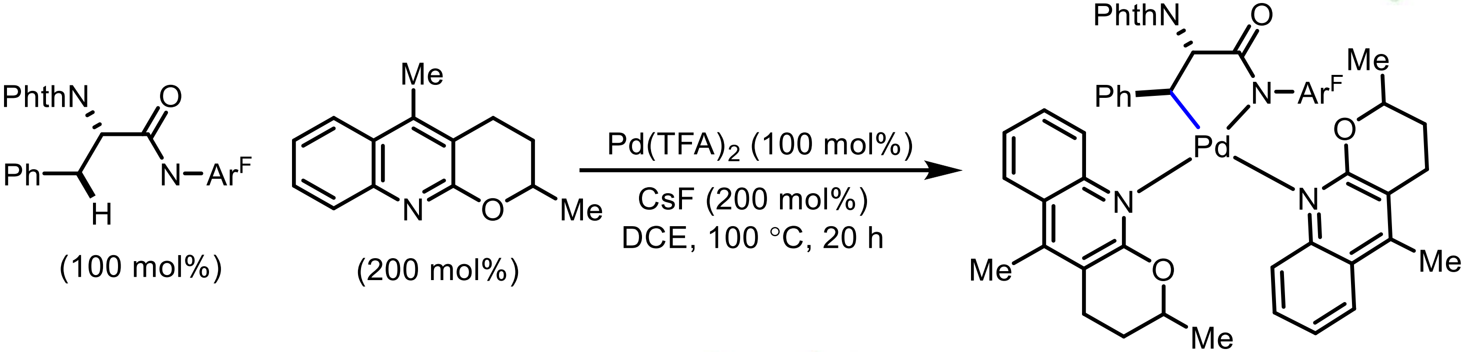
DG Strategy-Monodentate

- **β,β’-hetero-diarylation of amino acid**

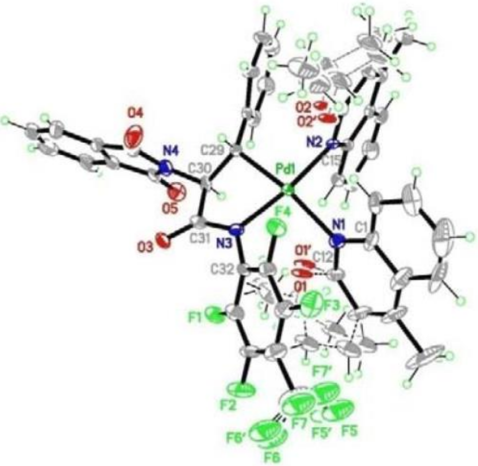


intermediate A





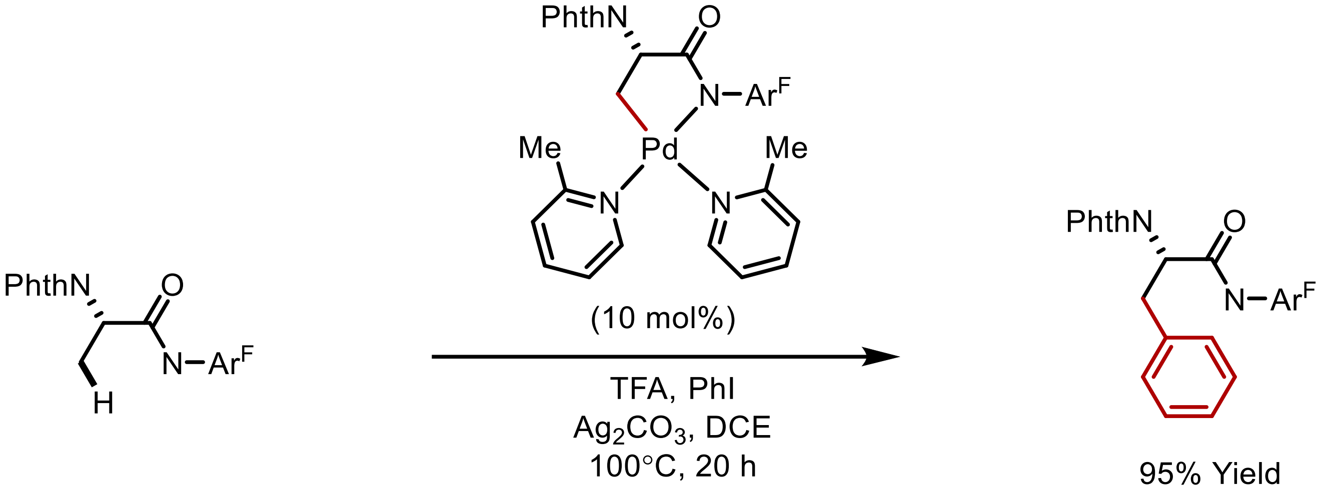
intermediate B

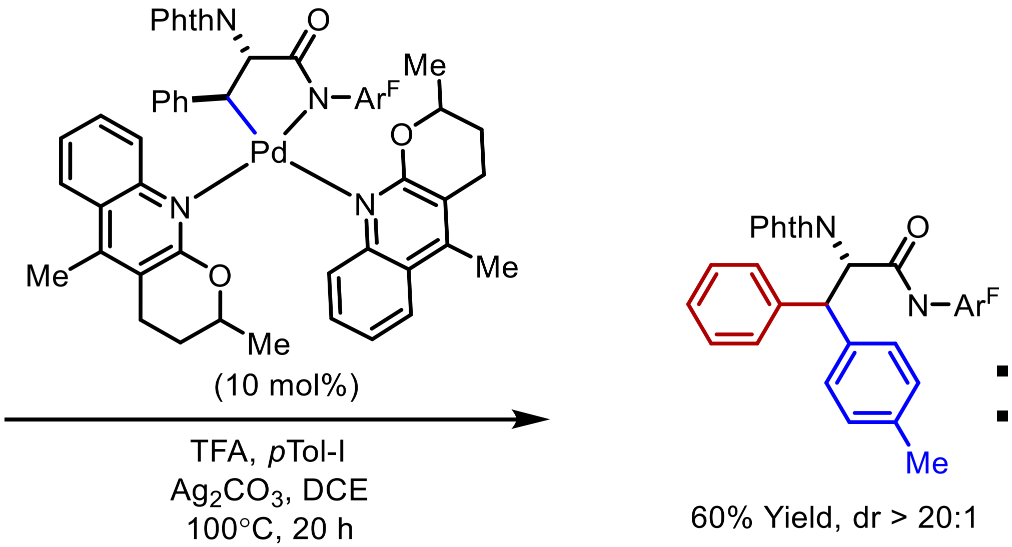


Yu, Science, 2014, 343, 1216

DG Strategy-Monodentate

- **β,β'-hetero-diarylation of amino acid**





- Pd(II)/Pd(IV) proposed
- TFA facilitates dissociation of one ligand

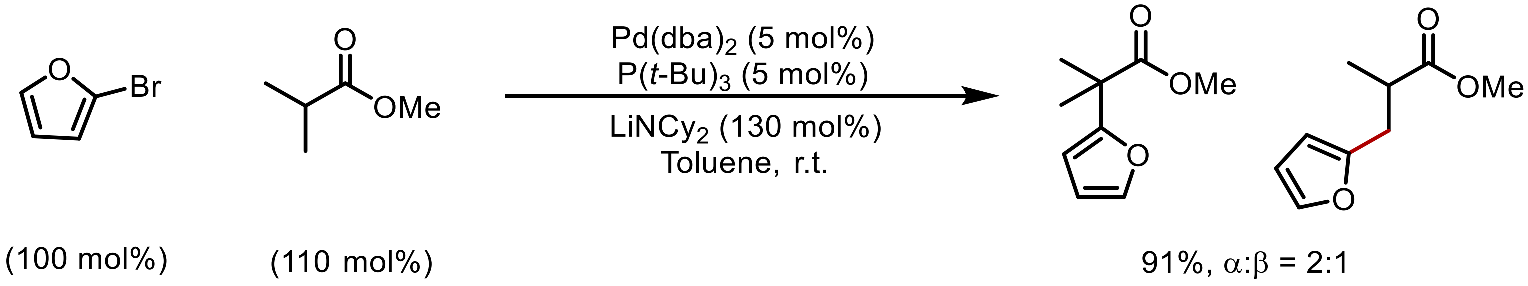
Yu, Science, 2014, 343, 1216

Content

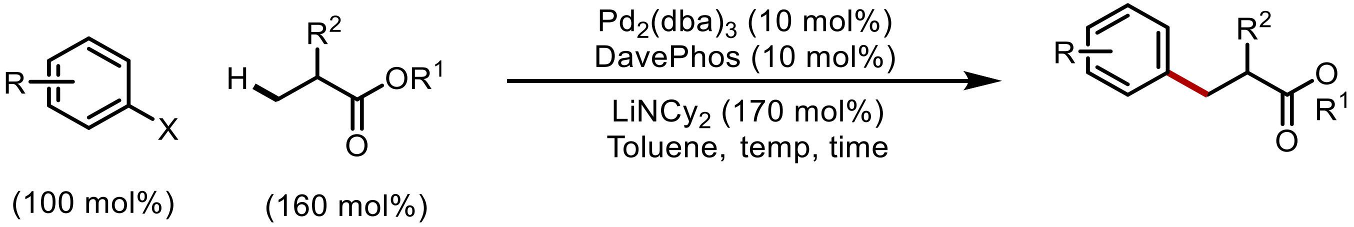
The image part with relationship ID rId4 was not found in the file.

Migratory coupling

- **Hartwig's discovery**



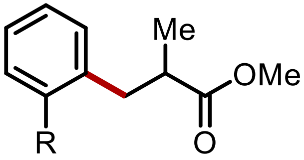
- **Baudoin's development**



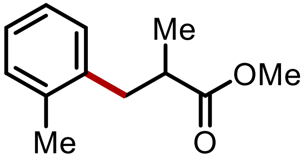
Hartwig, JACS, 2002, 124, 12557
Baudoin, ACIE, 2010, 49, 7261

Migratory coupling

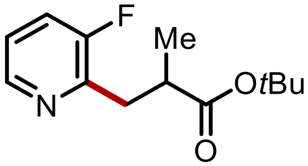
- **Baudoin's development**



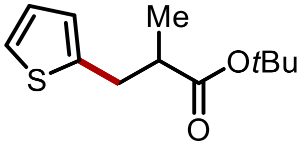
R =	
Cl	82% (X= Br, 22 °C, 2h)
Cl	63% (X = Cl, 50 °C, 22 min)
CF3	62% (X= Br, 110 °C 2h)
OCF3	75% (X= Br, 35 °C, 2h)



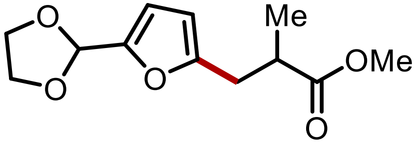
0%, X = Br
α-arylation only



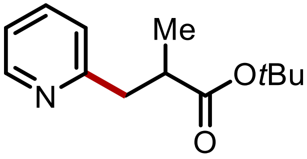
56% β:α 4:1
(X = Cl, 30 °C, 90 min)



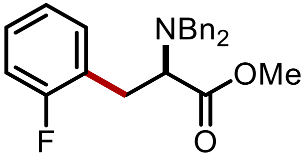
69%
(X = Cl, 70 °C, 70 min)



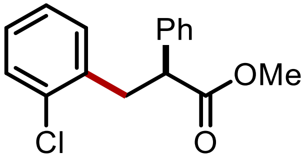
70%
(X = Cl, 50 °C, 45 min)



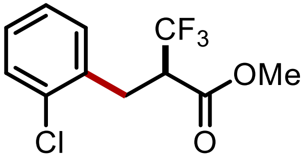
0%, X= Cl
α-arylation only



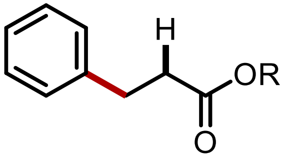
63%
(X = Br, 50 °C, 3.5 h)



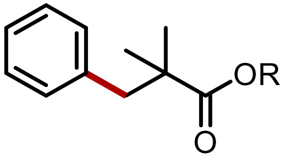
0%



0%



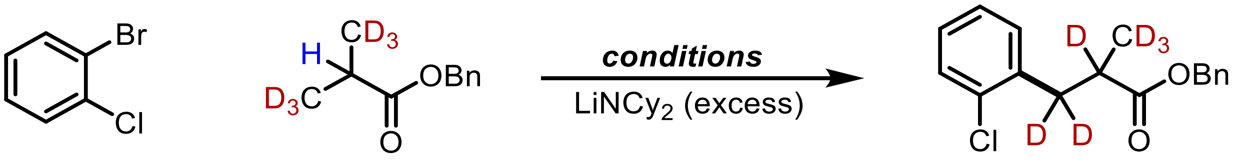
no α or β arylation



no β arylation

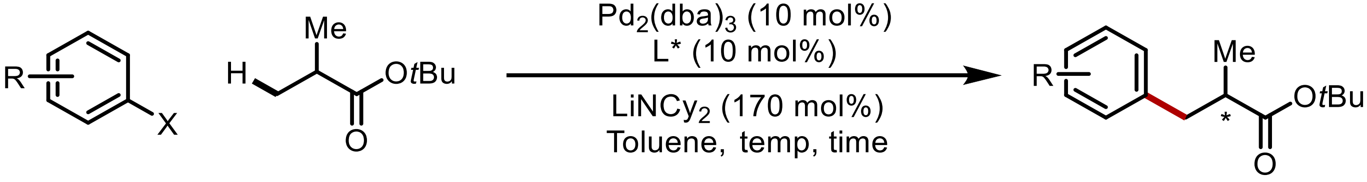
Baudoin, ACIE, 2010, 49, 7261

Migratory coupling



conditions

$LiNCy_2$ (excess)

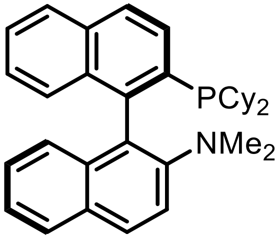


$Pd_2(dba)_3$ (10 mol%)
L* (10 mol%)

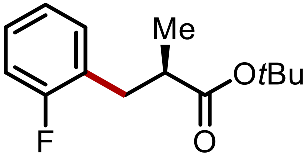
$LiNCy_2$ (170 mol%)
Toluene, temp, time

(100 mol%)

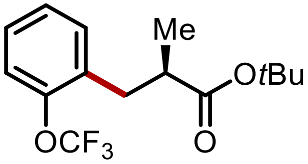
(160 mol%)



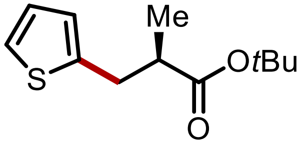
KenPhos



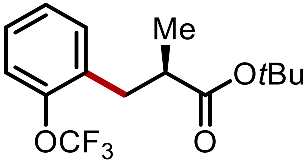
70%, e.r. 75:25
(X = Br, 30 °C, 3h)



55%, e.r. 76:24
(X = Br, 35 °C, 1.5h)



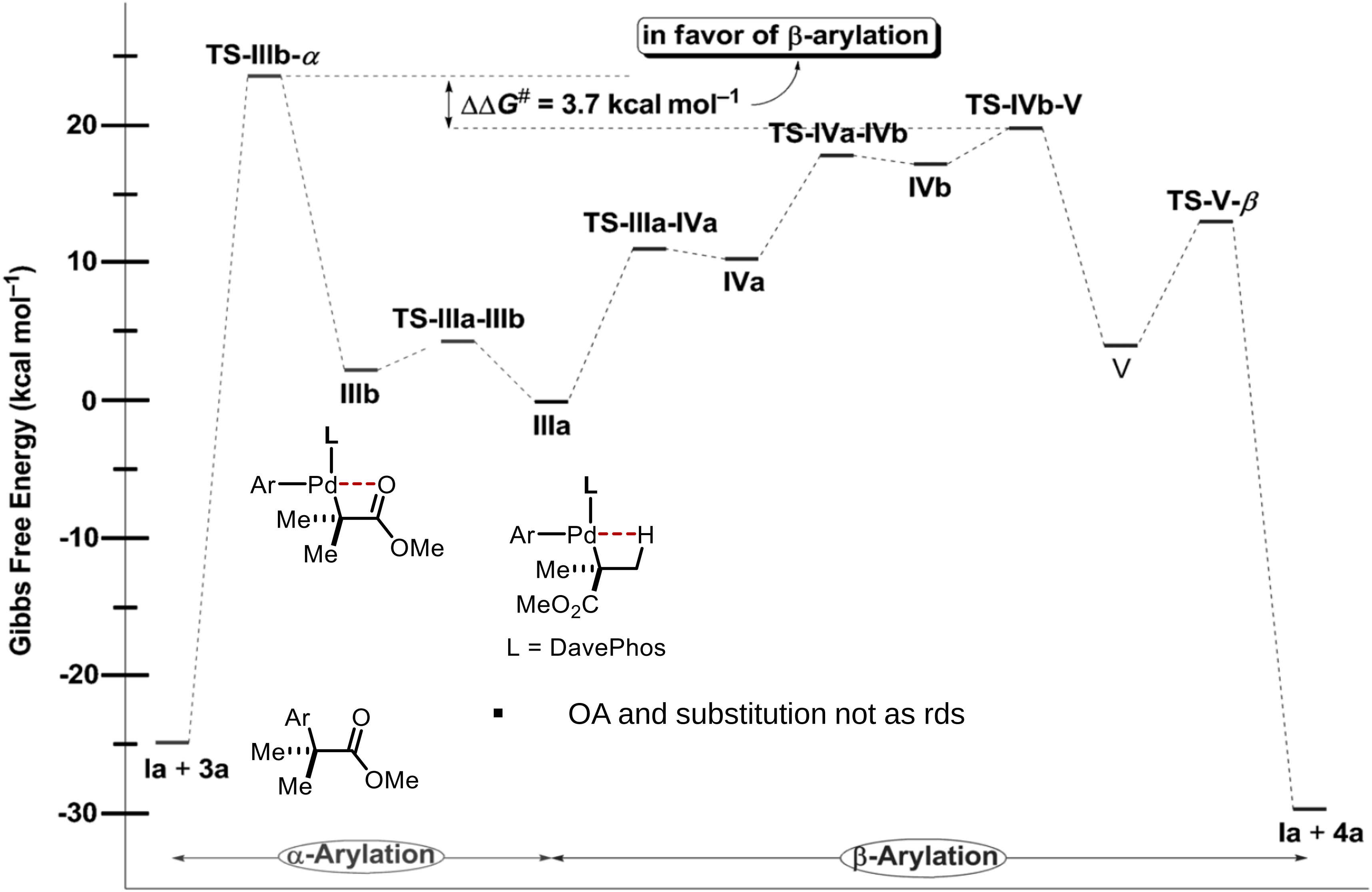
63%, e.r. 67:33
(X = Cl, 70 °C, 1.5h)



69%, e.r. 77:23
(X = Br, 30 °C, 2.5h)

Baudoin, ACIE, 2010, 49, 7261

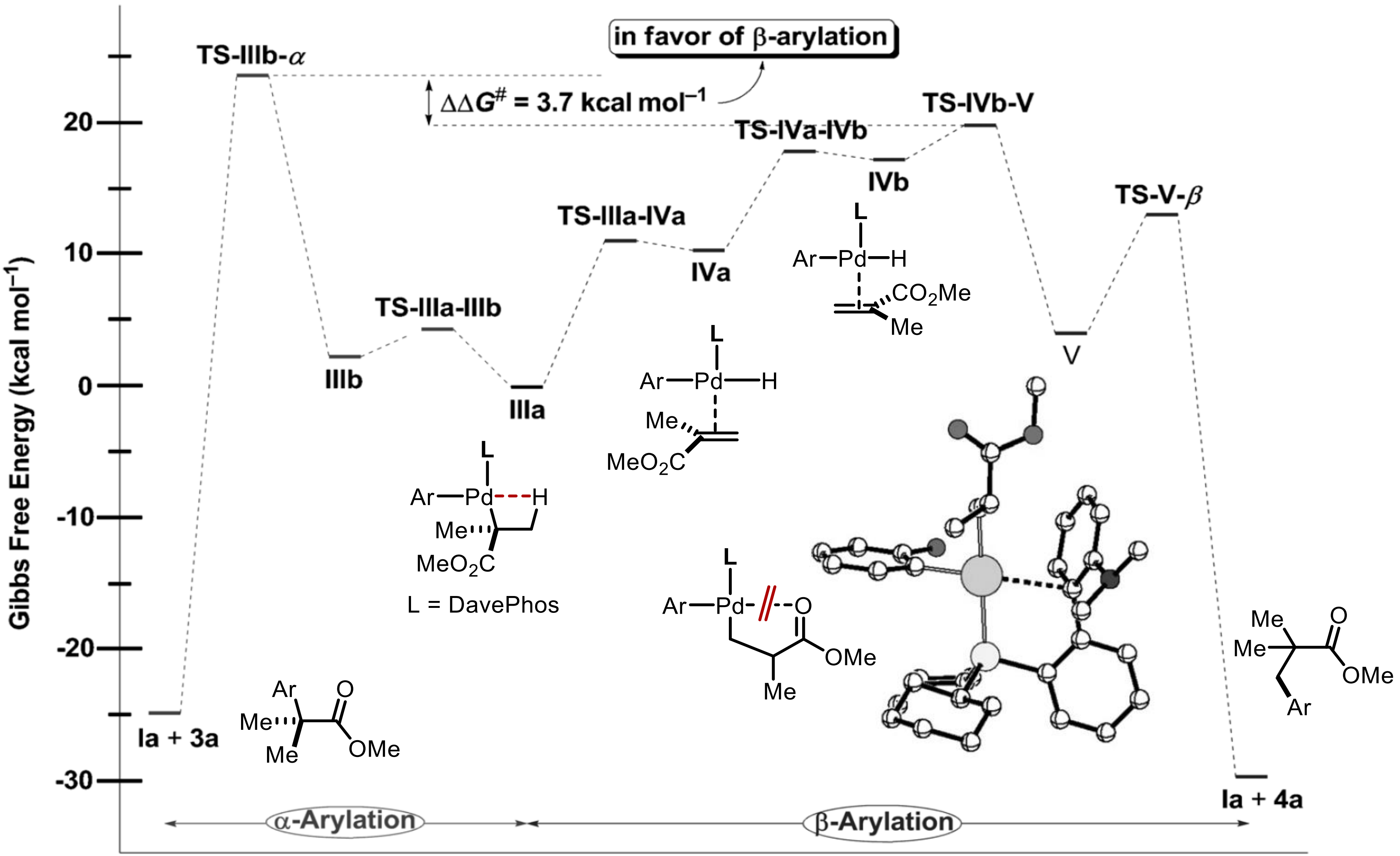
Migratory coupling



- OA and substitution not as rds

Baudoin, CEJ, 2012, 18, 1932

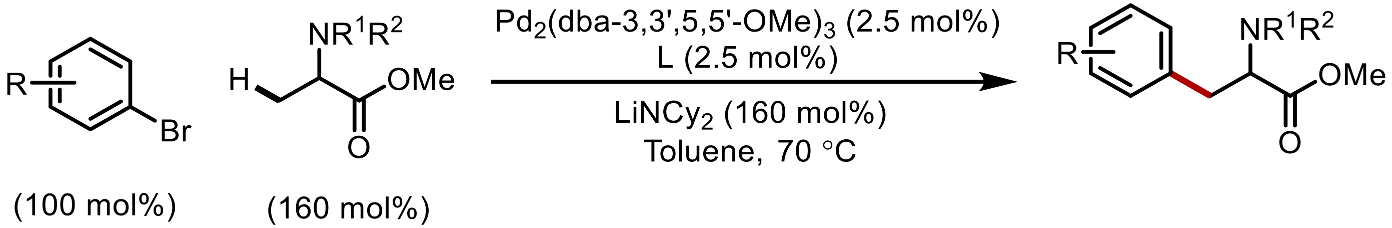
Migratory coupling



Baudoin, CEJ, 2012, 18, 1932

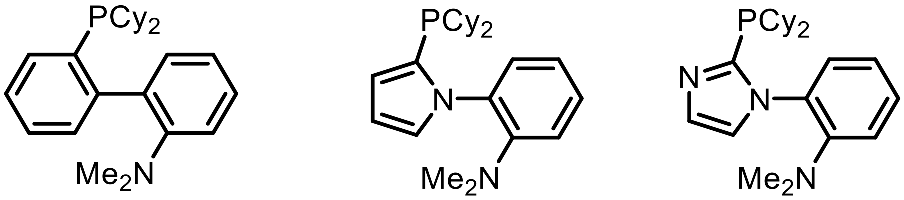
Migratory coupling

- **Arylation of amino ester**

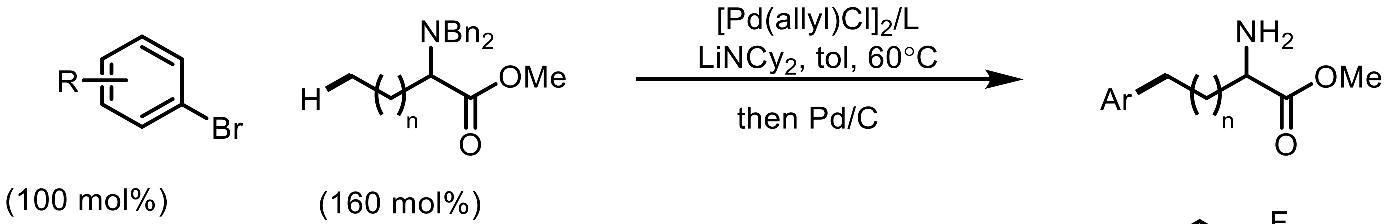


Pd_2(dba-3,3',5,5'-OMe)$_3$ (2.5 mol%)
L (2.5 mol%)
LiNCy$_2$ (160 mol%)
Toluene, 70 °C

(100 mol%) (160 mol%)

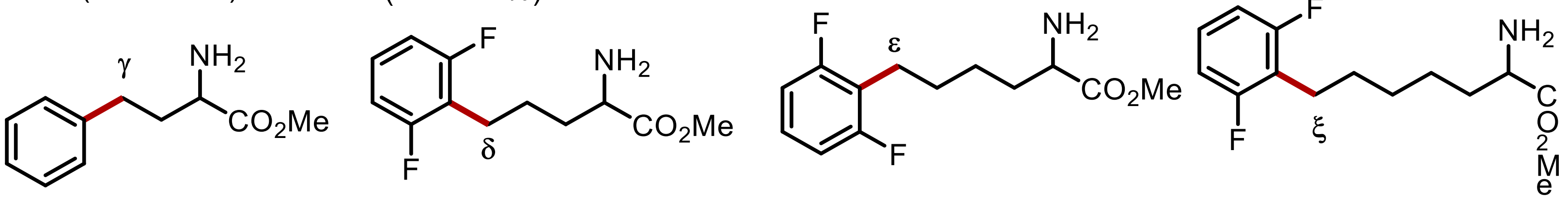


DavePhos



[Pd(allyl)Cl]$_2$/L
LiNCy$_2$, tol, 60°C
then Pd/C

(100 mol%) (160 mol%)

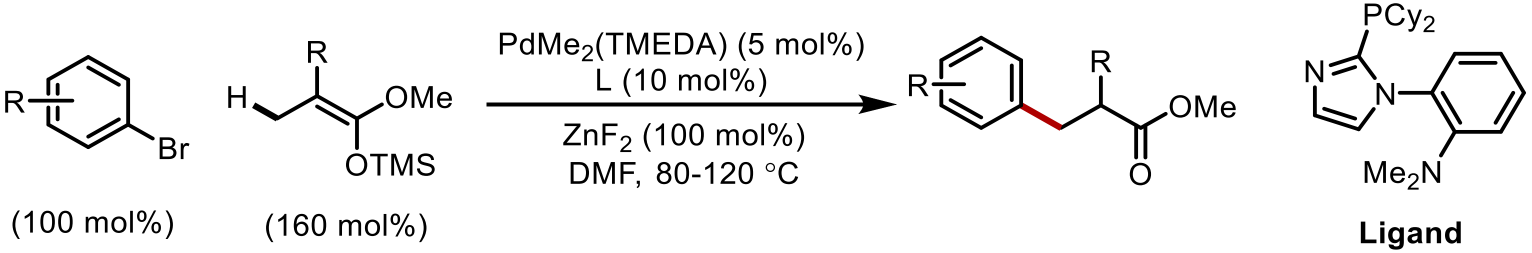


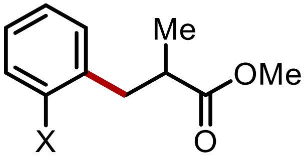
38% (γ:β 13:1) 33% 25% 22%

Baudoin, ACIE, 2012, 51, 10808

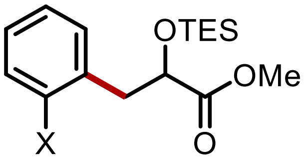
Migratory coupling

- **Use of silyl ketene acetals**



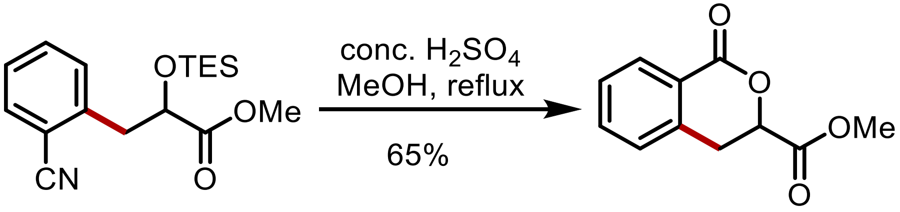


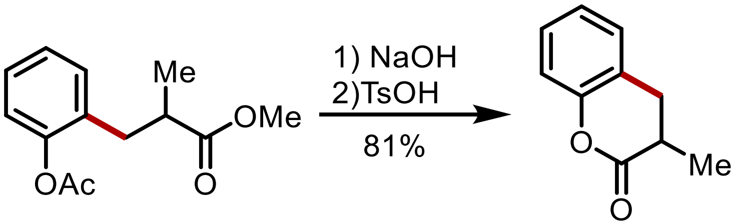
X = CN 72%
X = CO_2Me 43%
X = OAc 64%
X = NO_2 56%



X = F 59%
X = OMe 44%
X = CF3 50%

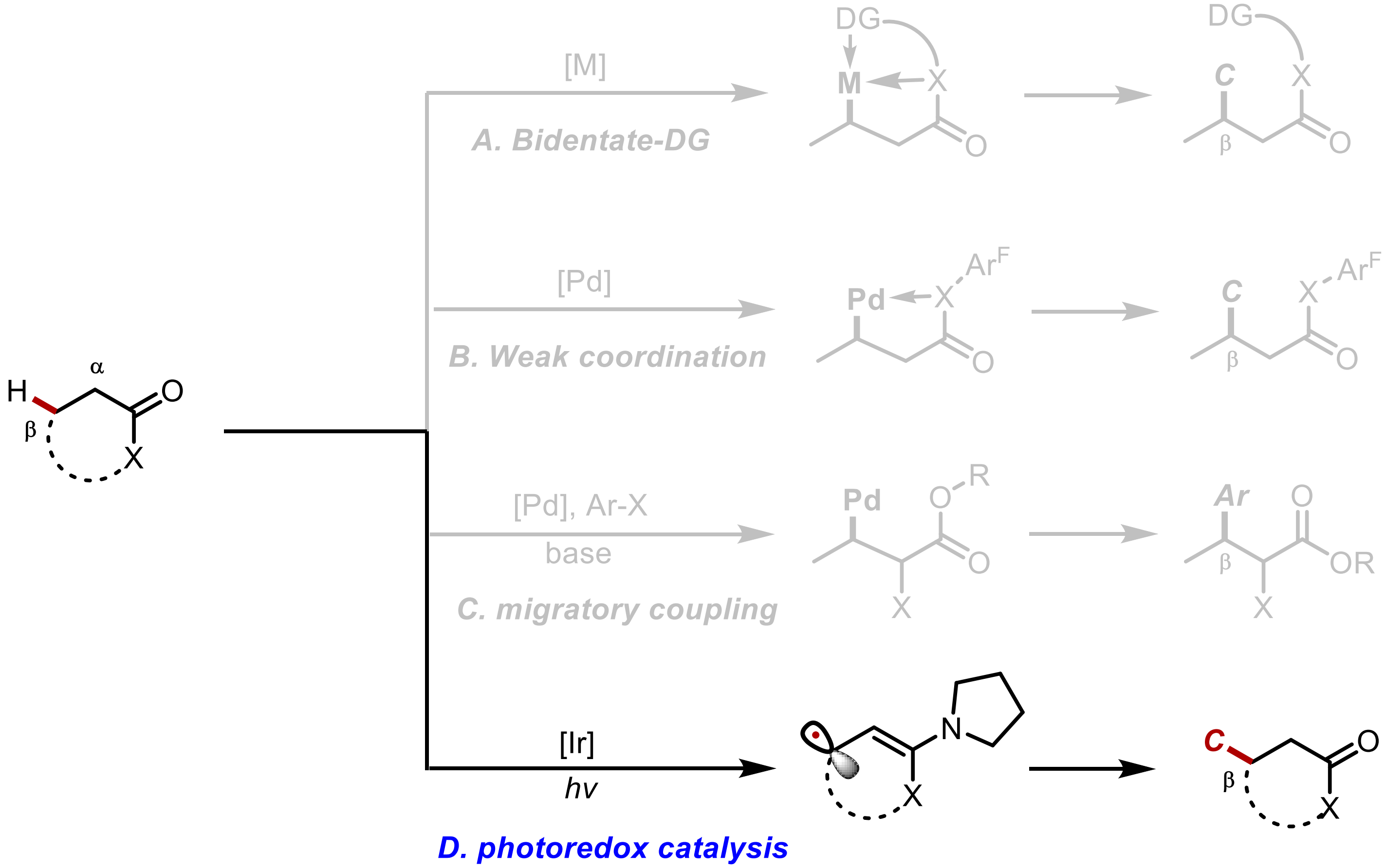
- Lower reactivity
- Higher FG tolerance





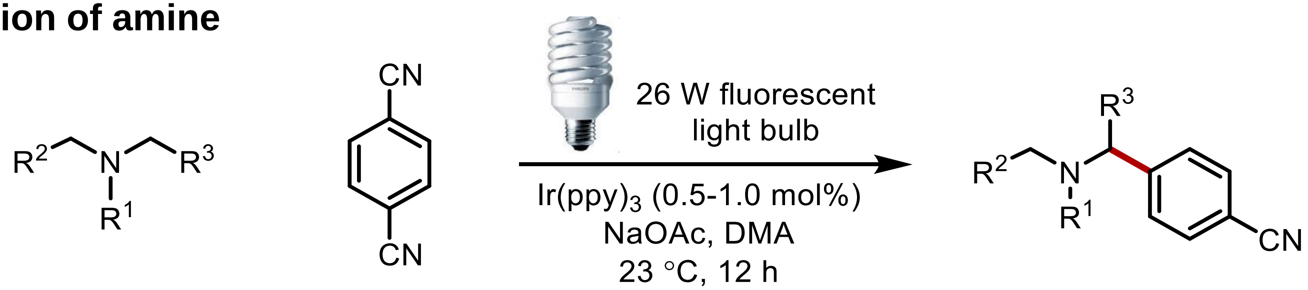
Baudoin, OL, 2013, 15, 5056

Content


[M]
A. Bidentate-DG
DG
M
X
O
C
β
[Pd]
B. Weak coordination
Pd
Ar^F
[Pd], Ar-X
base
C. migratory coupling
R
Ar
OR
H
α
[Ir]
hv
D. photoredox catalysis
N

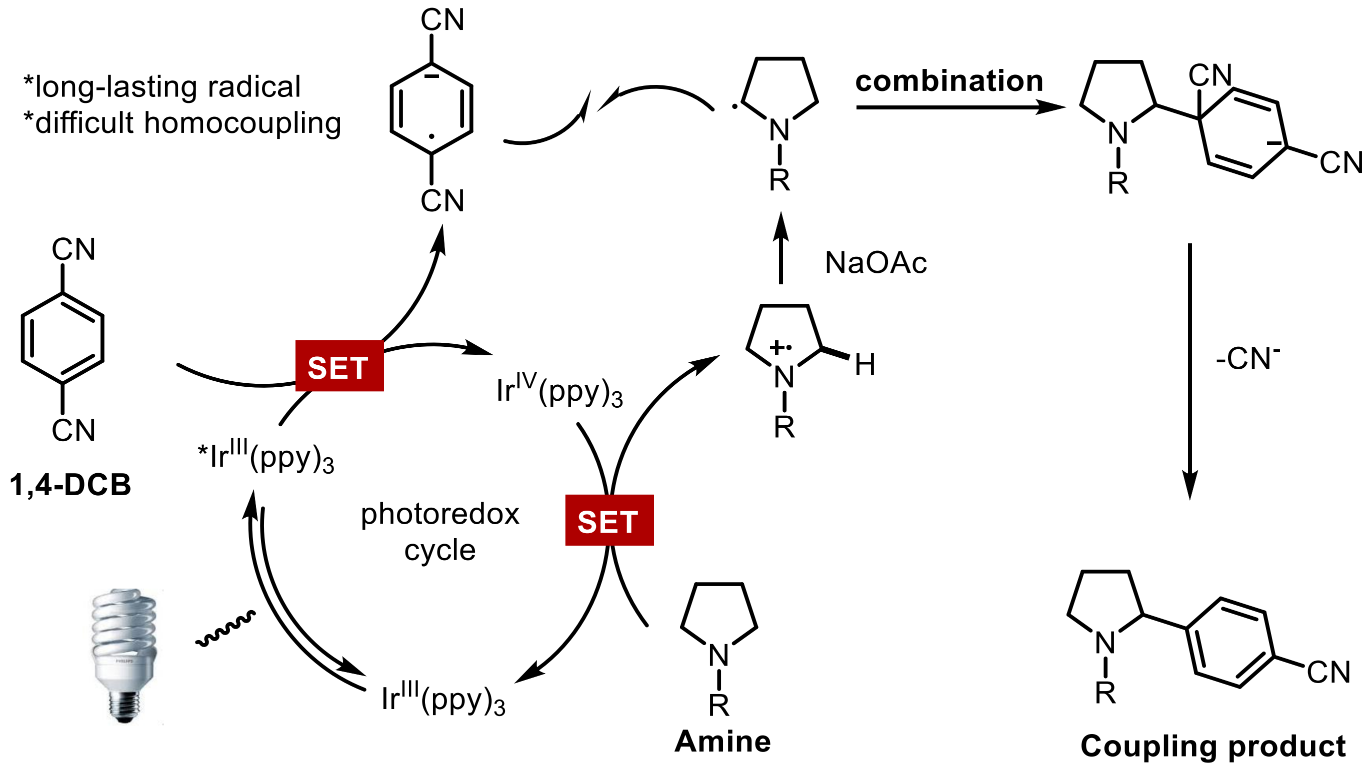
Photoredox Catalysis

- **α-arylation of amine**



26 W fluorescent light bulb

Ir(ppy)$_3$ (0.5-1.0 mol%)
NaOAc, DMA
23 °C, 12 h



*long-lasting radical
*difficult homocoupling

combination

NaOAc

-CN$^-$

SET

SET

Ir^{IV}(ppy)$_3$

*Ir^{III}(ppy)$_3$

photoredox cycle

Ir^{III}(ppy)$_3$

1,4-DCB

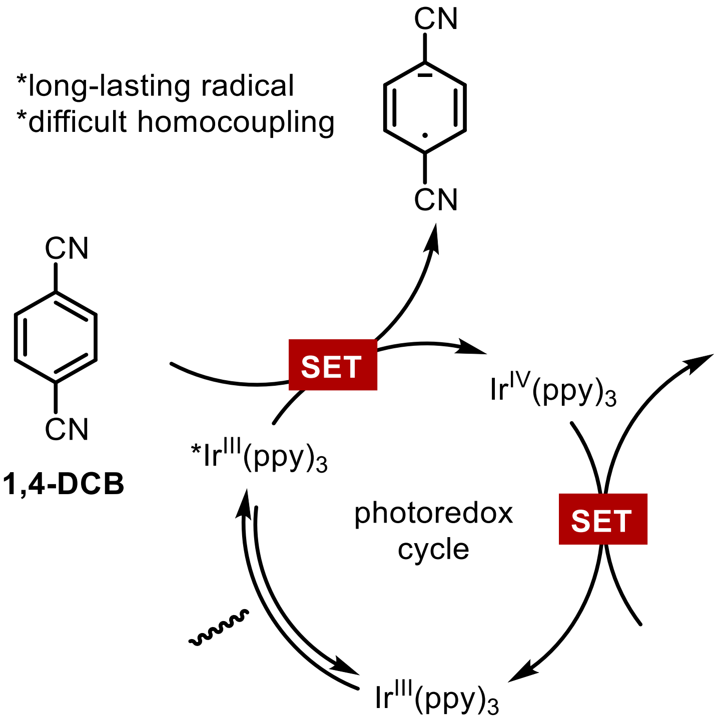
Amine

Coupling product

MacMillan, Science, 2011, 334, 1114

Photoredox Catalysis

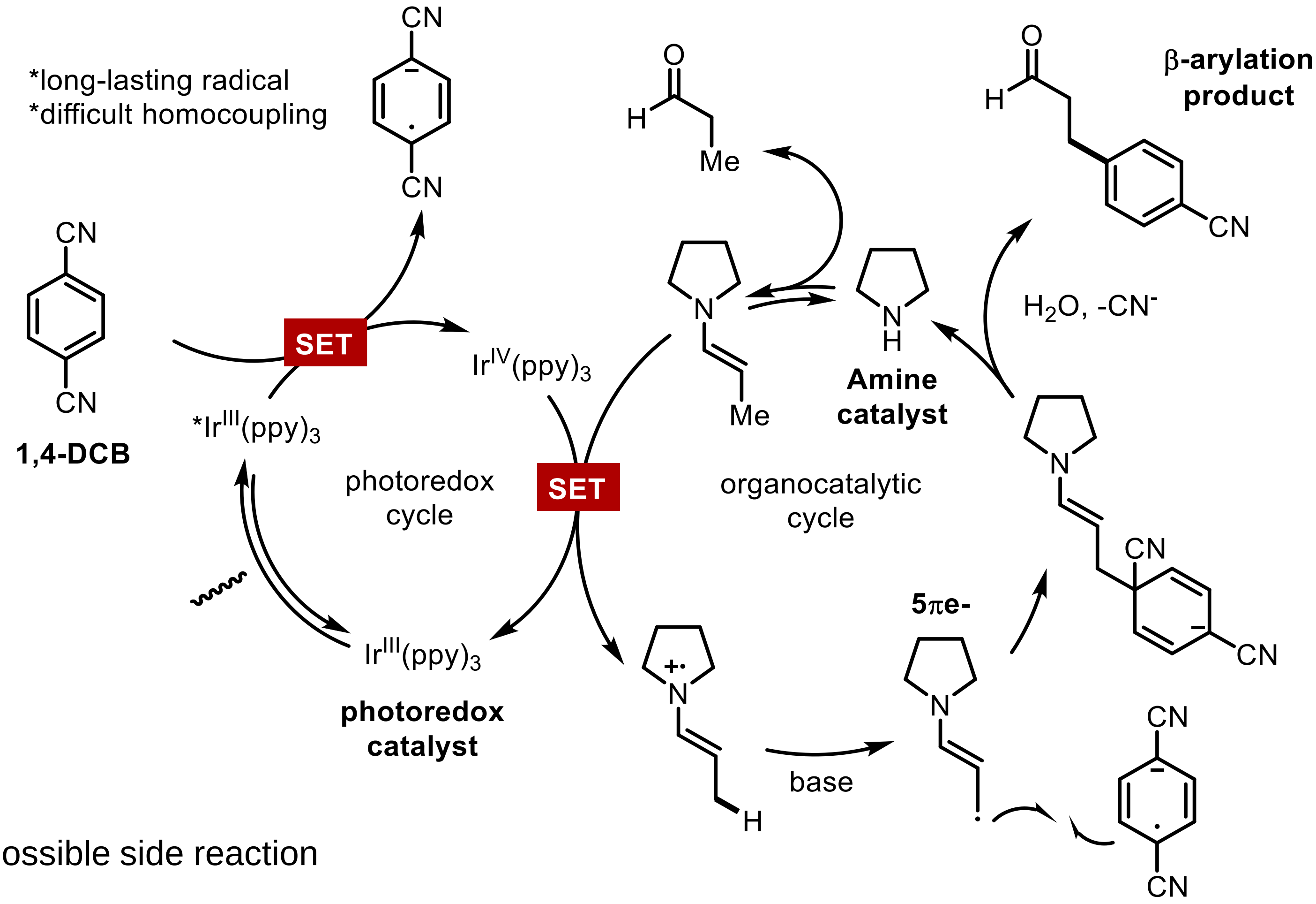
- **β-arylation of aldehyde and ketone**



MacMillan, Science, 2013, 339, 1593

Photoredox Catalysis

- **β-arylation of aldehyde and ketone**

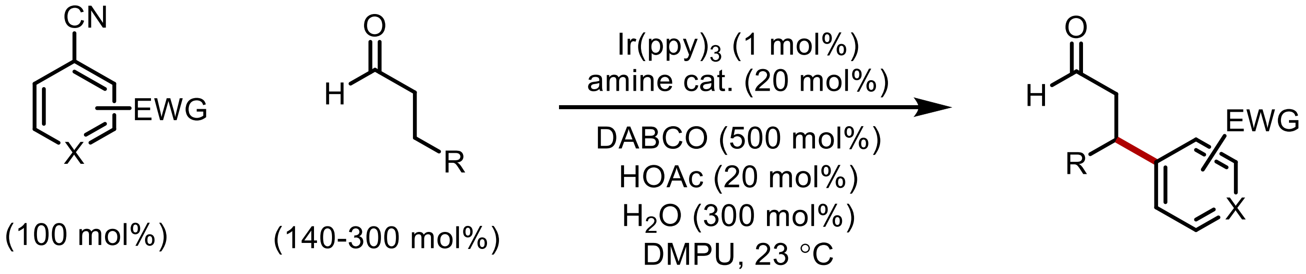


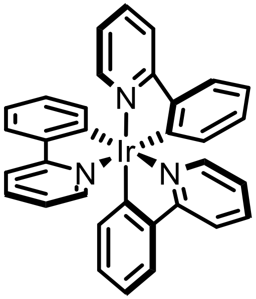
- possible side reaction

MacMillan, Science, 2013, 339, 1593

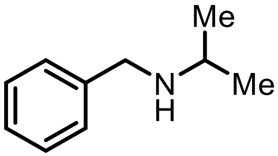
Photoredox Catalysis

- **β-arylation of aldehyde**





photoredox catalyst



amine catalyst

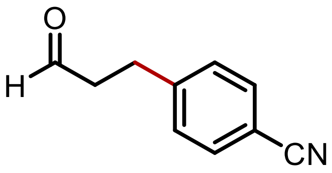
Amine

- easy to condense (e-rich)
- easy to be oxidized (e-rich)
- easy to turn over

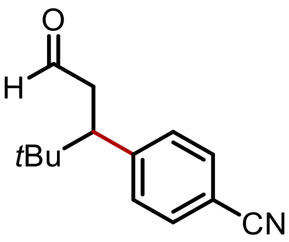
MacMillan, Science, 2013, 339, 1593

Photoredox Catalysis

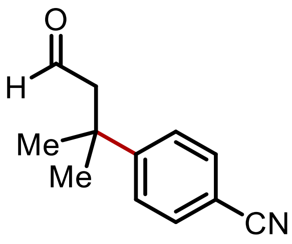
- **β-arylation of aldehyde**



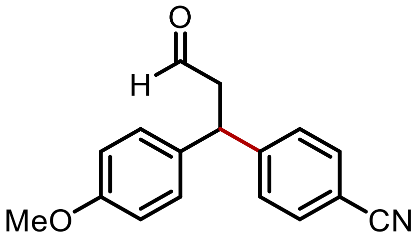
78%



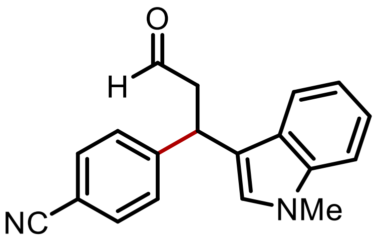
44%



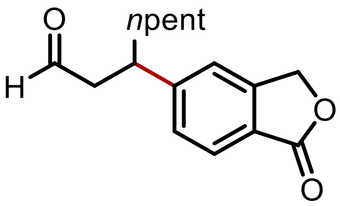
74%



88%



63%



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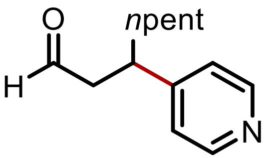
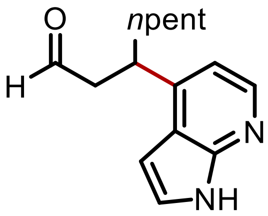


70%

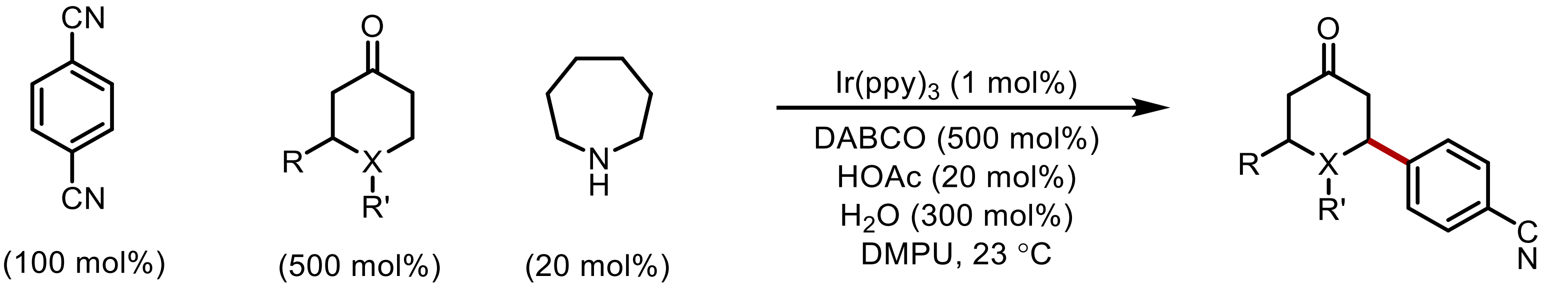


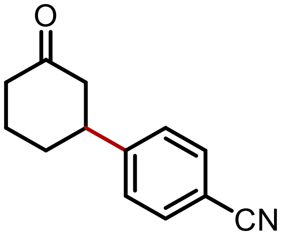
53%

MacMillan, Science, 2013, 339, 1593

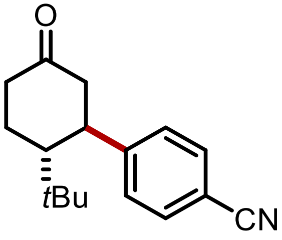
Photoredox Catalysis

- **β-arylation of ketone**

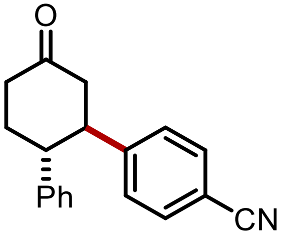




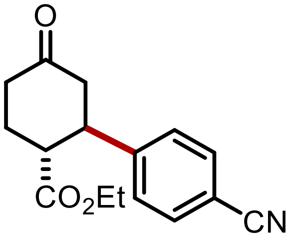
88%



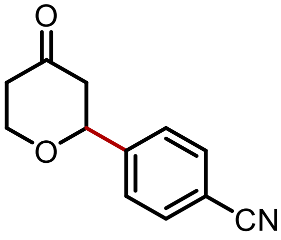
70%, > 20:1 dr



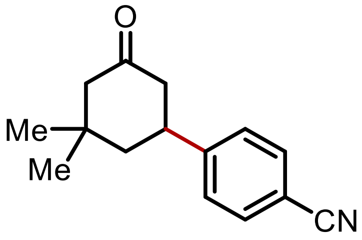
79%, > 20:1 dr



81%, > 20:1 dr



63%

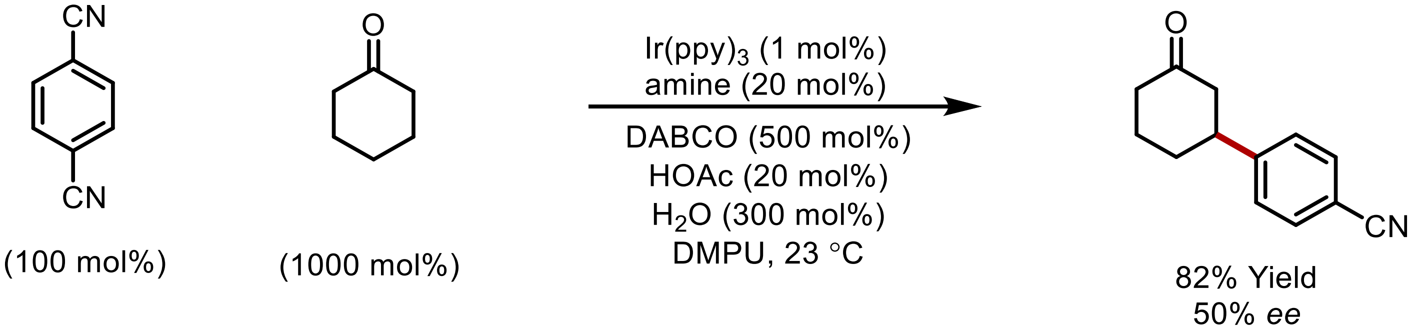


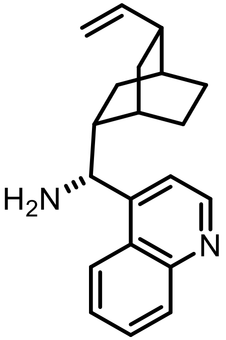
83%

MacMillan, Science, 2013, 339, 1593

Photoredox Catalysis

- **Enantioselective β-arylation of ketone**



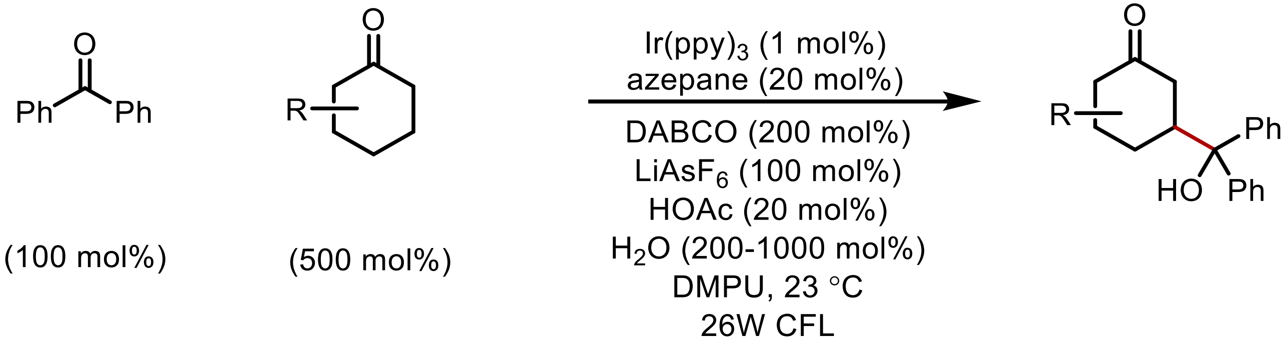


Chiral amine catalyst

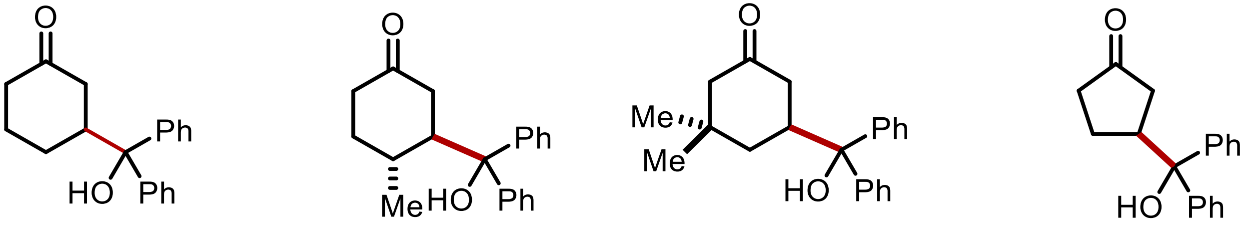
MacMillan, Science, 2013, 339, 1593

Photoredox Catalysis

- **β-aldol of ketone**


(100 mol%)
(500 mol%)

$Ir(ppy)_3$ (1 mol%)
azepane (20 mol%)
DABCO (200 mol%)
$LiAsF_6$ (100 mol%)
HOAc (20 mol%)
H_2O (200-1000 mol%)
DMPU, 23 °C
26W CFL

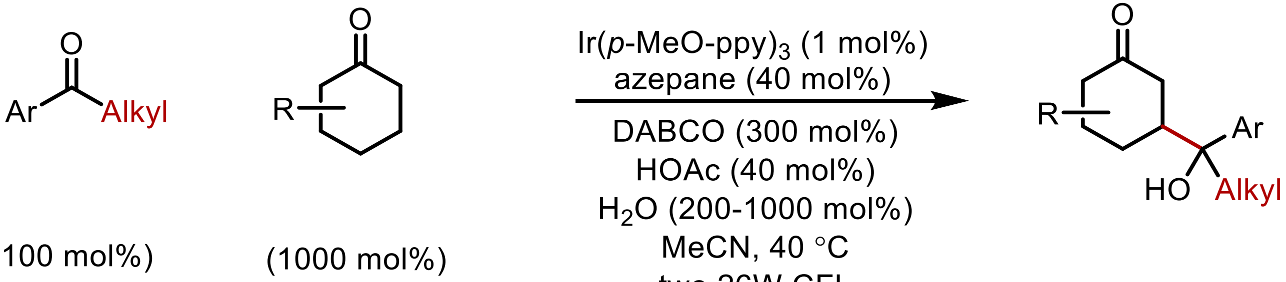

81%
79%, dr > 20:1
43%, dr > 20:1
65%


$LiAsF_6$

MacMillan, JACS, 2013, 135, 18323

Photoredox Catalysis

- **β-aldol of ketone**

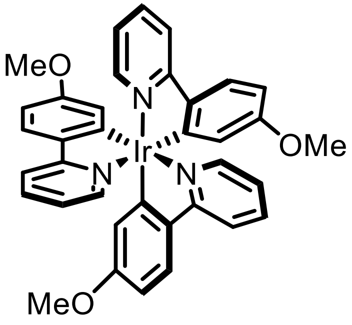


(100 mol%)

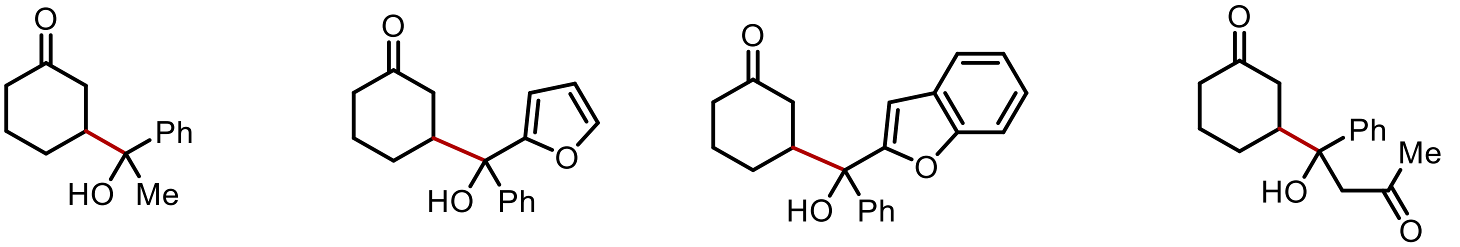
(1000 mol%)

Ir(*p*-MeO-ppy)$_3$ (1 mol%)
azepane (40 mol%)

DABCO (300 mol%)
HOAc (40 mol%)
H_2O (200-1000 mol%)
MeCN, 40 °C
two 26W CFL



Ir(*p*-MeO-ppy)$_3$



77%

69%

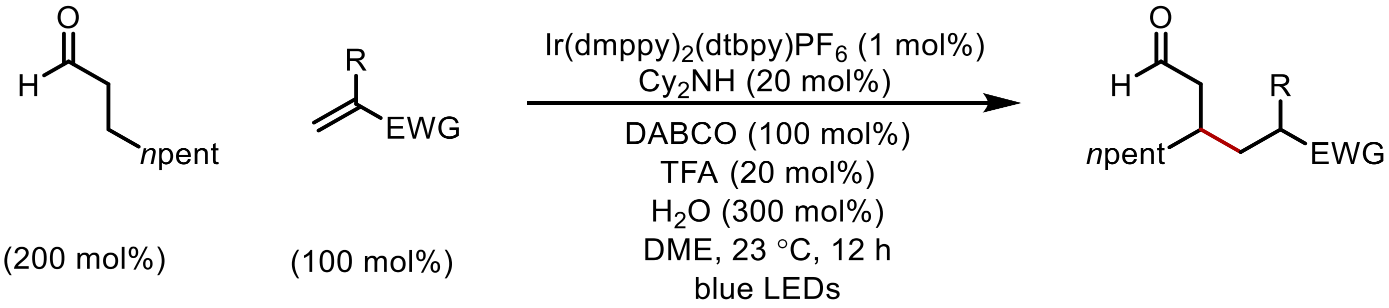
56%

54%

MacMillan, JACS, 2013, 135, 18323

Photoredox Catalysis

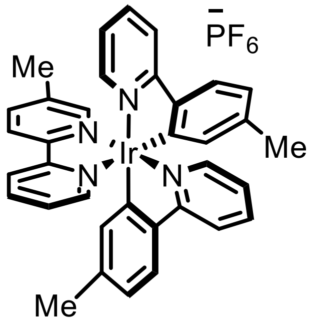
- **β-alkylation of aldehyde**



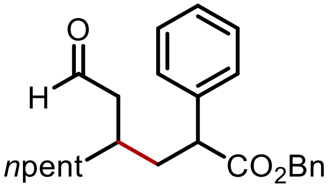
(200 mol%)

(100 mol%)

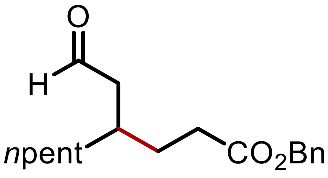
$Ir(dmppy)_2(dtbpy)PF_6$ (1 mol%)
Cy_2NH (20 mol%)
DABCO (100 mol%)
TFA (20 mol%)
H_2O (300 mol%)
DME, 23 °C, 12 h
blue LEDs



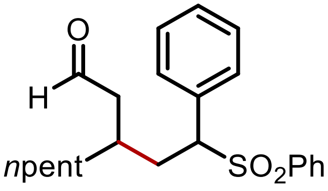
$Ir(dmppy)_2(dtbpy)PF_6$



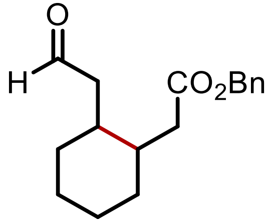
83%



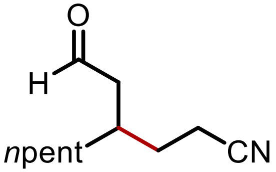
70%



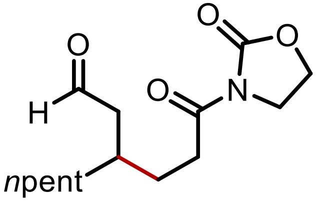
61%



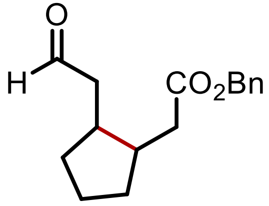
54%, 4:1 dr



80%



50%



47%, 9:1 dr

MacMillan, JACS, 2014, 136, ASAP

Summary

- **Bidentate DG**

    - Classic DG
    - Various C-C formation and metals
    - Highly applicable

- **Weak coordination**

    - Impressive ligand control
    - Various C-C bond formation
    - Amino acid synthesis

- **Migratory Coupling**

    - Easily available substrate
    - No poly-arylation
    - Amino ester synthesis

- **Photoredox catalysis**

    - Conceptual advance
    - Versatile radical chemistry
    - Cyclic substrates and aldehyde


Thank you!