Methylation Based on C-H Activation

Research Center for Molecular Recognition and Synthesis

Reporter: Jie Wang

Supervisor: Prof. Shengming Ma

2020/12/18

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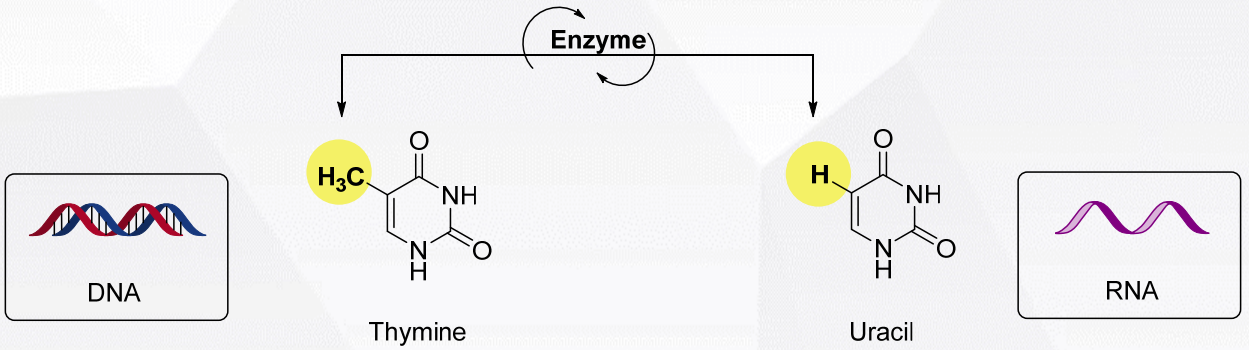
Background

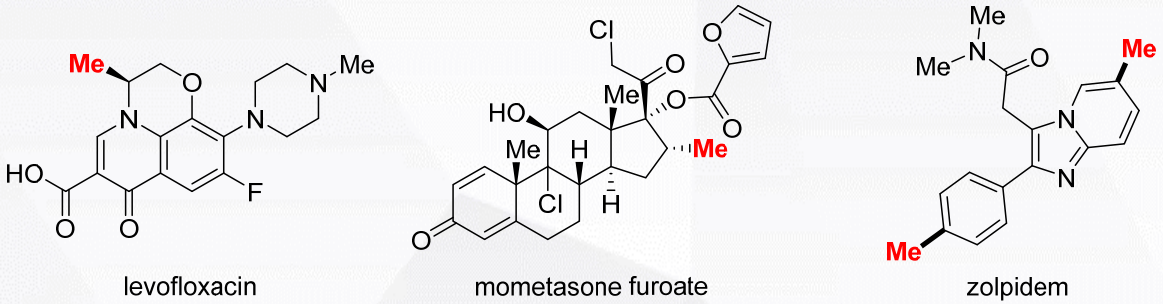
Methyl & “magic methyl effect”

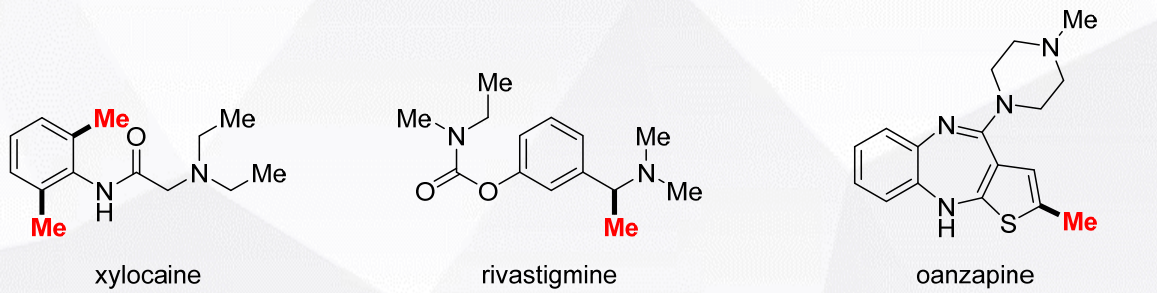
01

Background

Methyl & "Magic Methyl Effect"







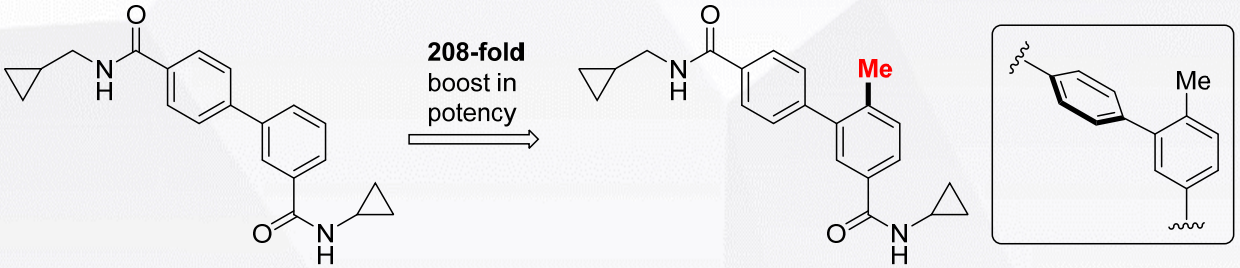
In 2018, **73%** of top 200 small-molecule drugs by Retail Sales contain at least one methyl group.

- Cernak, T. et al. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.
- Fraga, C. A. M. et al. *Chem. Rev.* **2011**, *111*, 5215-5246.

01

Background

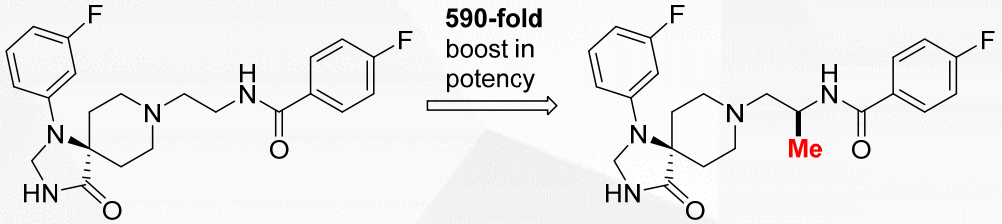
Methyl & "Magic Methyl Effect"



p38α IC_{50} > 2500 nM

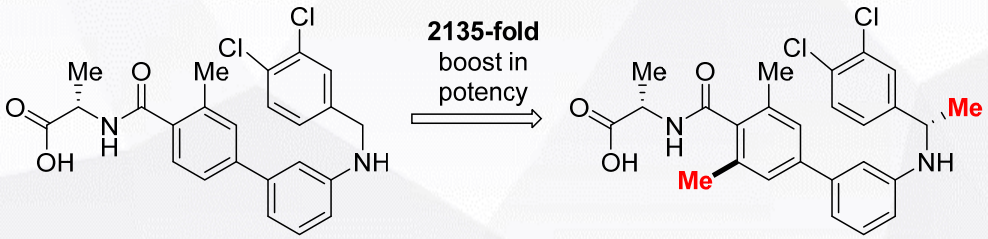
IC_{50} 12 nM

Low-energy conformer (possible)



PLD2 IC_{50} 11800 nM

IC_{50} 20 nM



$S1P_1$ IC_{50} 4270 nM

IC_{50} 2 nM

- Cernak, T. et al. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.

01 Background

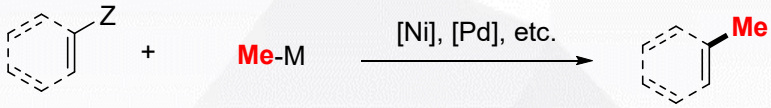
a) Methylation *via* **Nucleophilic Substitution**

X = OH, Cl, Br, I, etc.

b) Methylation *via* **Electrophilic Substitution**

Y = I, OTs, OTf, etc.

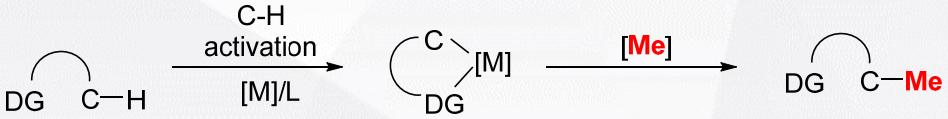
c) Methylation *via* **Cross-coupling**



Z = Cl, Br, I, OTf, etc.

M = B, Sn, Mg, Li, Al, Zn, etc.

d) Methylation *via* **C-H Activation**

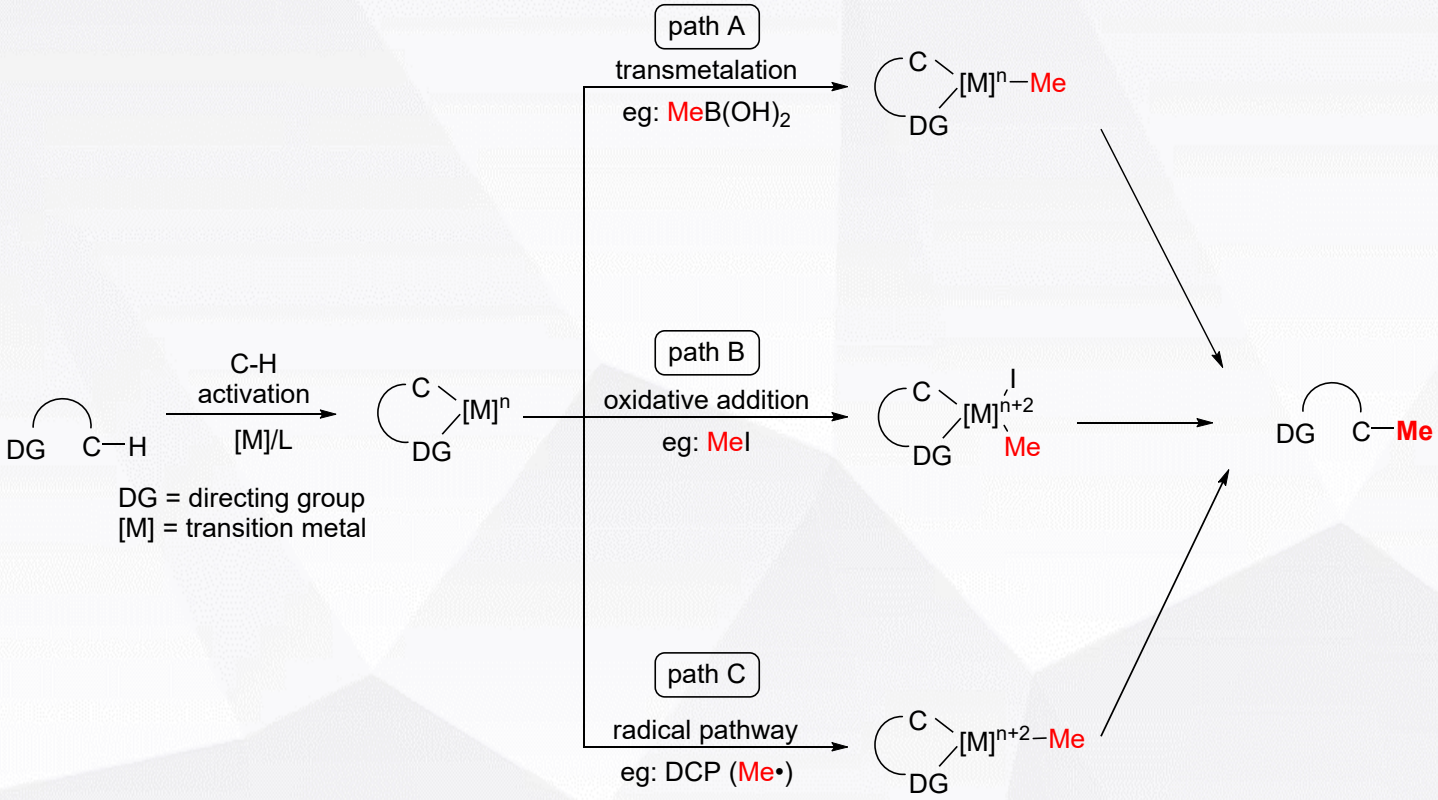


DG = directing group
[M] = transition metal

- ✓ ***Straightforward***
- ✓ ***Atom economic***
- ✓ ***Efficient***
- ✓ ***Late-stage modification***

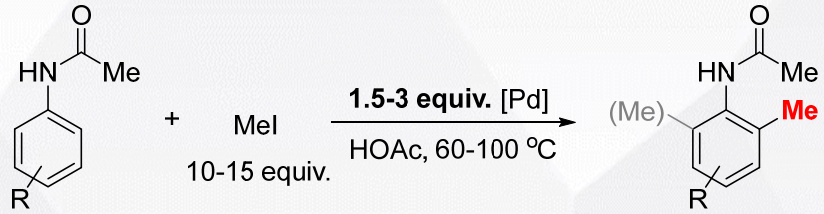
Background

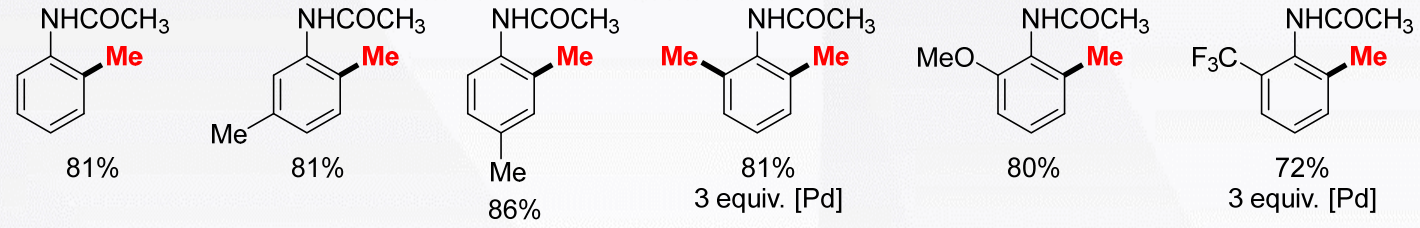
d) Methylation *via* **C-H Activation**

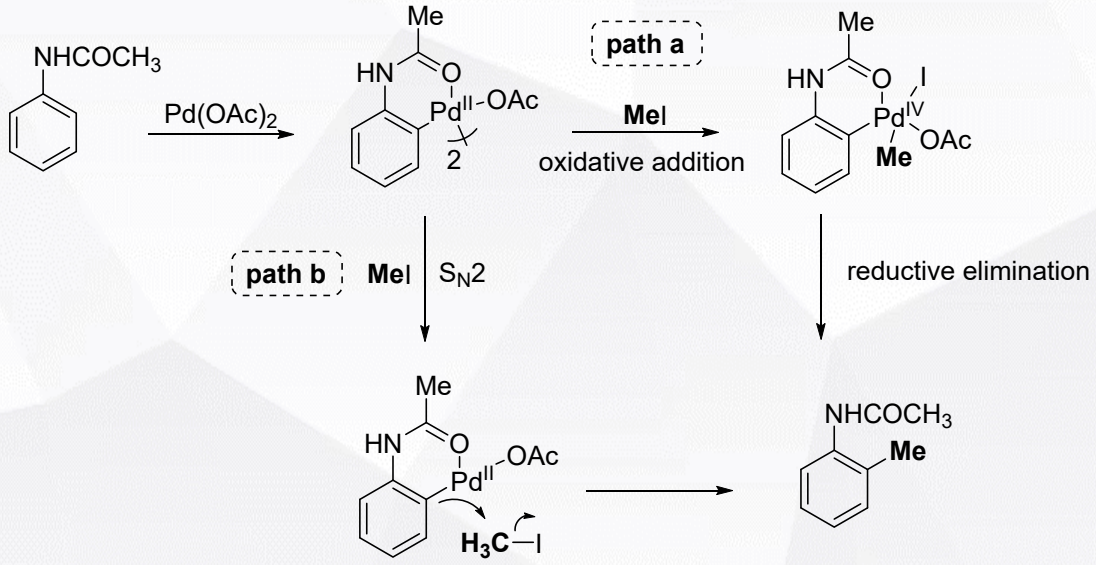


01

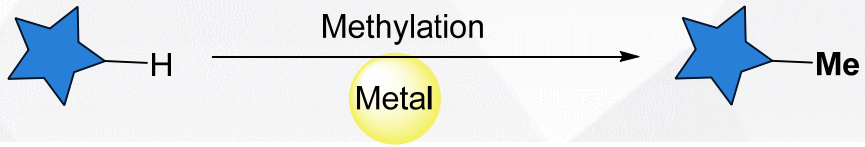
Background



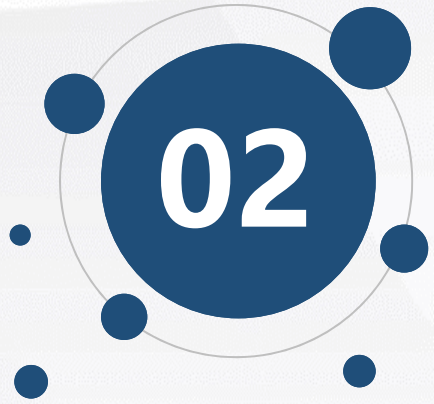




Tremont, S. J. et al. *J. Am. Chem. Soc.* **1984**, *106*, 5759-5760.



1																		18
1 H hydrogen 1.008 [1.0078, 1.0082]	2		Key: atomic number Symbol name conventional atomic weight standard atomic weight									13	14	15	16	17	2 He helium 4.0026
3 Li lithium 6.94 [6.938, 6.997]	4 Be beryllium 9.0122											5 B boron 10.81 [10.806, 10.821]	6 C carbon 12.011 [12.009, 12.012]	7 N nitrogen 14.007 [14.006, 14.008]	8 O oxygen 15.999 [15.999, 16.000]	9 F fluorine 18.998	10 Ne neon 20.180
11 Na sodium 22.990	12 Mg magnesium 24.305 [24.304, 24.307]	3	4	5	6	7	8	9	10	11	12	13 Al aluminium 26.982	14 Si silicon 28.085 [28.084, 28.086]	15 P phosphorus 30.974	16 S sulfur 32.06 [32.059, 32.076]	17 Cl chlorine 35.45 [35.446, 35.457]	18 Ar argon 39.95 [39.792, 39.963]
19 K potassium 39.098	20 Ca calcium 40.078(4)	21 Sc scandium 44.956	22 Ti titanium 47.867	23 V vanadium 50.942	24 Cr chromium 51.996	25 Mn manganese 54.938	26 Fe iron 55.845(2)	27 Co cobalt 58.933	28 Ni nickel 58.693	29 Cu copper 63.546(3)	30 Zn zinc 65.38(2)	31 Ga gallium 69.723	32 Ge germanium 72.630(8)	33 As arsenic 74.922	34 Se selenium 78.971(8)	35 Br bromine 79.904 [79.901, 79.907]	36 Kr krypton 83.798(2)
37 Rb rubidium 85.468	38 Sr strontium 87.62	39 Y yttrium 88.906	40 Zr zirconium 91.224(2)	41 Nb niobium 92.906	42 Mo molybdenum 95.95	43 Tc technetium	44 Ru ruthenium 101.07(2)	45 Rh rhodium 102.91	46 Pd palladium 106.42	47 Ag silver 107.87	48 Cd cadmium 112.41	49 In indium 114.82	50 Sn tin 118.71	51 Sb antimony 121.76	52 Te tellurium 127.60(3)	53 I iodine 126.90	54 Xe xenon 131.29
55 Cs caesium 132.91	56 Ba barium 137.33	57-71 lanthanoids	72 Hf hafnium 178.49(2)	73 Ta tantalum 180.95	74 W tungsten 183.84	75 Re rhenium 186.21	76 Os osmium 190.23(3)	77 Ir iridium 192.22	78 Pt platinum 195.08	79 Au gold 196.97	80 Hg mercury 200.59	81 Tl thallium 204.38 [204.38, 204.39]	82 Pb lead 207.2	83 Bi bismuth 208.98	84 Po polonium	85 At astatine	86 Rn radon
87 Fr francium	88 Ra radium	89-103 actinoids	104 Rf rutherfordium	105 Db dubnium	106 Sg seaborgium	107 Bh bohrium	108 Hs hassium	109 Mt meitnerium	110 Ds darmstadtium	111 Rg roentgenium	112 Cn copernicium	113 Nh nihonium	114 Fl flerovium	115 Mc moscovium	116 Lv livermorium	117 Ts tennessine	118 Og oganesson



Methylation

Based on C-H Activation

***Precious** Metals:*

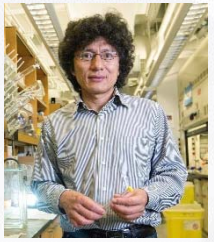
44 Ru	45 Rh	46 Pd
	77 Ir	

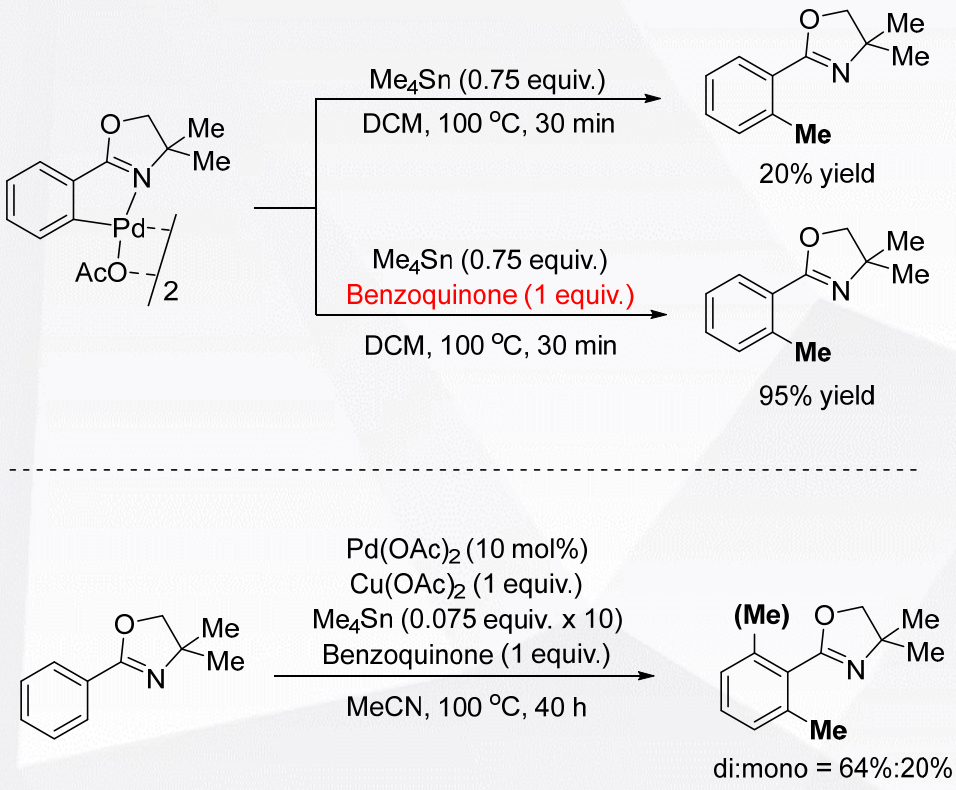
Methylation

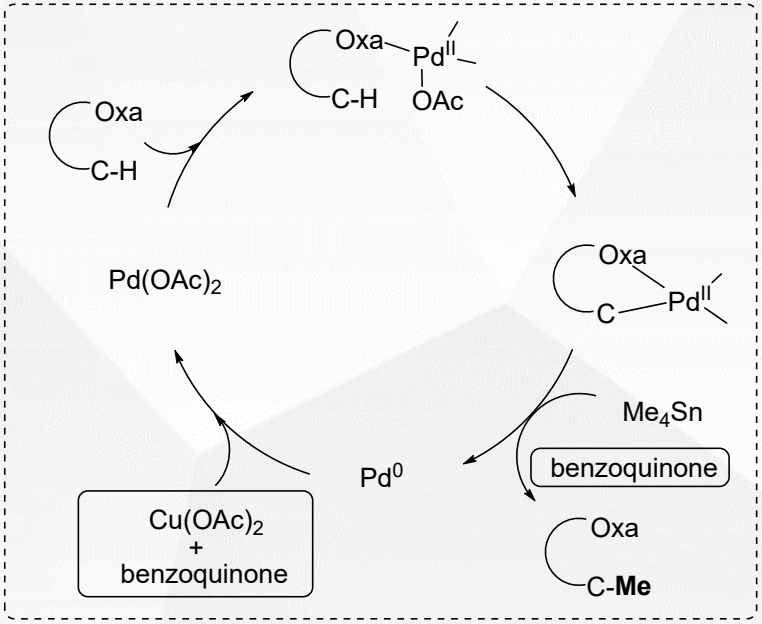
Based on C-H Activation

46 **Pd** — **Palladium catalysis**

>> Yu, J.-Q 2006-a:







Yu, J.-Q. et al. *J. Am. Chem. Soc.* **2006**, *128*, 78-79.

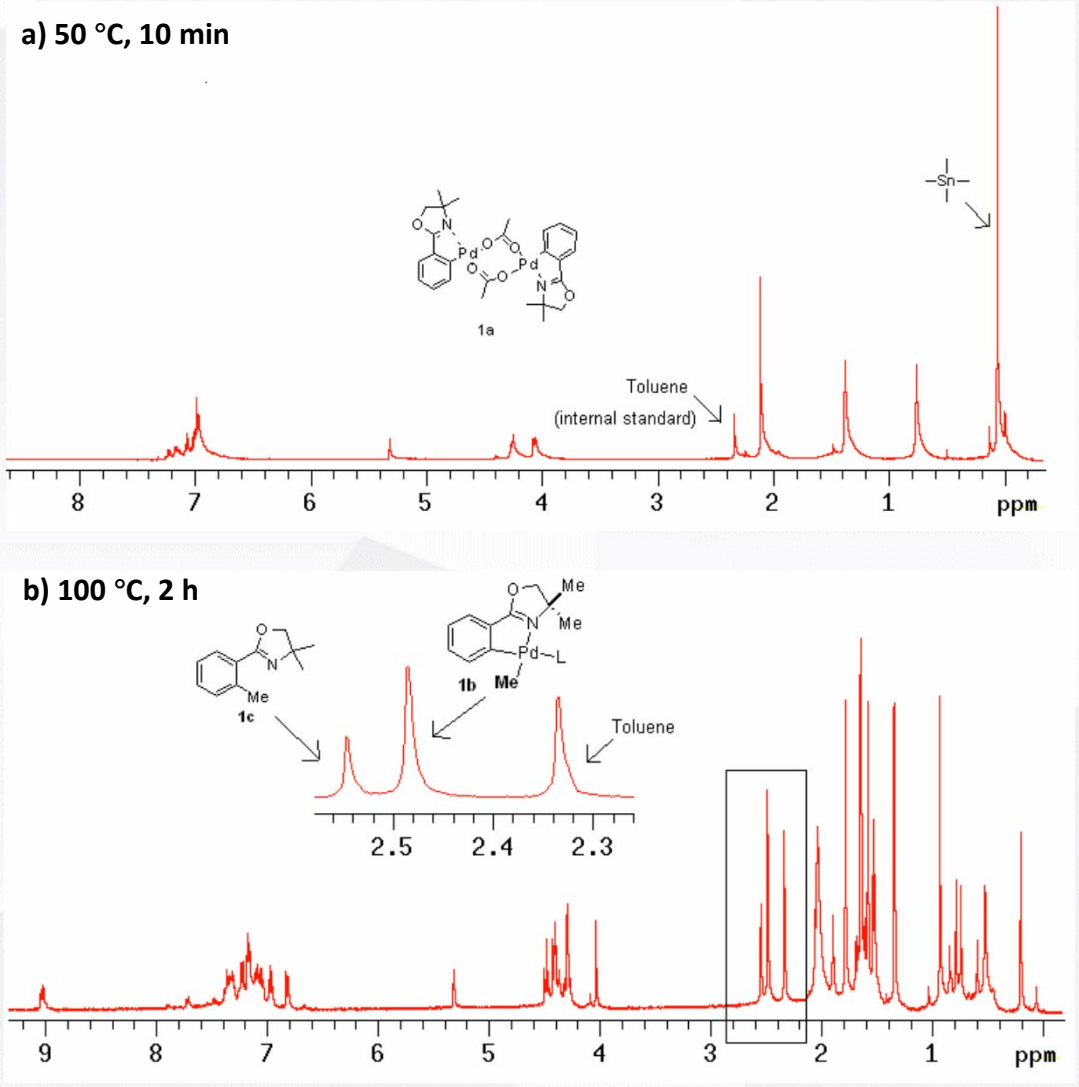
02

Methylation : Pd

Based on C-H Activation

>> Yu, J.-Q 2006-a:

No benzoquinone



Yu, J.-Q. et al. *J. Am. Chem. Soc.* **2006**, *128*, 78-79.

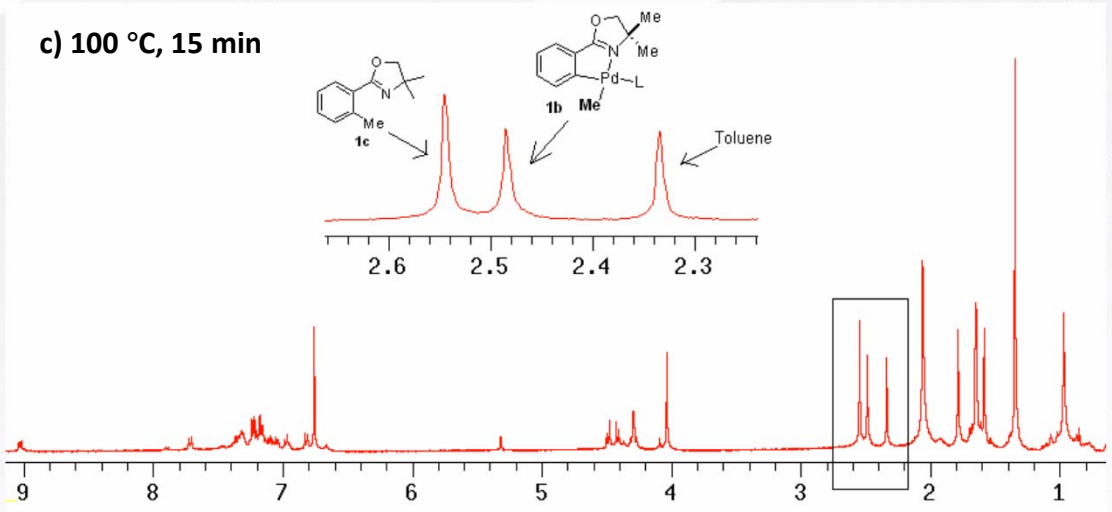
02

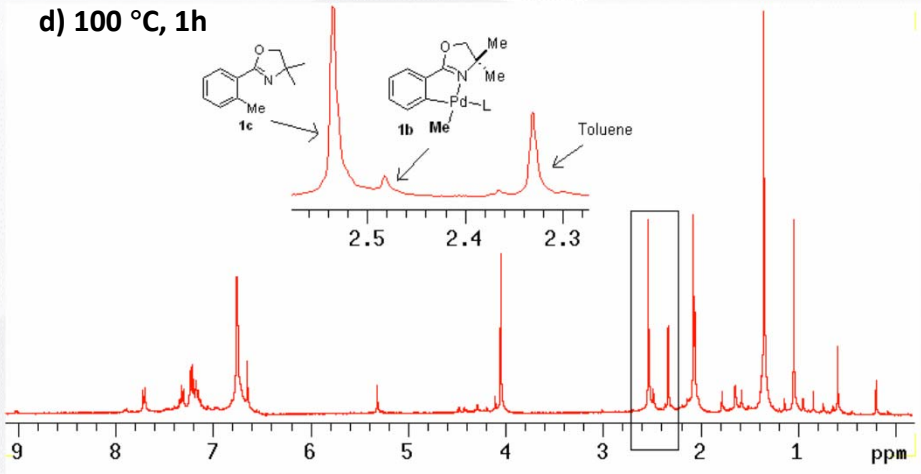
Methylation: Pd

Based on C-H Activation

>> Yu, J.-Q 2006-a:

Benzoquinone(1 equiv.) was added





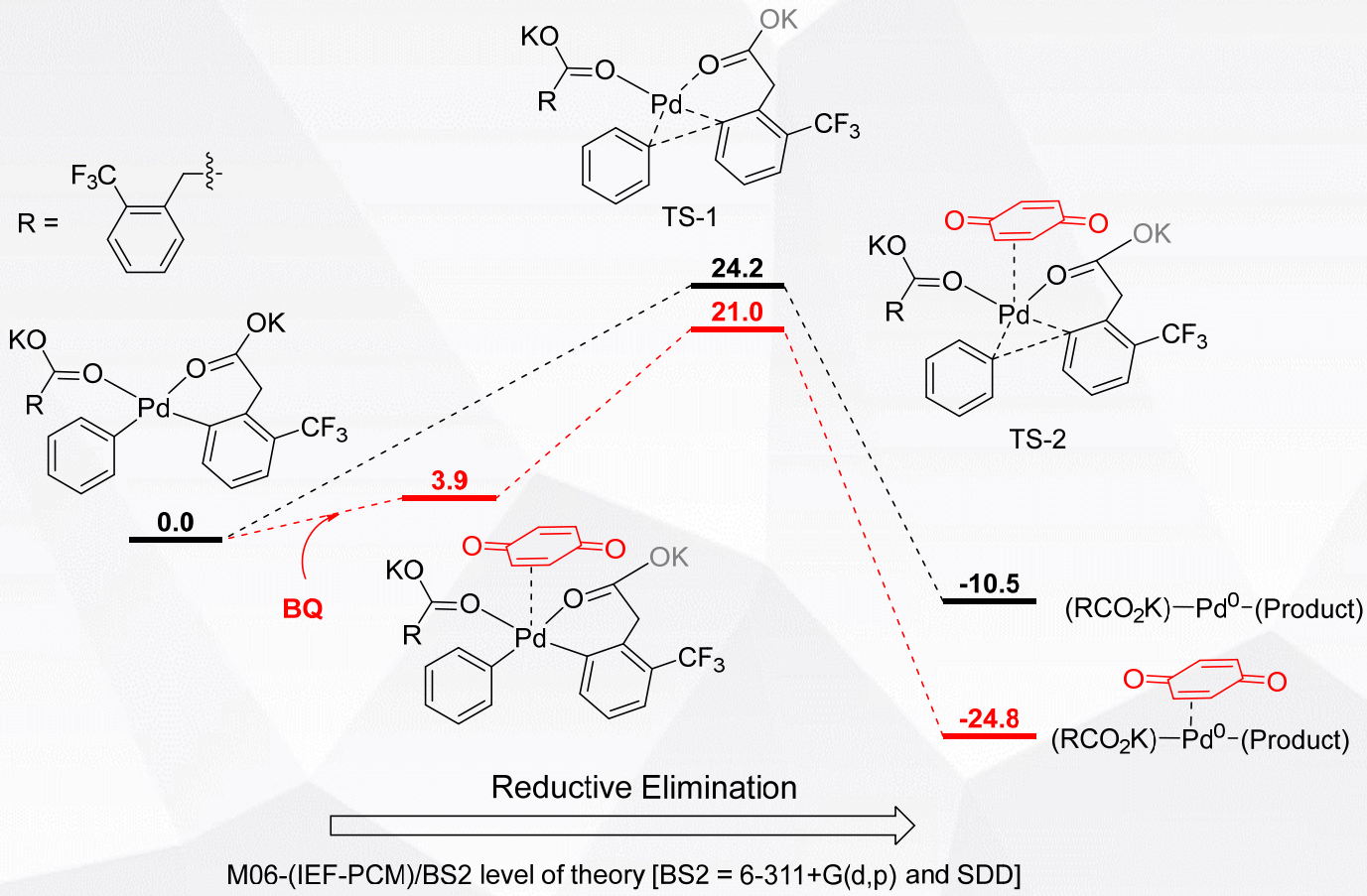
Yu, J.-Q. et al. *J. Am. Chem. Soc.* **2006**, *128*, 78-79.

02

Methylation: Pd

Based on C-H Activation

Extended explanation for benzoquinone:



Benzoquinone may coordinate with Pd to promote the reductive elimination step.

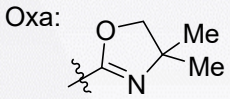
Stahl, S. S. et al. *Science* **2020**, *370*, 1454-1460.

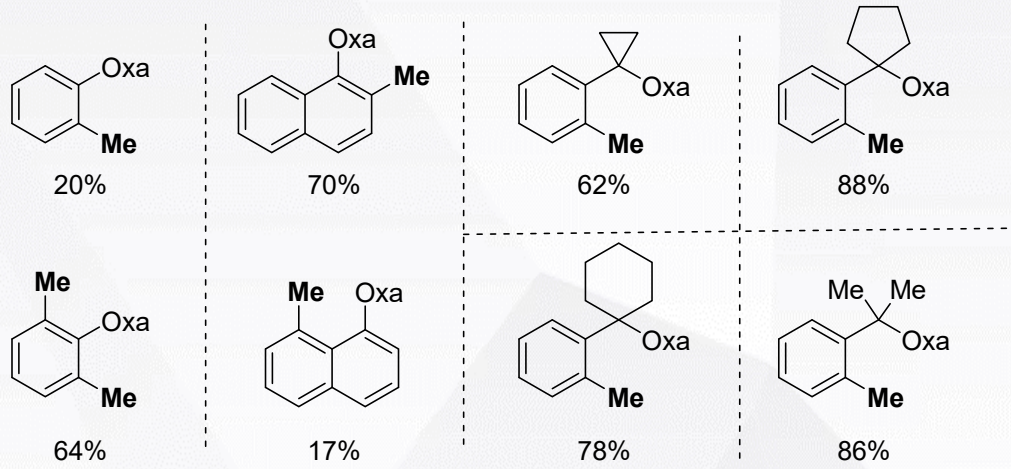
Methylation: Pd

Based on C-H Activation

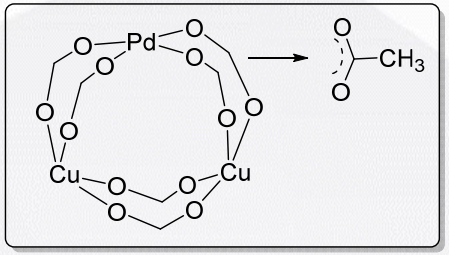
>> Yu, J.-Q 2006-a:

Oxa:





Condition: $Pd(OAc)_2$ (10 mol %), Me_4Sn (0.075 equiv. x 10), $Cu(OAc)_2$ (1 equiv.), benzoquinone (1 equiv.), MeCN, 100 °C, 40 h.



- Yu, J.-Q. et al. *J. Am. Chem. Soc.* **2006**, *128*, 78-79.
- Thornton, P. et al. *Inorg. Chim. Acta.* **1986**, *120*, 173.

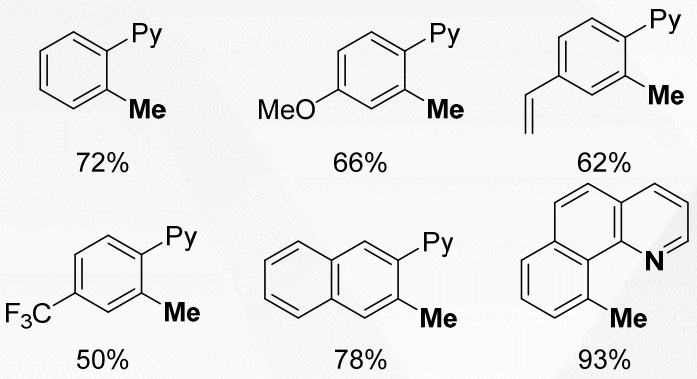
02

Methylation: Pd

Based on C-H Activation

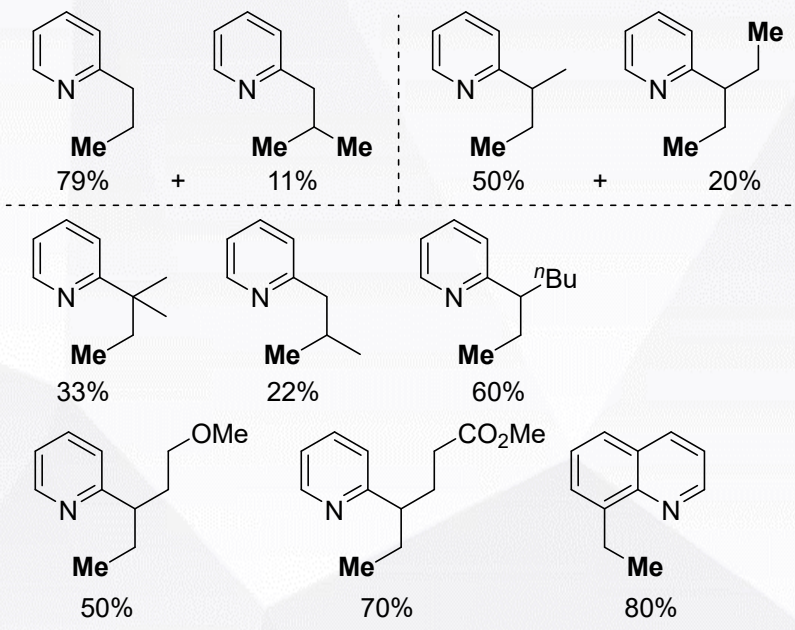
>> Yu, J.-Q 2006-b:

C(sp^2)-H



Condition: $Pd(OAc)_2$ (10 mol%), benzoquinone (1 equiv.) $Cu(OAc)_2$ (1 equiv.), **methylboroxine** (2 equiv.), 100 °C, 24 h, CH_2Cl_2, air.

C(sp^3)-H



Condition: $Pd(OAc)_2$ (10 mol%), benzoquinone (2 equiv.) $Cu(OAc)_2$ (2 equiv.), **methylboroxine** (2 equiv.), 100 °C, 24 h, HOAc, O_2.

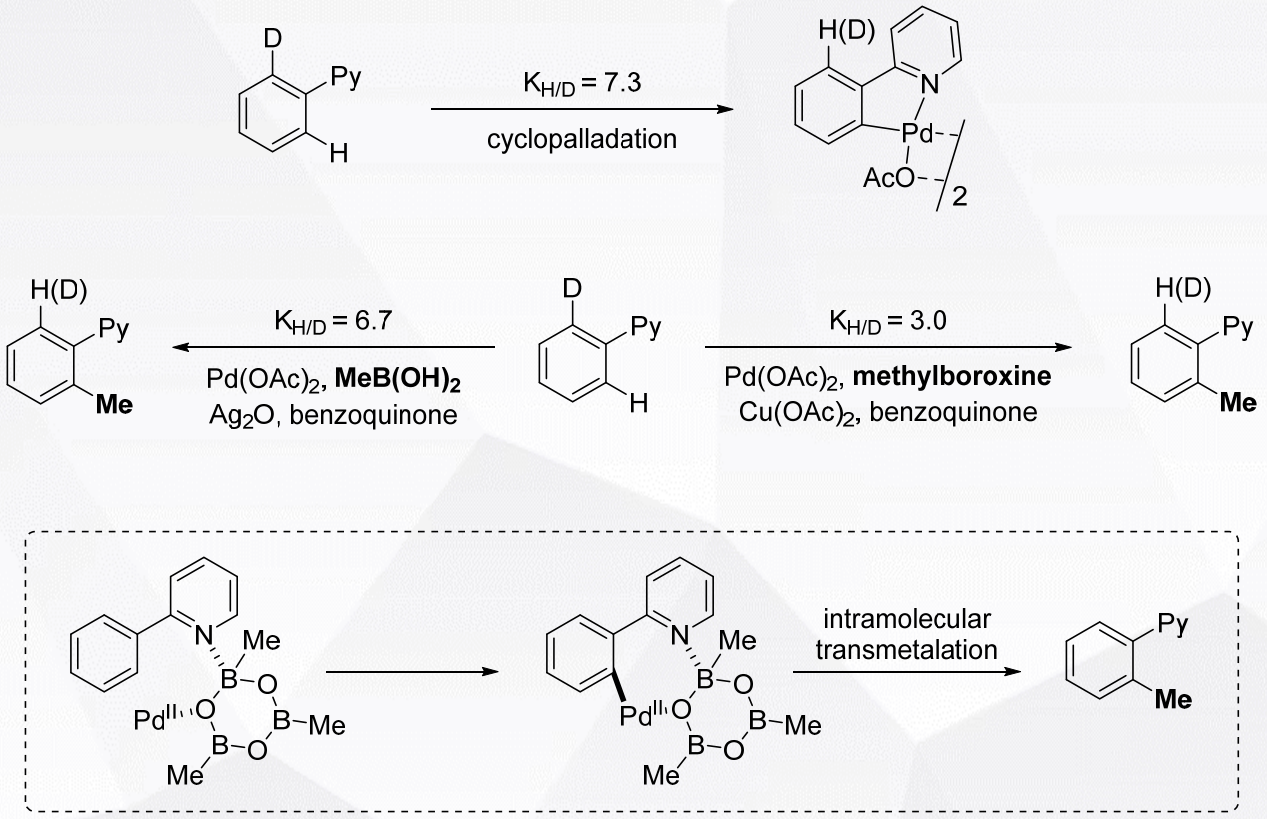
Yu, J.-Q. et al. *J. Am. Chem. Soc.* **2006**, *128*, 12634-12635.

02

Methylation: Pd

Based on C-H Activation

>> Yu, J.-Q 2006-b:



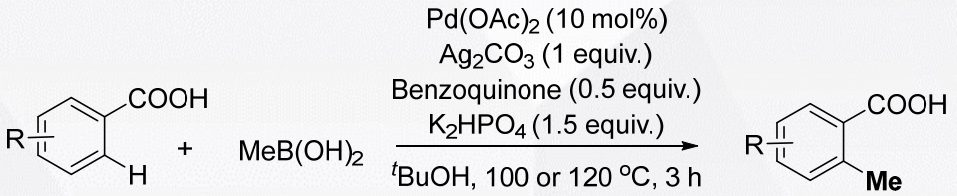
Yu, J.-Q. et al. *J. Am. Chem. Soc.* **2006**, *128*, 12634-12635.

02

Methylation: Pd

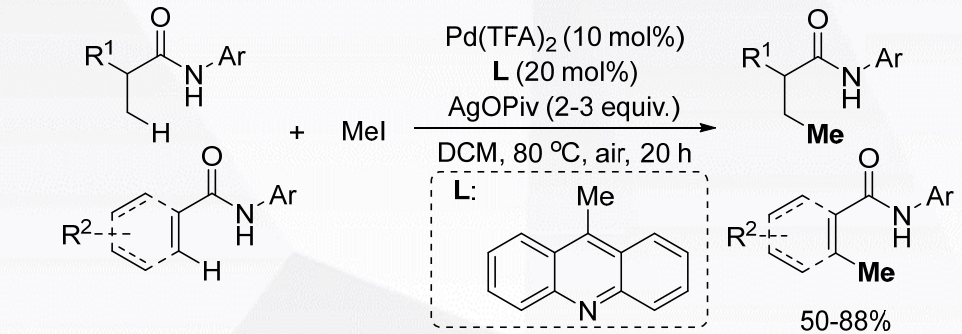
Based on C-H Activation

2007:

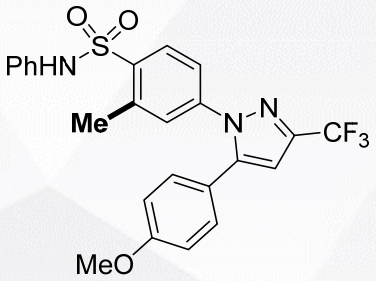


63-75%

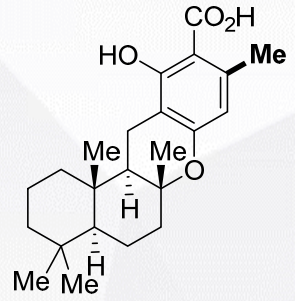
2014:



50-88%



2011: Celecoxib analogue
70%



2013: (+)-hongoquercin (A)
Methylation: 60%

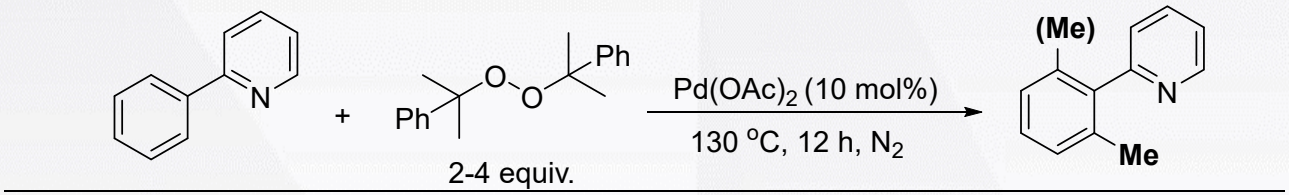
- Yu, J.-Q. et al. *J. Am. Chem. Soc.* **2007**, *129*, 3510-3511.
- Yu, J.-Q. et al. *J. Am. Chem. Soc.* **2014**, *136*, 13194-13197.
- Yu, J.-Q. et al. *J. Am. Chem. Soc.* **2011**, *133*, 7222-7228.
- Baran, P. S.; Yu, J.-Q. et al. *Angew. Chem. Int. Ed.* **2013**, *52*, 7317-7320.

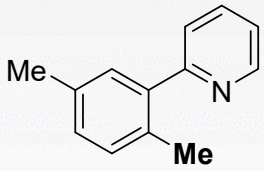
02

Methylation: Pd

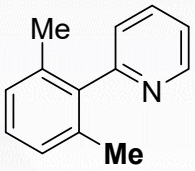
Based on C-H Activation

>> Li, C.-J 2008:

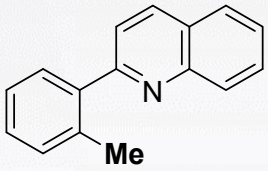




63%



55%



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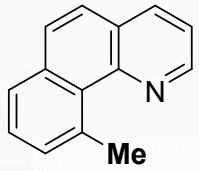
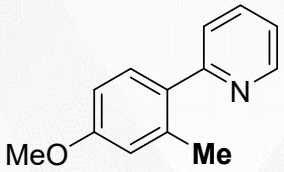


76%



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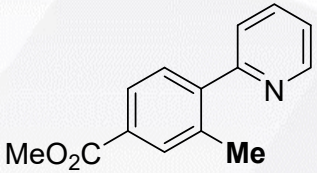

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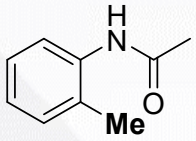
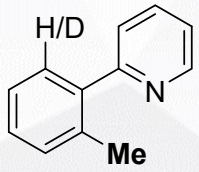


42%



mono:di = 42(1:1):30

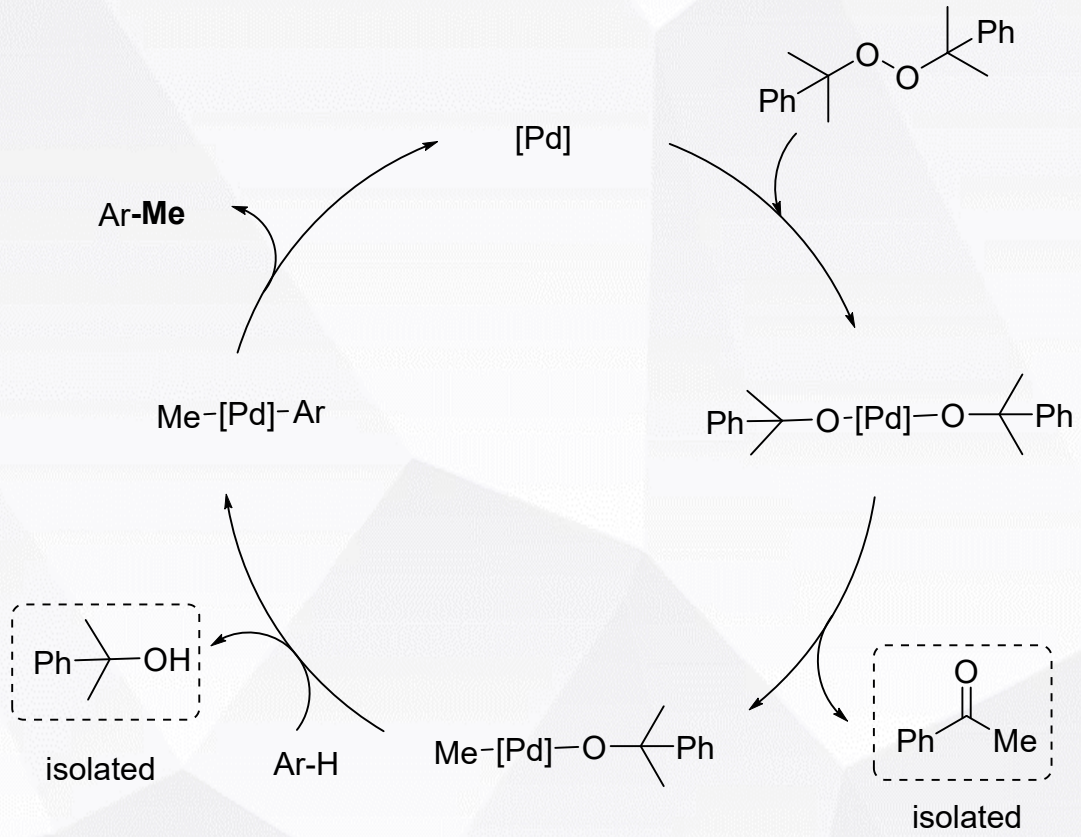
Li, C.-J. et al. *J. Am. Chem. Soc.* **2008**, *130*, 2900-2901.

02

Methylation: Pd

Based on C-H Activation

>> Li, C.-J 2008:



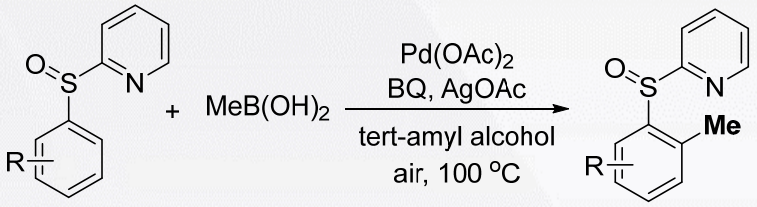
Li, C.-J. et al. *J. Am. Chem. Soc.* **2008**, *130*, 2900-2901.

02

Methylation: Pd

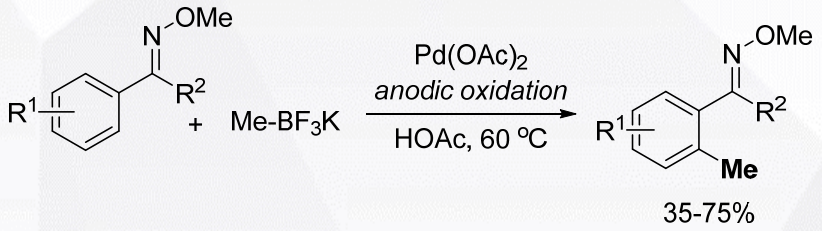
Based on C-H Activation

2011: Carretero



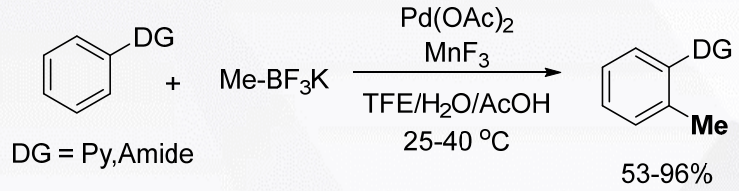
Carretero, J. C. et al. *J. Org. Chem.* **2011**, *76*, 9525-9530.

2017: Mei



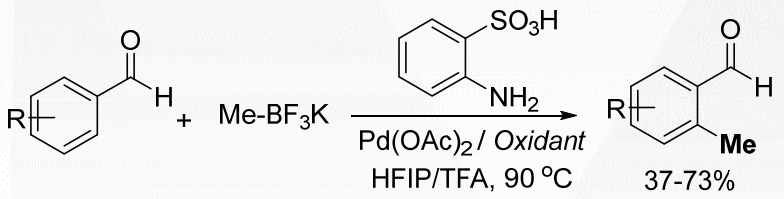
Mei, T.-S. et al. *Chem. Commun.* **2017**, *53*, 12189-12192.

2013: Sanford



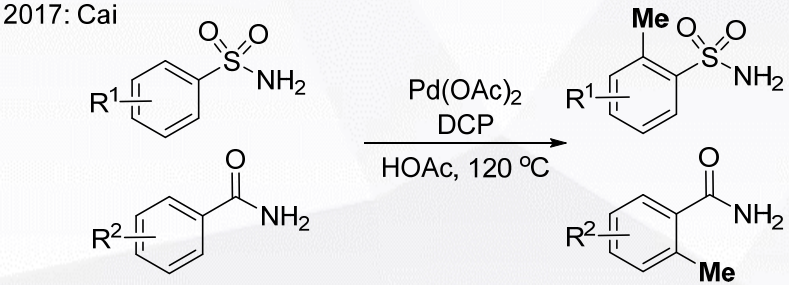
Sanford, M. S. et al. *Org. Lett.* **2013**, *15*, 2302-2305.

2018: Sorensen



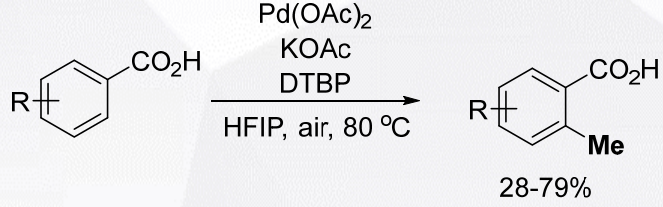
Sorensen, E. J. et al. *J. Am. Chem. Soc.* **2018**, *140*, 2789-2792.

2017: Cai



Cai, C. et al. *Org. Chem. Front.* **2017**, *4*, 2207-2210.

2019: Cheng



Cheng, G. et al. *J. Org. Chem.* **2019**, *84*, 9786-9791.

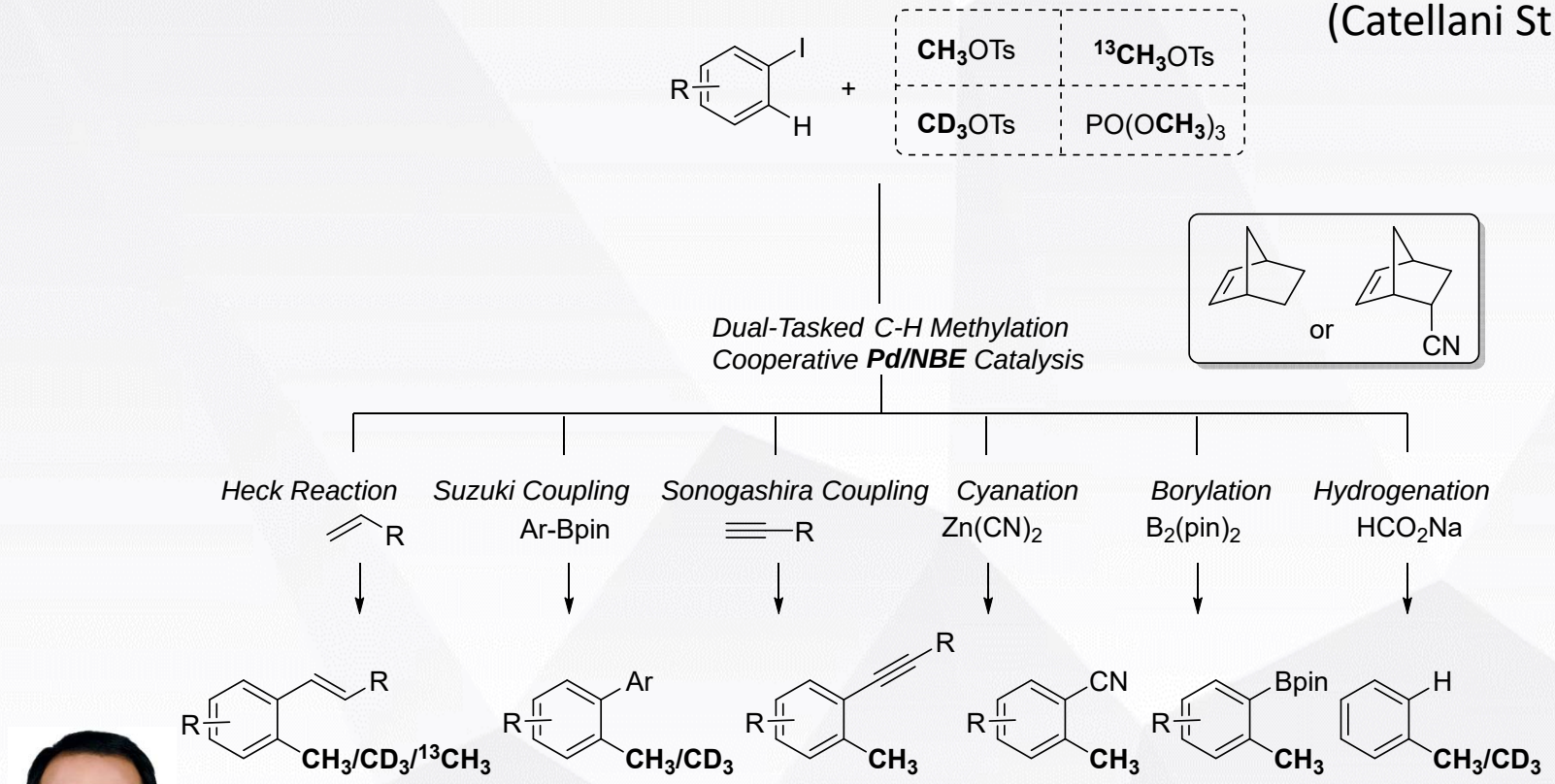
02

Methylation: Pd

Based on C-H Activation

>> Zhou, Q. 2019:

(Catellani Strategy)



Zhou, Q. et al. *J. Am. Chem. Soc.* **2019**, *141*, 15986-15993.

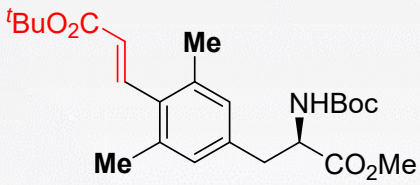
02

Methylation: Pd

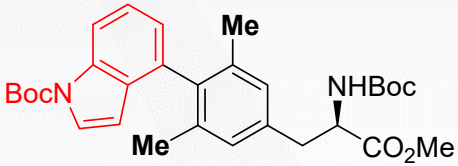
Based on C-H Activation

>> Zhou, Q. 2019:

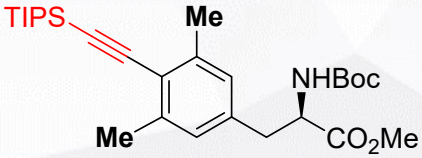
Methylation of Biologically Important Substrate



79%

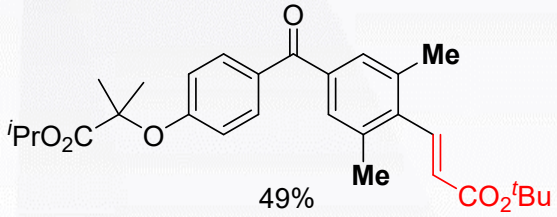


58%



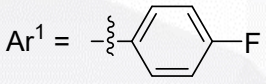
83%, 99% ee

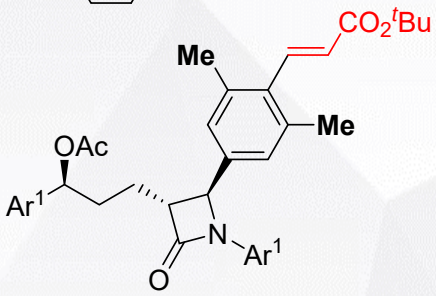
Late-Stage Modification of Medicinal Agents



49%

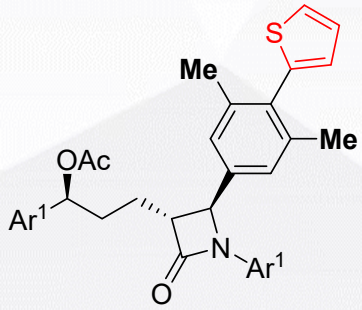
from fenofibrate "Tricor"





61%

from ezetimibe "Zatia"



31%

Zhou, Q. et al. *J. Am. Chem. Soc.* **2019**, *141*, 15986-15993.

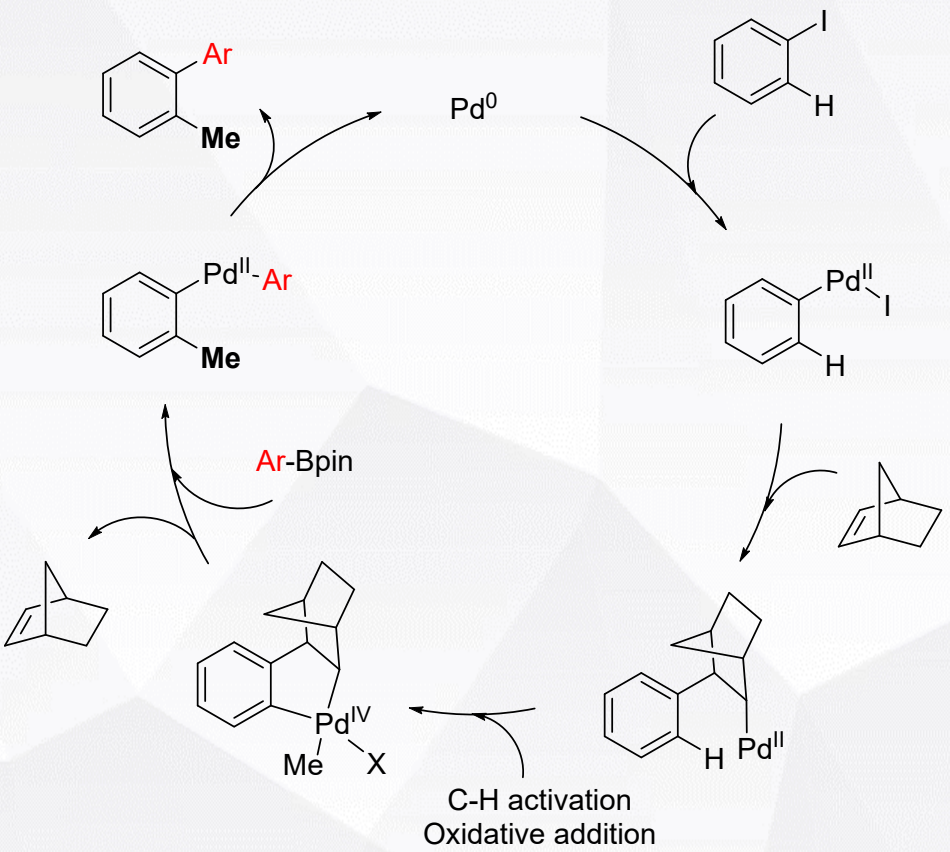
02

Methylation: Pd

Based on C-H Activation

>> Zhou, Q. 2019:

Proposed mechanism: $Pd^0/Pd^{II}/Pd^{IV}$ (Catellani Strategy)



- Zhou, Q. et al. *J. Am. Chem. Soc.* **2019**, *141*, 15986-15993.
- Peng, Y. et al. *J. Org. Chem.* **2018**, *83*, 13211-13216.

02

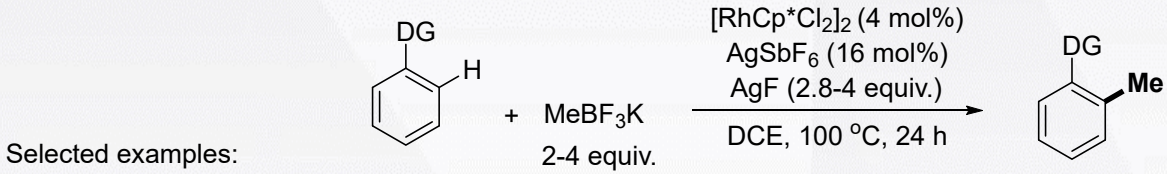
Methylation:

Based on C-H Activation

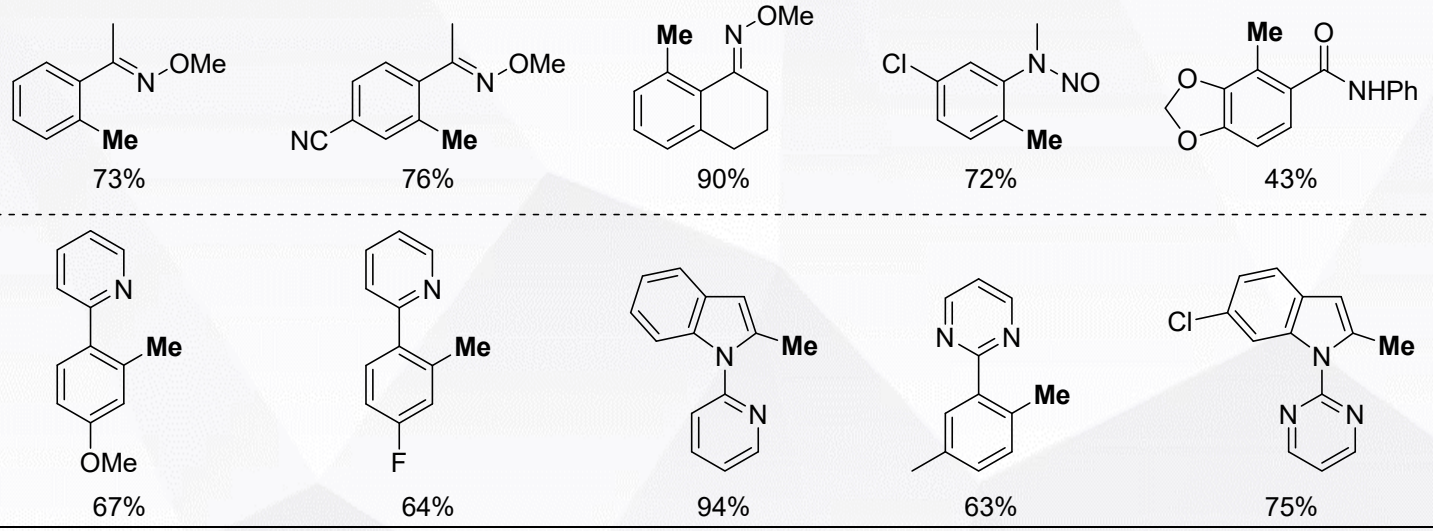
45 Rh

Rhodium catalysis

>> Li, X. 2015:



Selected examples:



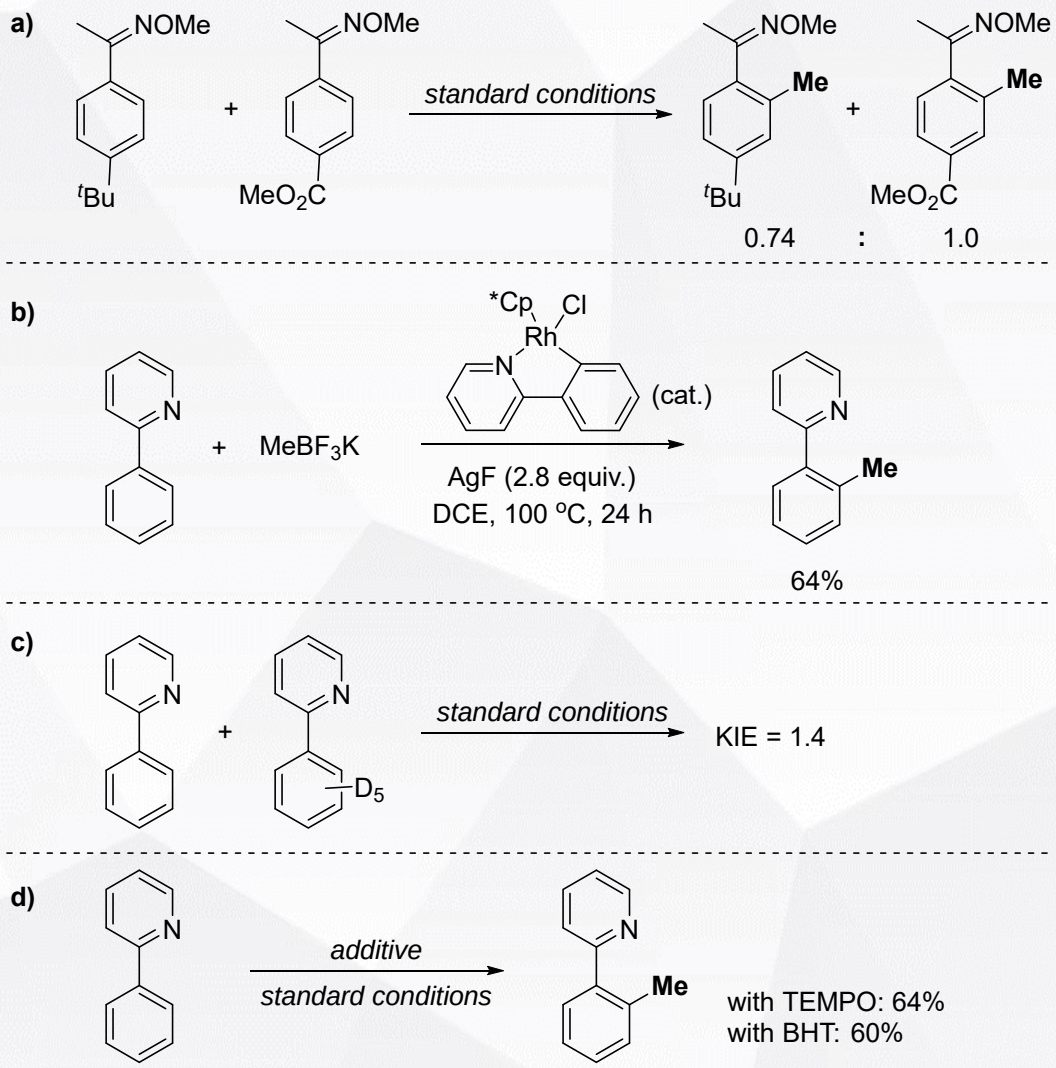
Li, X. et al. *Org. Lett.* **2015**, *17*, 2812-2815.

02

Methylation: Rh

Based on C-H Activation

>> Li, X. 2015:



Li, X. et al. *Org. Lett.* **2015**, *17*, 2812-2815.

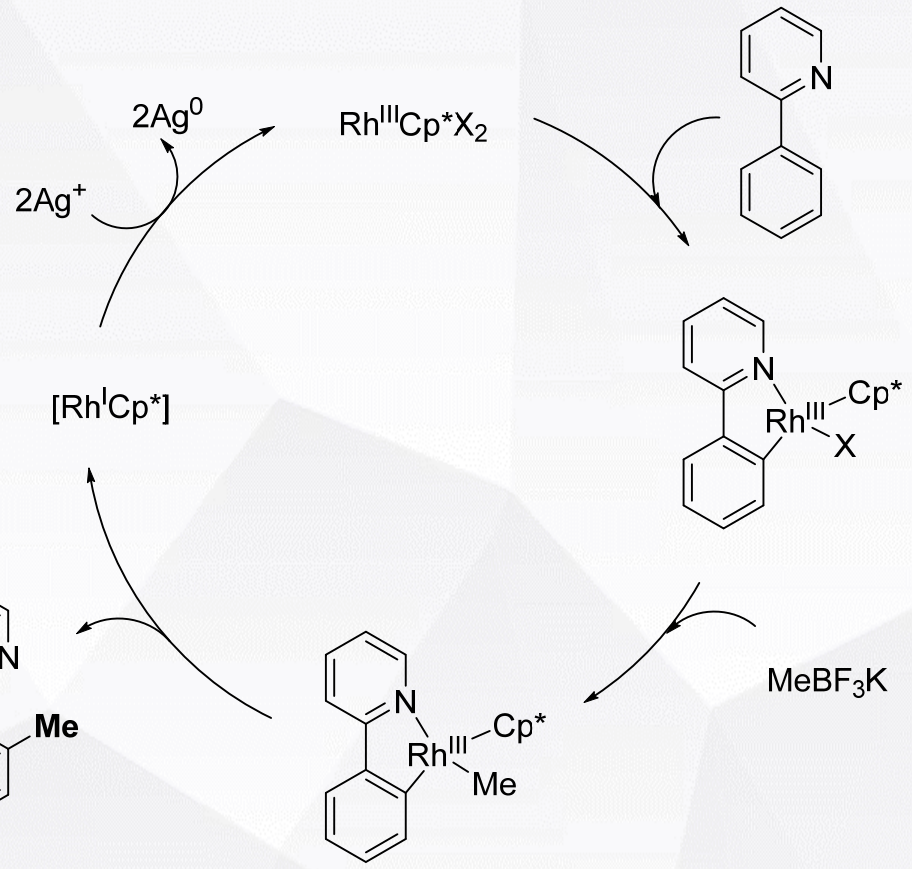
02

Methylation: Rh

Based on C-H Activation

>> Li, X. 2015:

Proposed mechanism: Rh^{I}/Rh^{III}



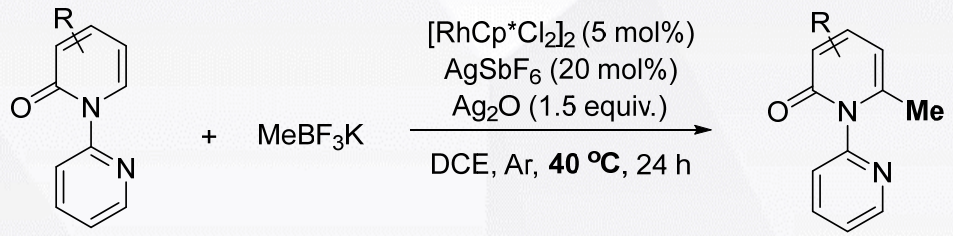
Li, X. et al. *Org. Lett.* **2015**, *17*, 2812-2815.

02

Methylation: Rh

Based on C-H Activation

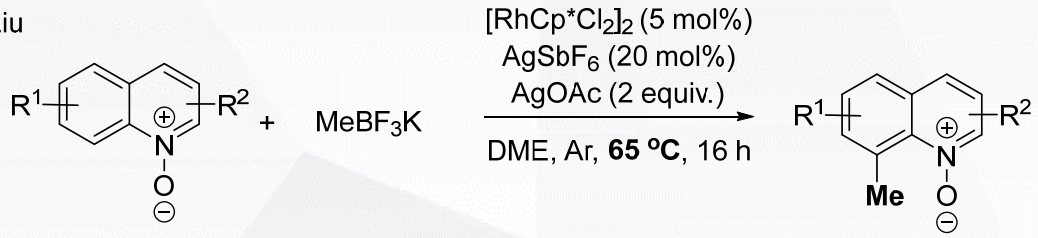
2016: Liu



Liu, H. et al. *Org. Lett.* **2016**, *18*, 5376-5379.

78-93%

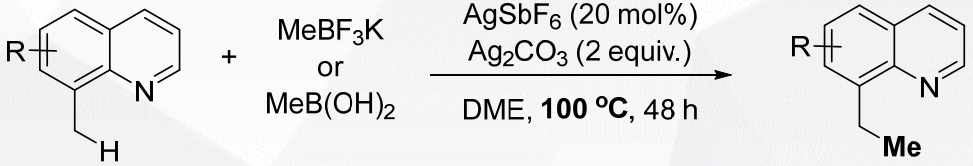
2017: Liu



Liu, H. et al. *Adv. Synth. Catal.* **2017**, *359*, 3029-3034.

52-96%

2019: Sharma



Sharma, U. et al. *Org. Lett.* **2020**, *22*, 305-309.

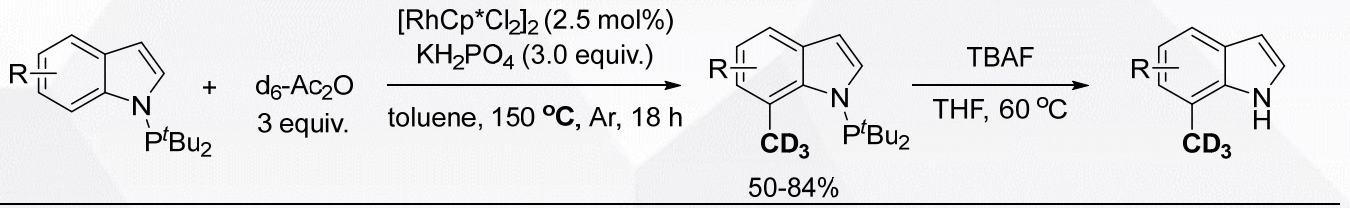
39-92%

02

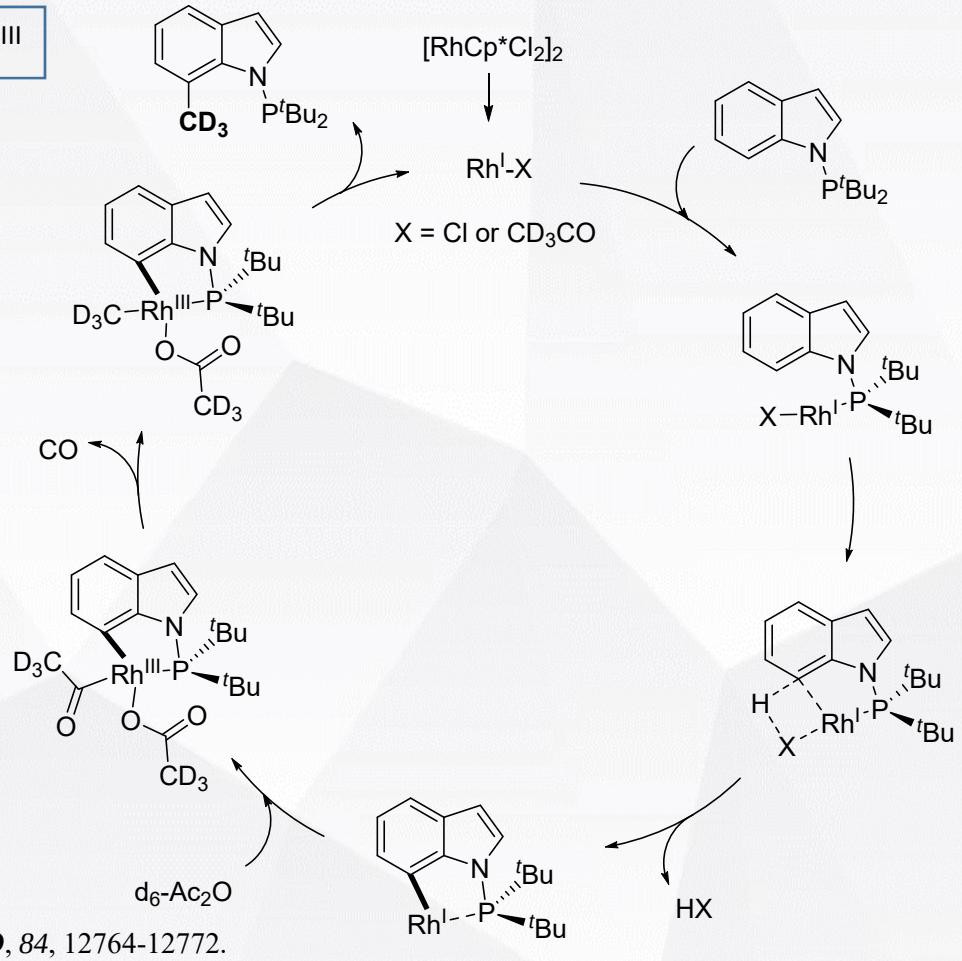
Methylation: Rh

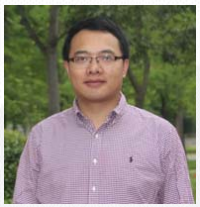
Based on C-H Activation

>> Shi, Z. 2019:



Proposed mechanism: Rh^{I}/Rh^{III}





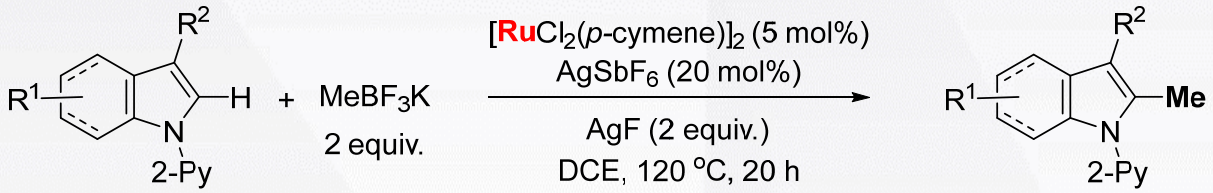
Shi, Z. et al. *J. Org. Chem.* **2019**, *84*, 12764-12772.

02

Methylation: Ru/Ir

Based on C-H Activation

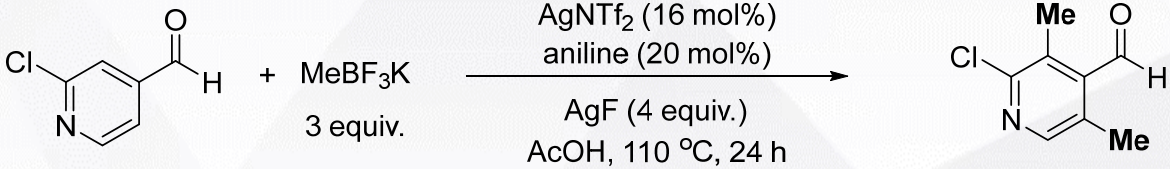
2016: Ackermann



58-93%

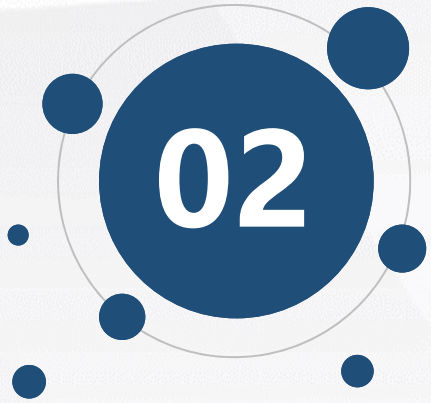
Ackermann, L. et al. *Synthesis* **2017**, *49*, 127-134.

2018: Sorensen



18%

Sorensen, E. J. et al. *Chem. Sci.* **2018**, *9*, 8951-8956.



Methylation

Based on C-H Activation

***Cheap** Metals:*

25	26	27	28
Mn	**Fe**	**Co**	**Ni**

02

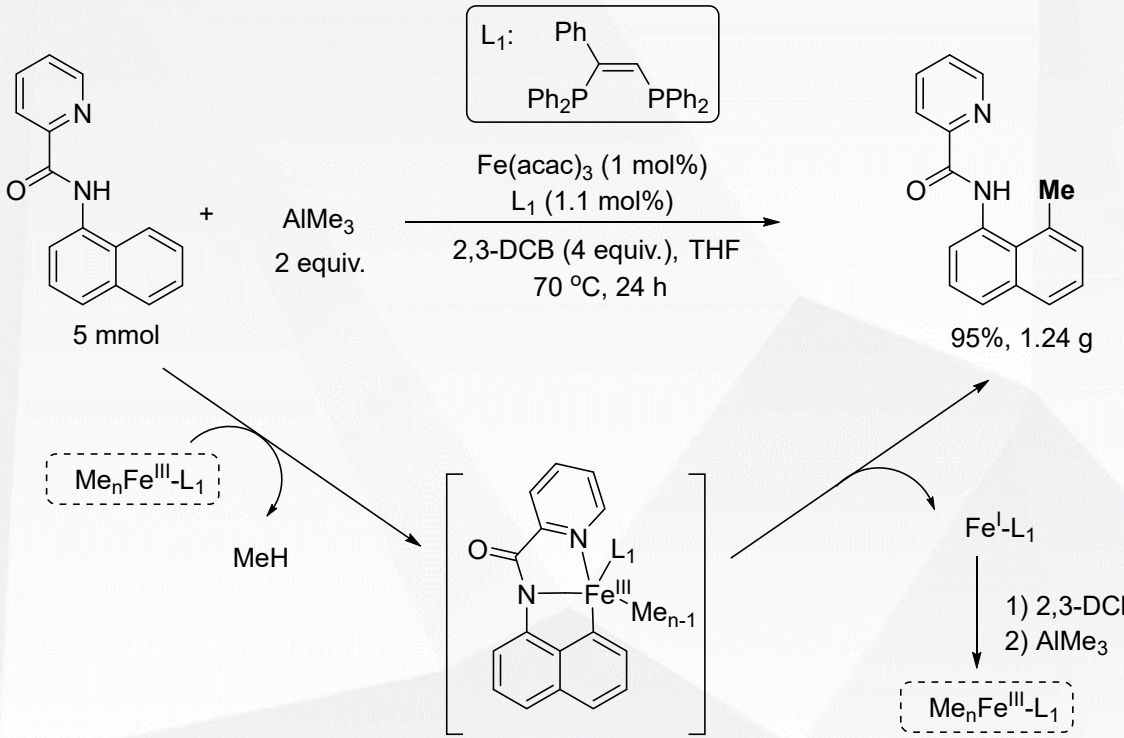
Methylation:

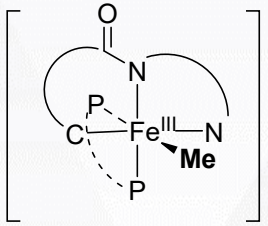
Based on C-H Activation

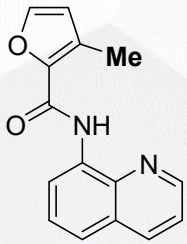
26 Fe

Iron catalysis

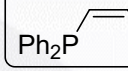
>> Nakamura, E. 2015:







L2: dppen



99%
65% with 0.01 mmol% Fe, **TON up to 6500**

- Nakamura, E. et al. *J. Am. Chem. Soc.* **2015**, *137*, 7660-7663.
- Nakamura, E. et al. *Adv. Synth. Catal.* **2015**, *357*, 2175-2179.
- Yoshikai, N. et al. *ChemSusChem.* **2019**, *12*, 3049-3053.

02

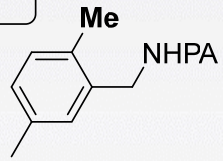
Methylation: Fe

Based on C-H Activation

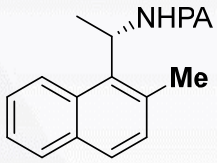
>> Nakamura, E. 2015:

Selected examples:

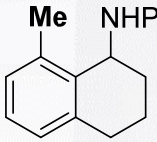
C(sp^2)-H



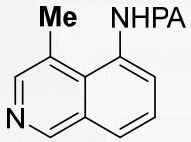
96%



95%, 99% ee

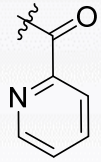


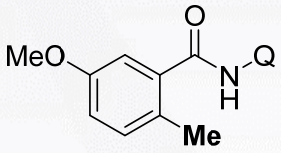
88%



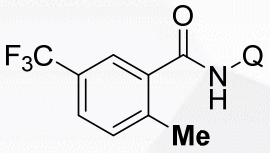
< 5%

PA =

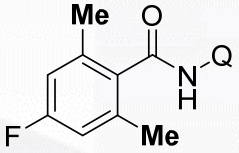




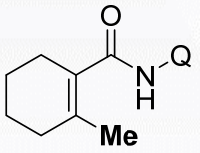
87%



95%

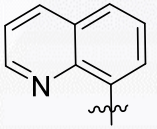


90%, mono: 7%



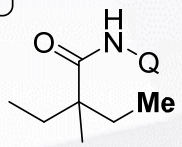
81%

Q =

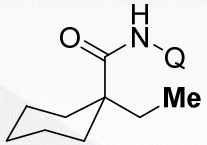


C(sp^3)-H

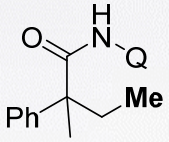
10 mol% Fe & 11 mol% Ph-dppen



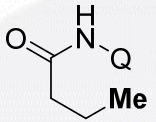
64%, di < 5%



82%



58%, di < 5%



0%

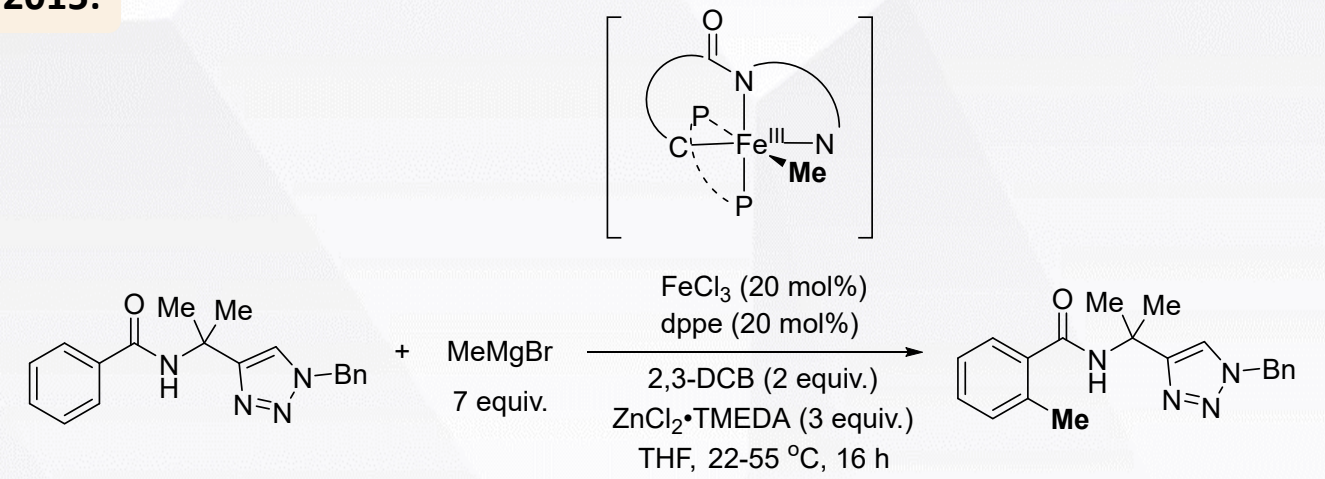
Nakamura, E. et al. *J. Am. Chem. Soc.* **2015**, *137*, 7660-7663.

02

Methylation: Fe

Based on C-H Activation

>> Ackermann, L. 2015:



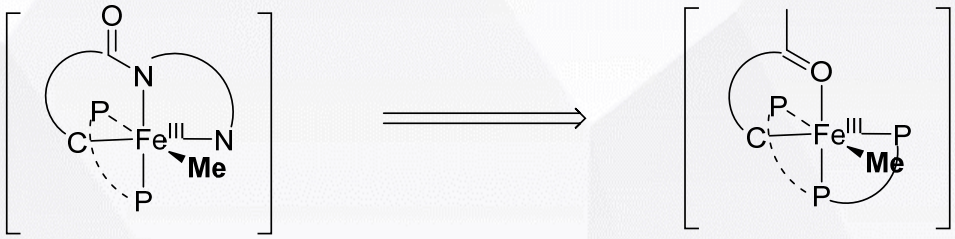
Ackermann, L. et al. *Chem. Eur. J.* **2015**, *21*, 8812-8815.

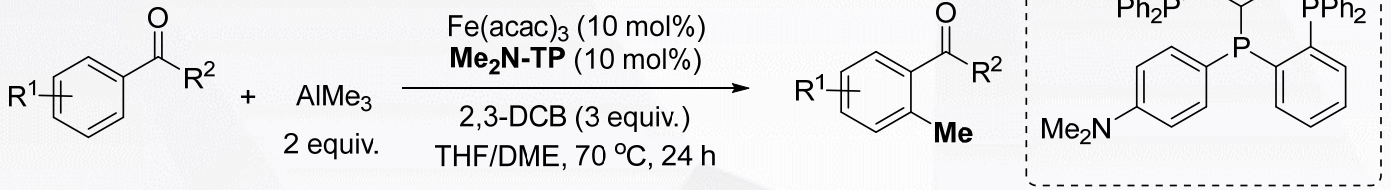
02

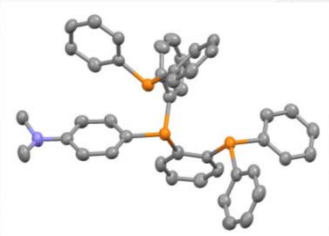
Methylation: Fe

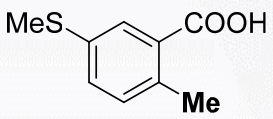
Based on C-H Activation

>> Nakamura, E. 2016:

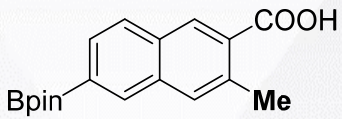




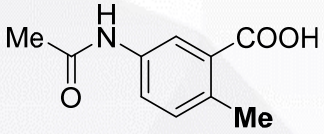




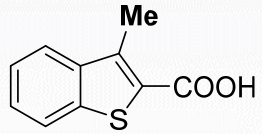
89%



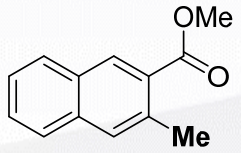
95%
(89%, 1.11 g)



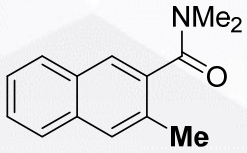
50%



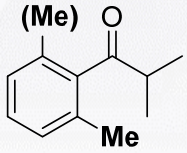
55%



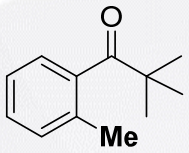
76%



66%



mono:di = 70%:22%



98%
K_H/K_D= 1.23

Nakamura, E. et al. *J. Am. Chem. Soc.* **2016**, *138*, 10132-10135.

02

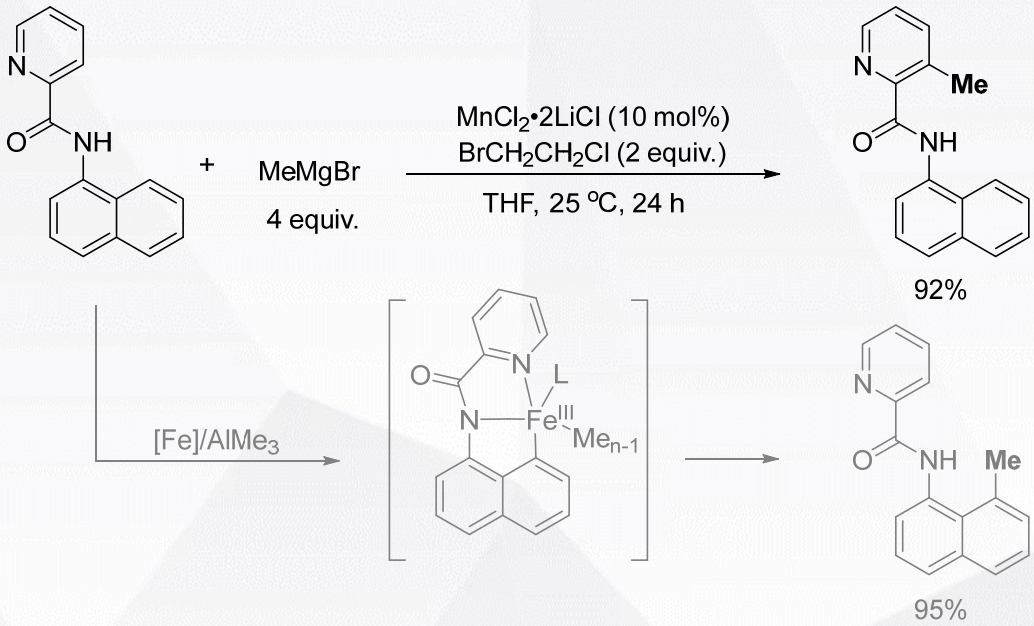
Methylation:

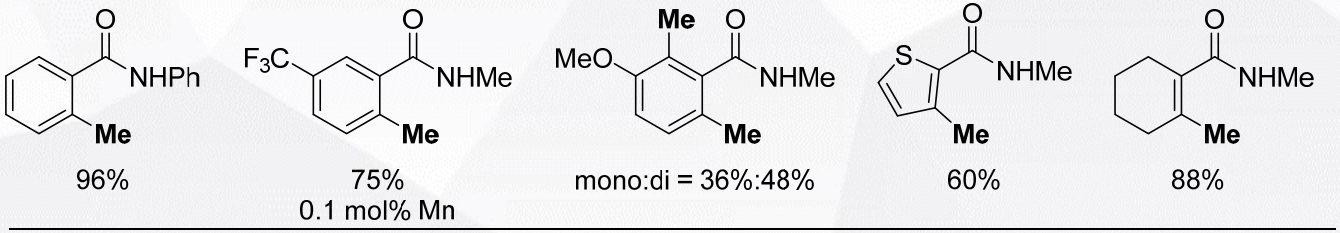
Based on C-H Activation

25 Mn

Manganese catalysis

>> Nakamura, E. 2017:





condition: [Mn] (1 mol%)

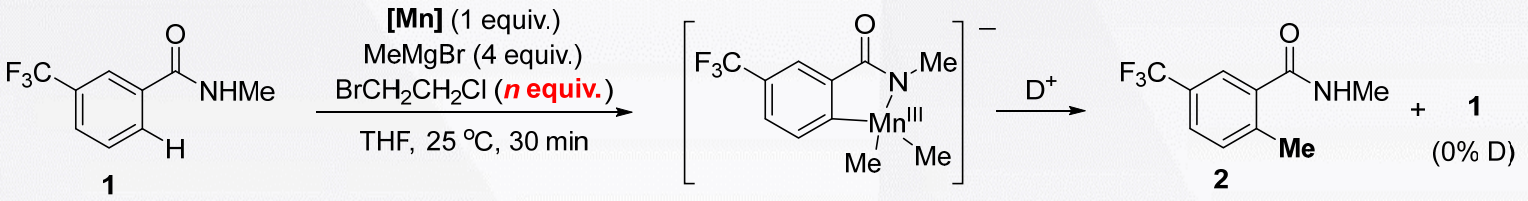
Nakamura, E. et al. *Org. Lett.* **2017**, *19*, 5458-5461.

02

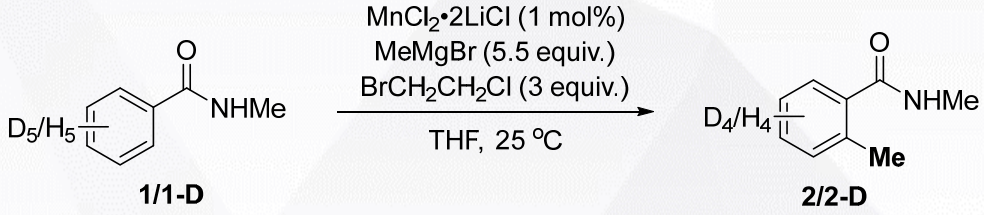
Methylation: Mn

Based on C-H Activation

>> Nakamura, E. 2017:



$Mn(acac)_2$	$n = 2$	55%	40%
$Mn(acac)_3$	$n = 2$	41%	54%
$Mn(acac)_2$	$n = 0$	0%	100%
$Mn(acac)_3$	$n = 0$	17%	82%



1/1-D **2/2-D**

time / h	1.5	2	2.5	3
yield of **2** (%)	9	14	20	25
yield of **2-D** (%)	5	7	9	12

$K_H/K_D = 2.0 \pm 0.1$

- Nakamura, E. et al. *Org. Lett.* **2017**, *19*, 5458-5461.
- Girolami, G. S. et al. *J. Am. Chem. Soc.* **1988**, *110*, 6245-6246.

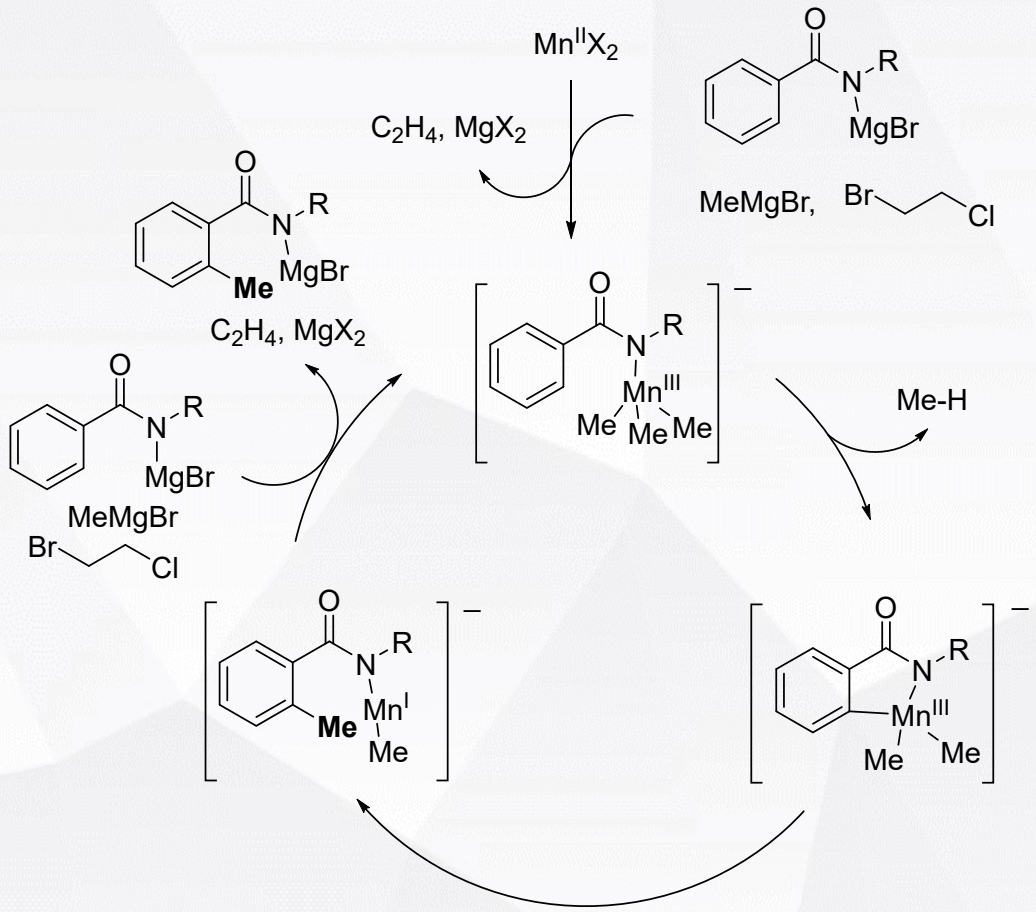
02

Methylation: Mn

Based on C-H Activation

>> Nakamura, E. 2017:

Proposed mechanism: Mn^{I}/Mn^{III}



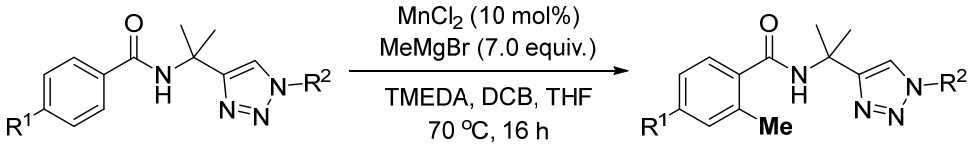
- Nakamura, E. et al. *Org. Lett.* **2017**, *19*, 5458-5461.
- Girolami, G. S. et al. *J. Am. Chem. Soc.* **1988**, *110*, 6245-6246.

02

Methylation: Mn

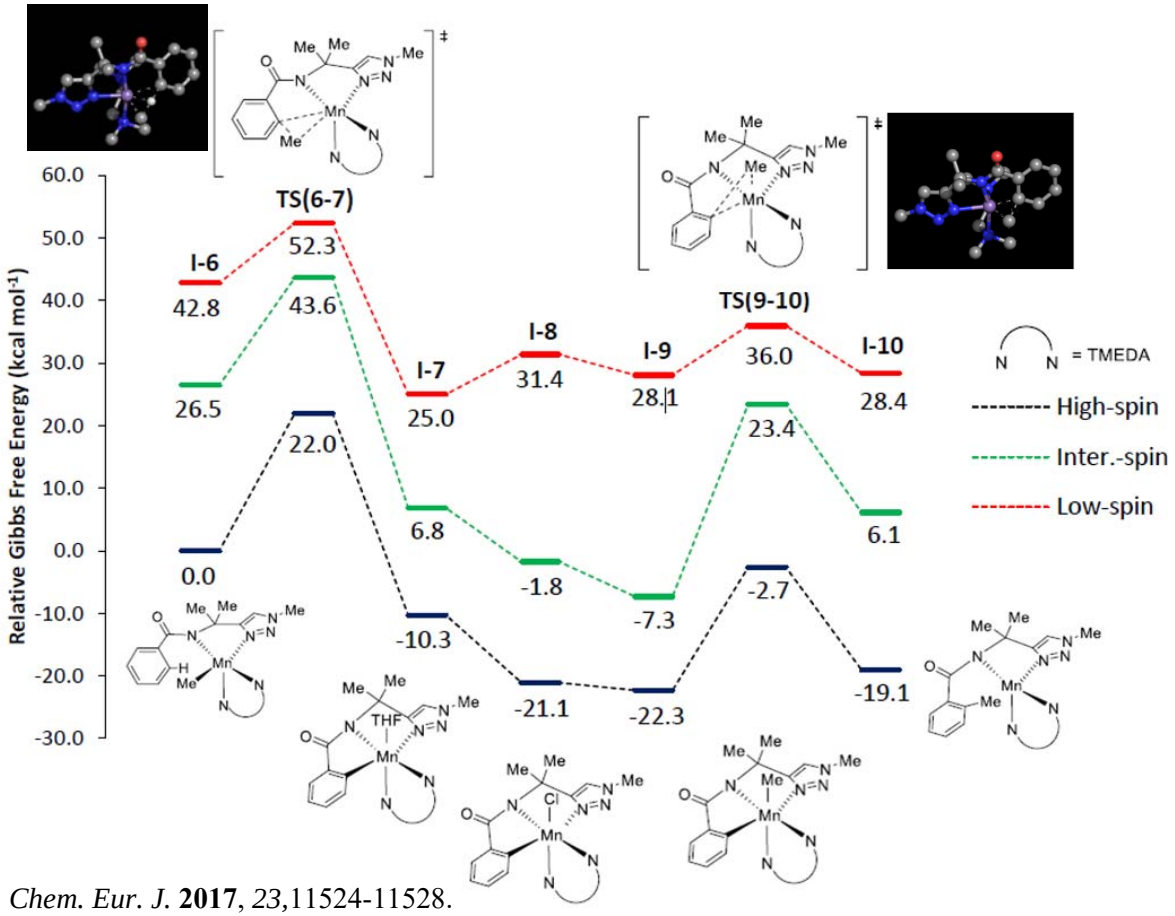
Based on C-H Activation

>> Ackermann, L. 2017:



R^1 = H, ^{t}Bu; R^2 = ^{n}Bu

R^1 = H, OMe; R^2 = Bn



Ackermann, L. et al. *Chem. Eur. J.* **2017**, *23*,11524-11528.

02

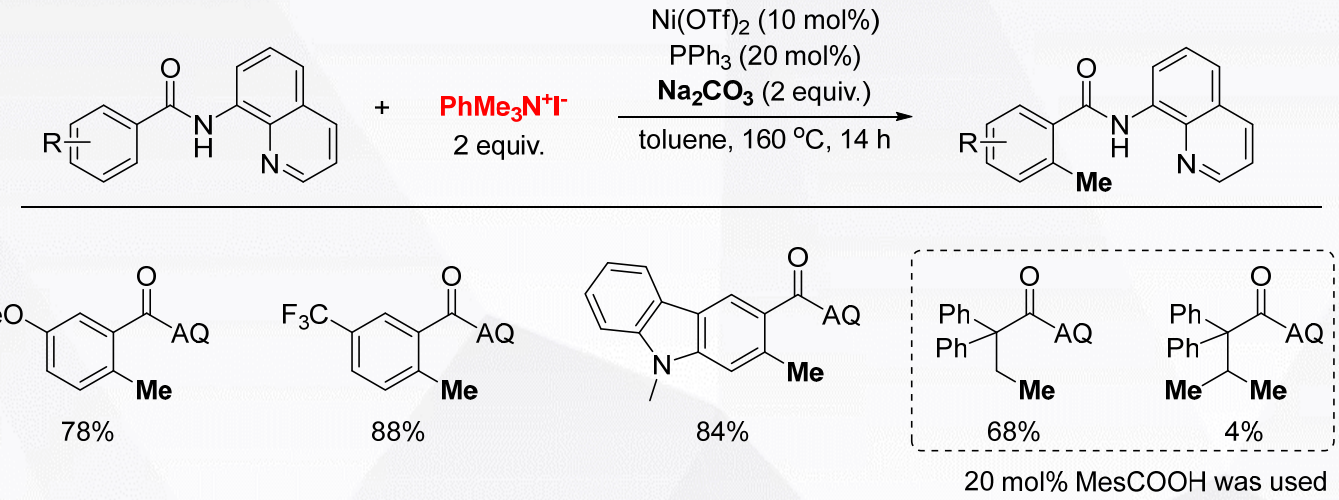
Methylation:

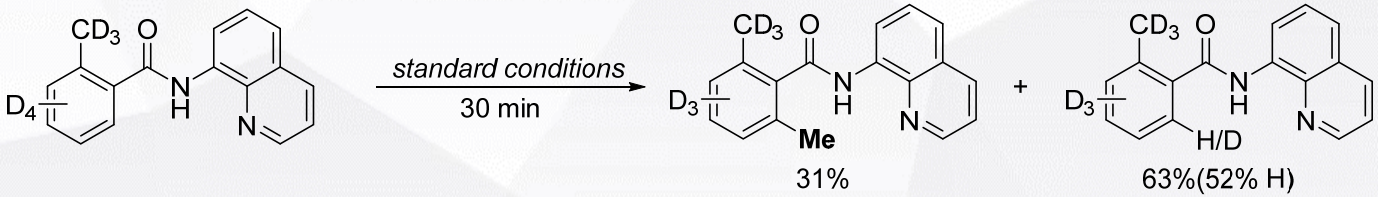
Based on C-H Activation

28 Ni

Nickel catalysis

>> Chatani, N. 2016:





Chatani, N. et al. *Angew. Chem. Int. Ed.* **2016**, *55*, 3162-3165.

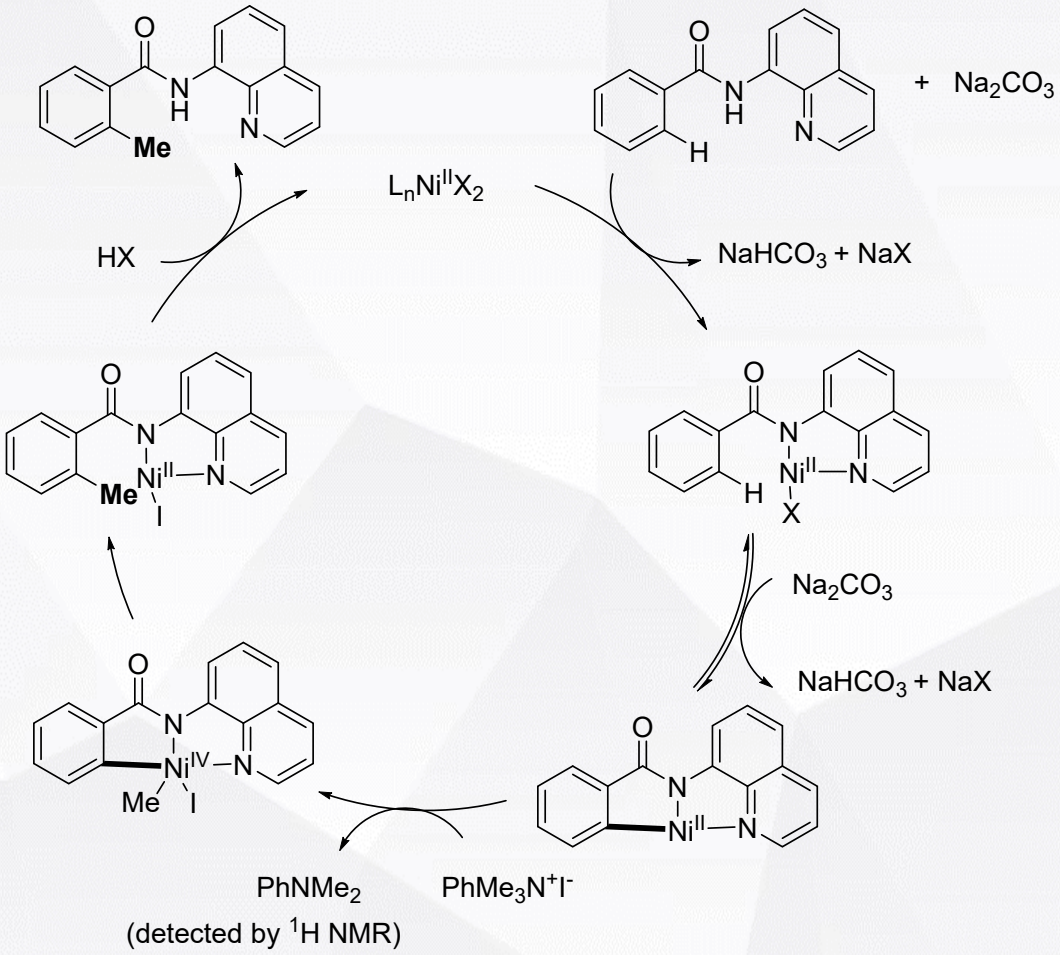
02

Methylation: Ni

Based on C-H Activation

>> Chatani, N. 2016:

Proposed mechanism: Ni^{II}/Ni^{IV}



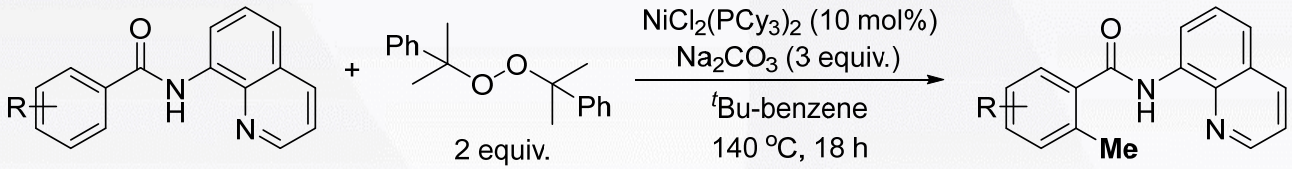
Chatani, N. et al. *Angew. Chem. Int. Ed.* **2016**, *55*, 3162-3165.

02

Methylation: Ni

Based on C-H Activation

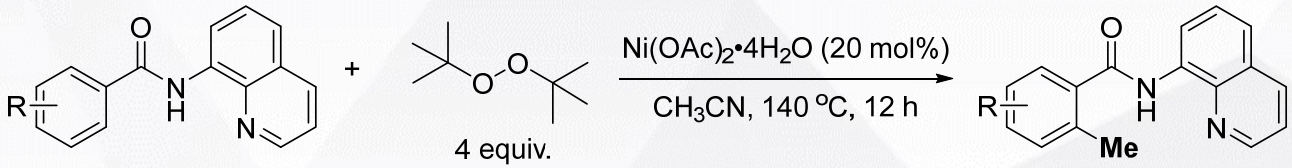
2016: Chatani



44-84%

Chatani, N. et al. *Org. Lett.* **2016**, *18*, 1698-1701.

2019: Chen



42-85%

Chen, X.; Tan, Z. et al. Eur. *J. Org. Chem.* **2019**, 6930-6934.

02

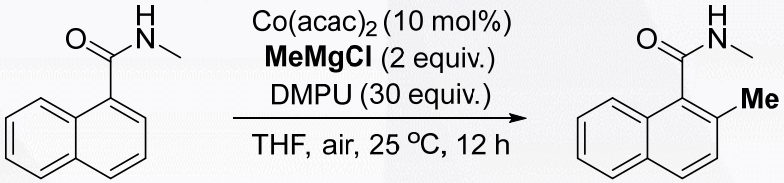
Methylation:

Based on C-H Activation

27 Co

Cobalt catalysis

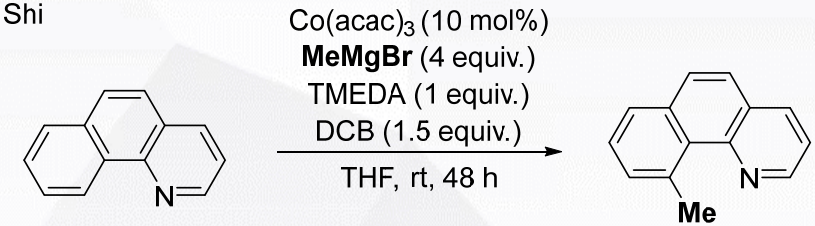
2011: Nakamura



Nakamura, E. et al. *Org. Lett.* **2011**, *13*, 3232-3234.

68%

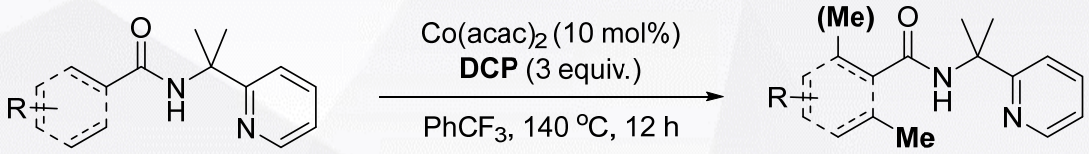
2011: Shi



Shi, Z. et al. *Angew. Chem. Int. Ed.* **2011**, *50*, 1109-1113.

83%

2016: Lu



Lu, H.; Li, G. et al. *Chem. Eur. J.* **2016**, *22*, 12286-12289.

51-84%

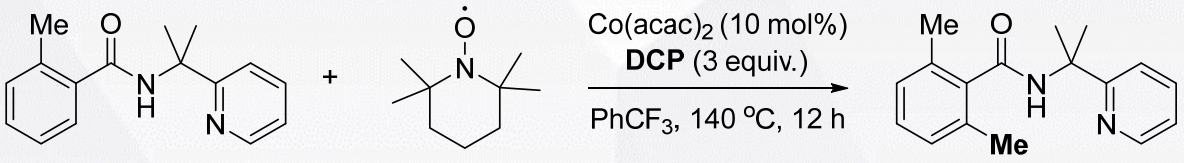
02

Methylation: Co

Based on C-H Activation

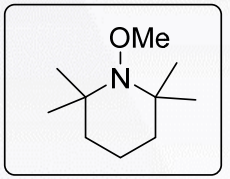
>> Lu, H. 2016:

a) radical trapping experiment



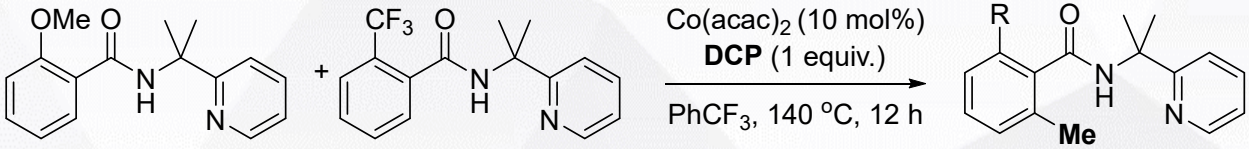
1a TEMPO **2a**

TEMPO (equiv.)	yield of **2a**
1.0	66%
2.0	41%
3.0	0%



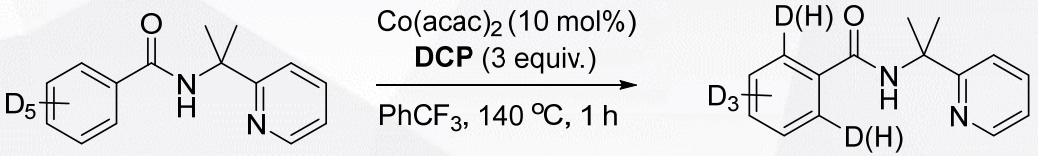
detected by GCMS

b) intermolecular competition experiment



CF_3/OMe = 37%/12%

c) H/D scrambling experiment



(>95% D) recovered 37% (82% D)

Lu, H.; Li, G. et al. *Chem. Eur. J.* **2016**, *22*, 12286-12289.

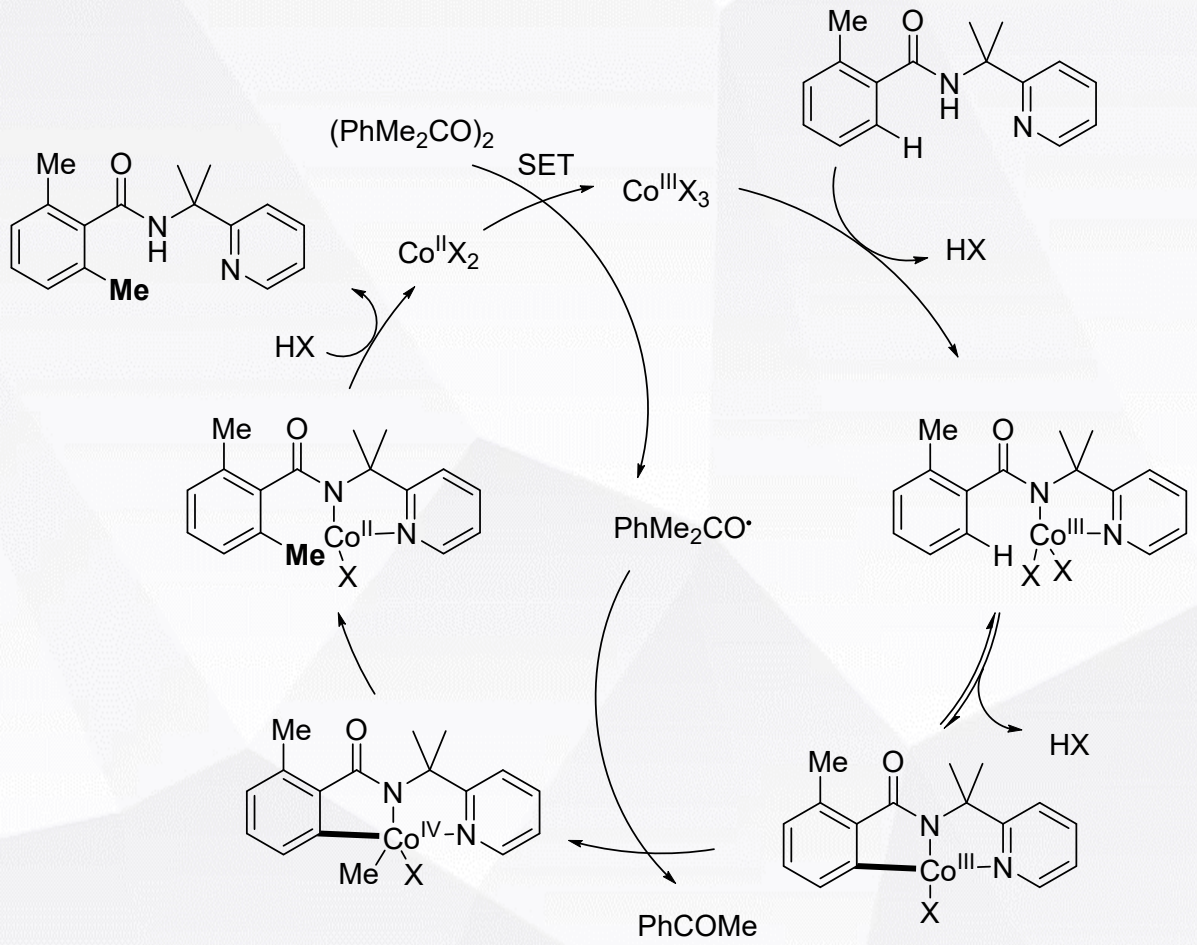
02

Methylation: Co

Based on C-H Activation

>> Lu, H. 2016:

Proposed mechanism: Co^{II}/Co^{IV}



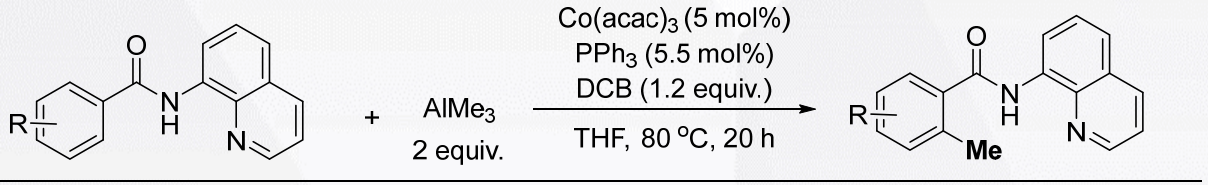
Lu, H.; Li, G. et al. *Chem. Eur. J.* **2016**, *22*, 12286-12289.

02

Methylation: Co

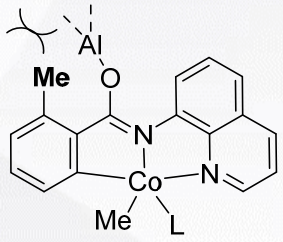
Based on C-H Activation

>> Xu, K. 2016:



90% | 92% | 86% | 92%

73% | 0% | 87% (10% [Co]) | 46% (10% [Co])



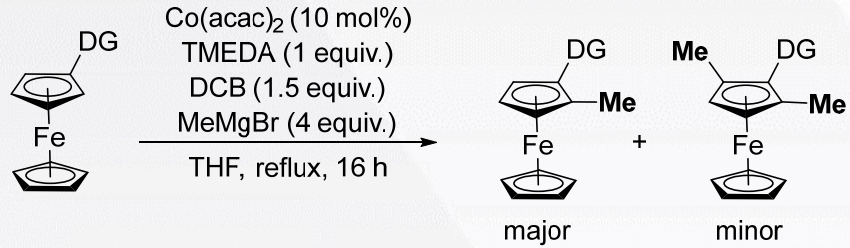
Xu, K. et al. *Org. Lett.* **2016**, *18*, 5628-5631.

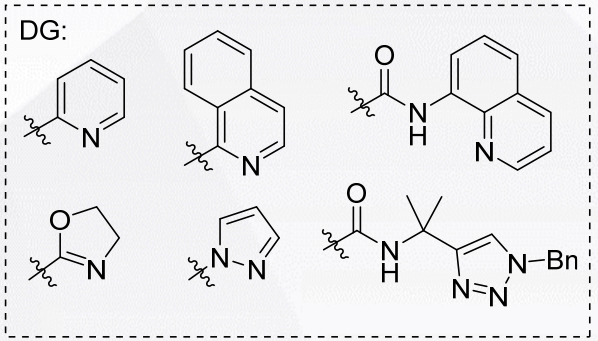
02

Methylation: Co

Based on C-H Activation

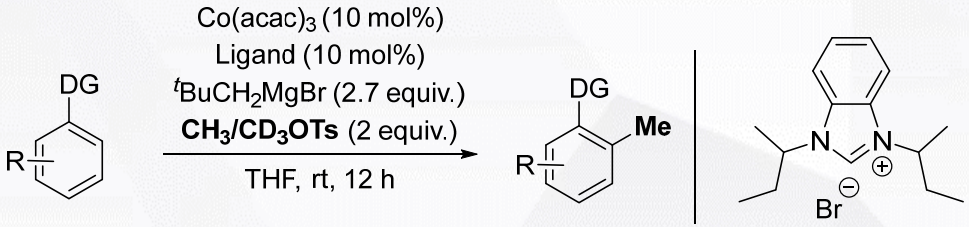
2017: Butenschön

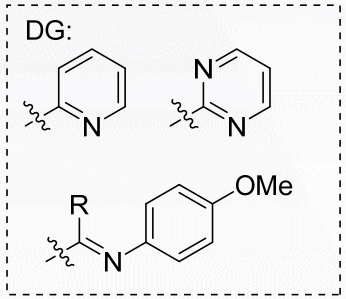




Butenschön, H. et al. *Eur. J. Org. Chem.* **2017**, 3041-3048.

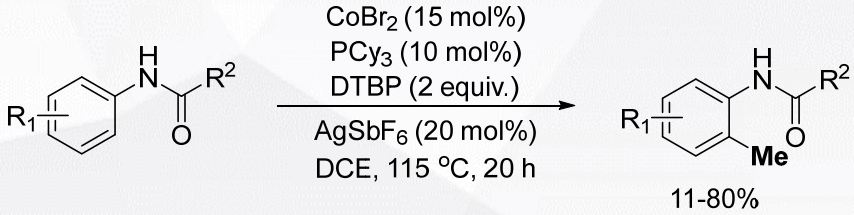
2018: Yoshikai





Yoshikai, N. et al. *Org. Chem. Front.* **2018**, *5*, 2214-2218.

2019: Cai



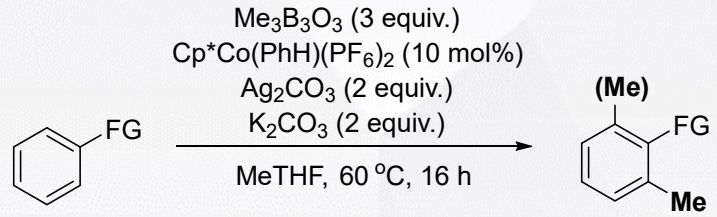
Cai, C. et al. *Org. Chem. Front.* **2019**, *6*, 2043-2047.

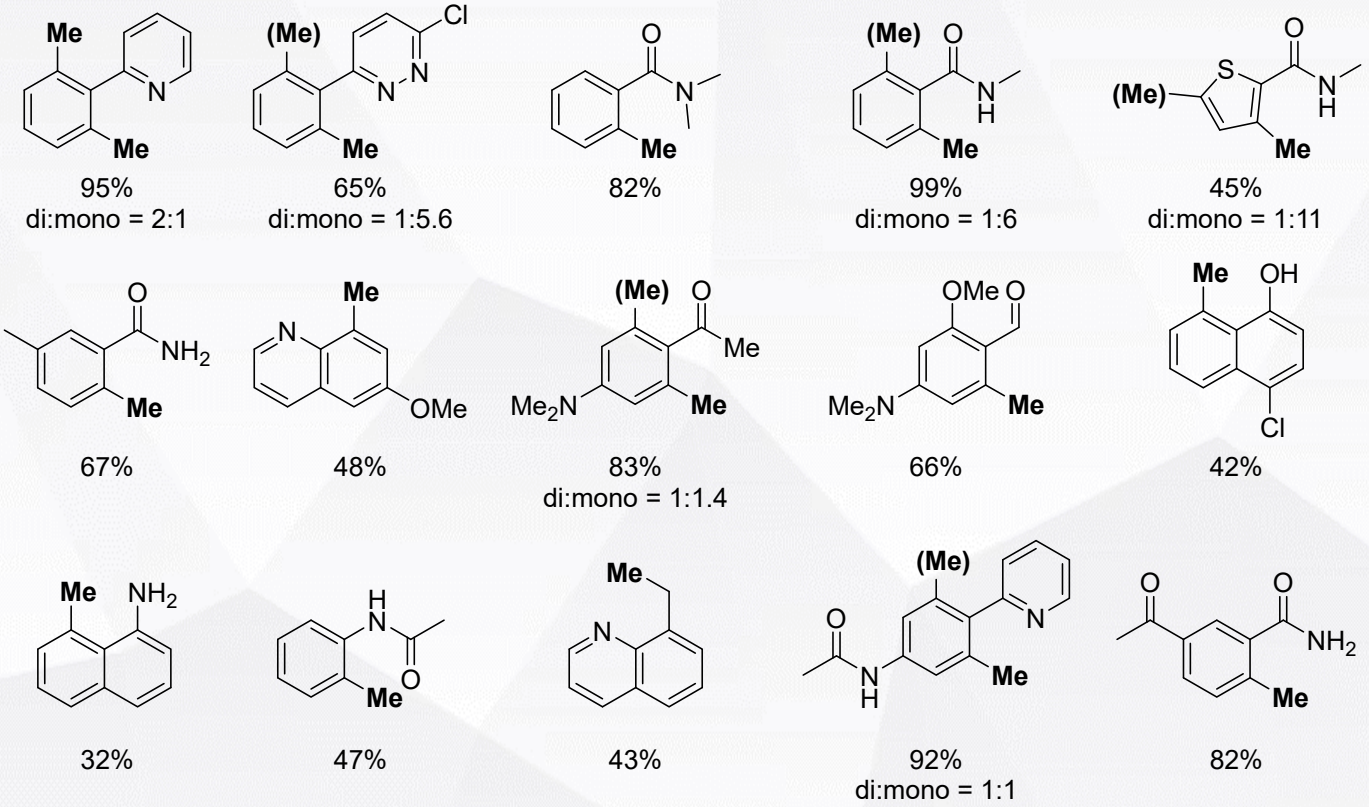
02

Methylation: Co

Based on C-H Activation

>> Ackermann, L. 2020:





Ackermann, L.; Johansson, M. J. et al. *Nat. Chem.* **2020**, *12*, 511-519.

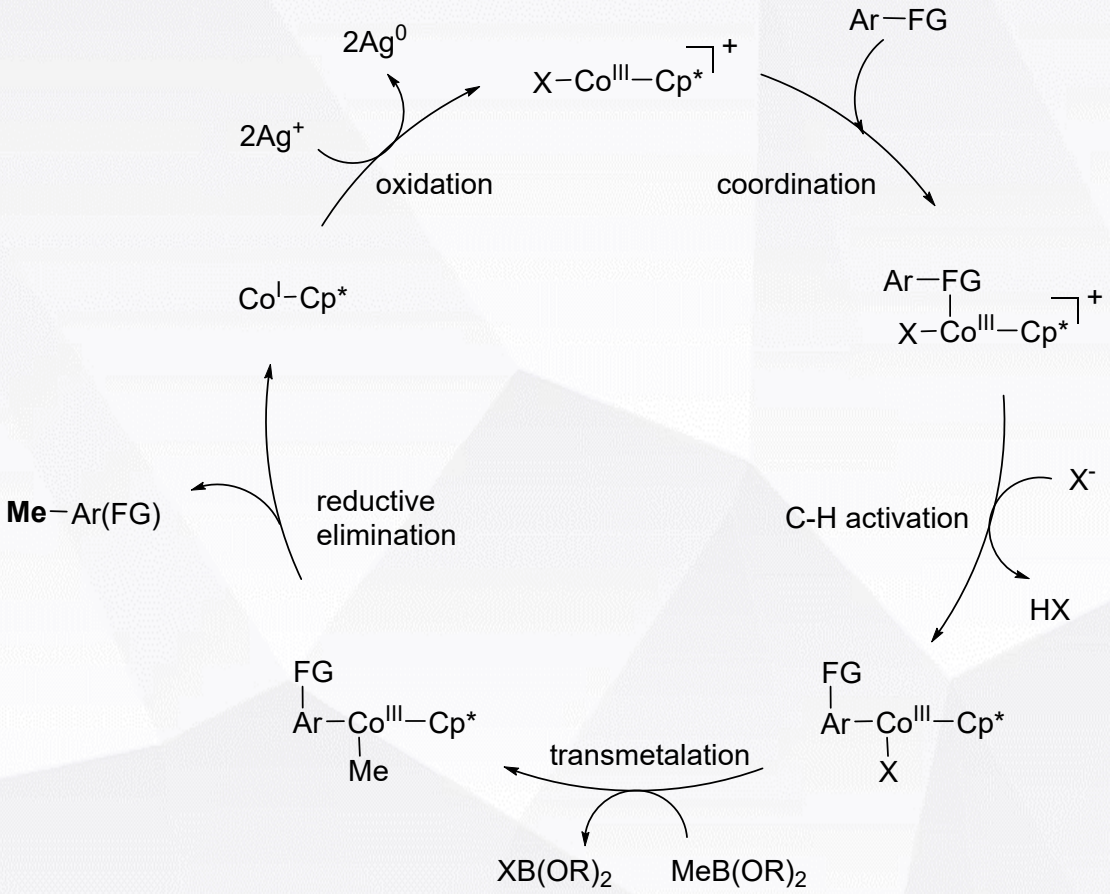
02

Methylation: Co

Based on C-H Activation

>> Ackermann, L. 2020:

Proposed mechanism: Co^{I}/Co^{III}



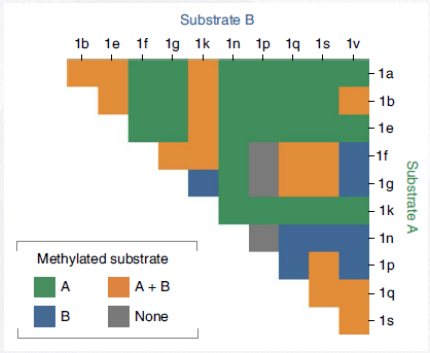
Ackermann, L.; Johansson, M. J. et al. *Nat. Chem.* **2020**, *12*, 511-519.

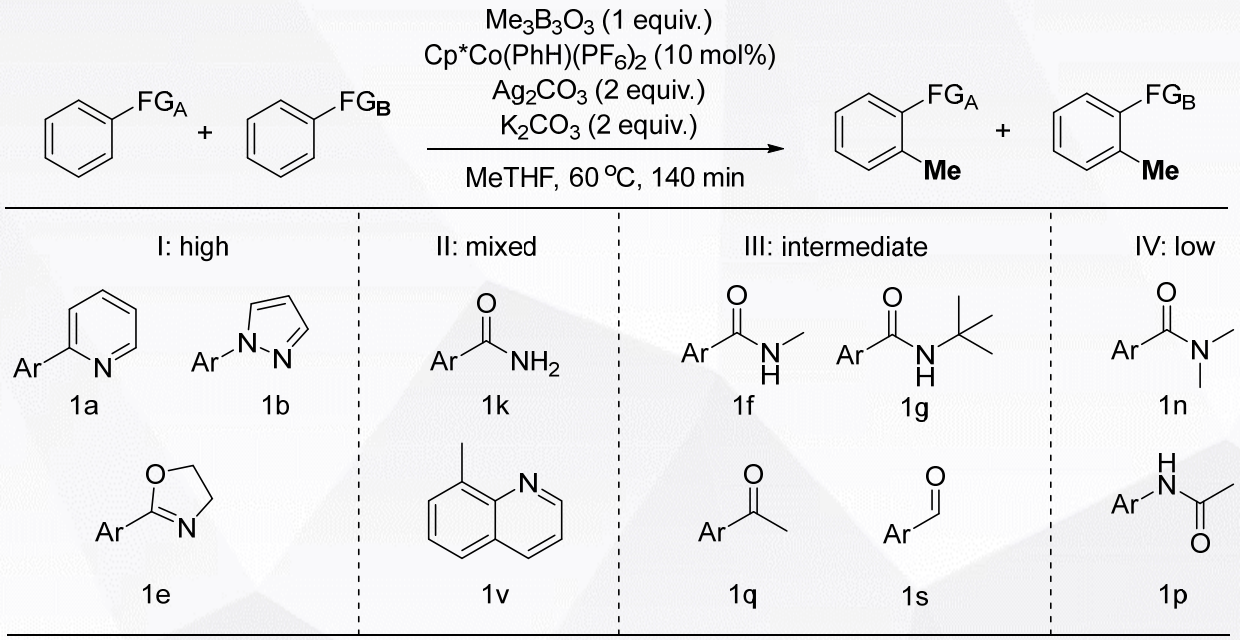
02

Methylation: Co

Based on C-H Activation

>> Ackermann, L. 2020:





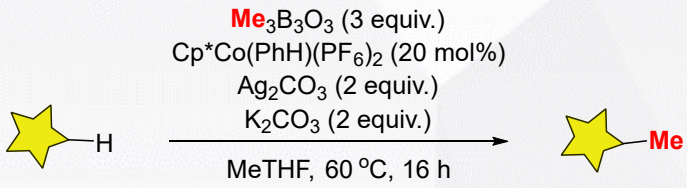
Ackermann, L.; Johansson, M. J. et al. *Nat. Chem.* **2020**, *12*, 511-519.

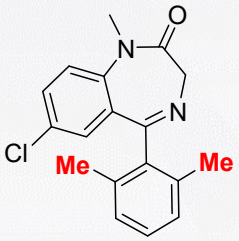
02

Methylation: Co

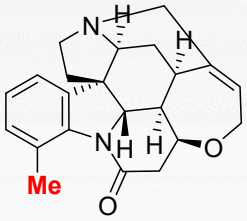
Based on C-H Activation

>> Ackermann, L. 2020:

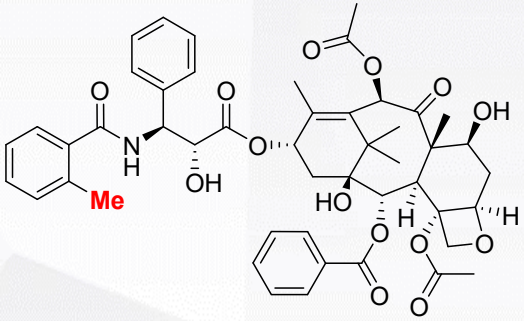




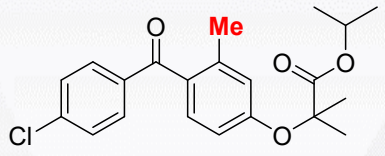
di:mono = 55%:31%
From diazepam



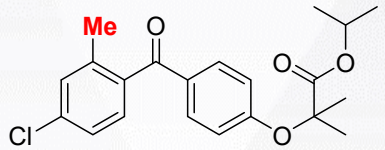
28%
From strychnine



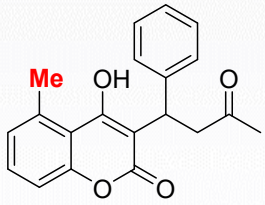
32%
From paclitaxel



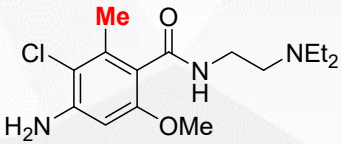
35%



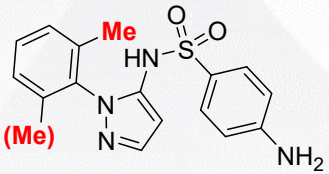
11%
From fenofibrate (inseparable)



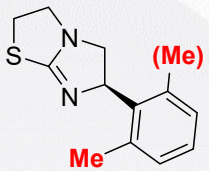
56%
From warfarin



24%
From metoclopramide



mono:di = 48%:24%
From sulfaphenazole



mono:di = 32%:20%
From levamisole

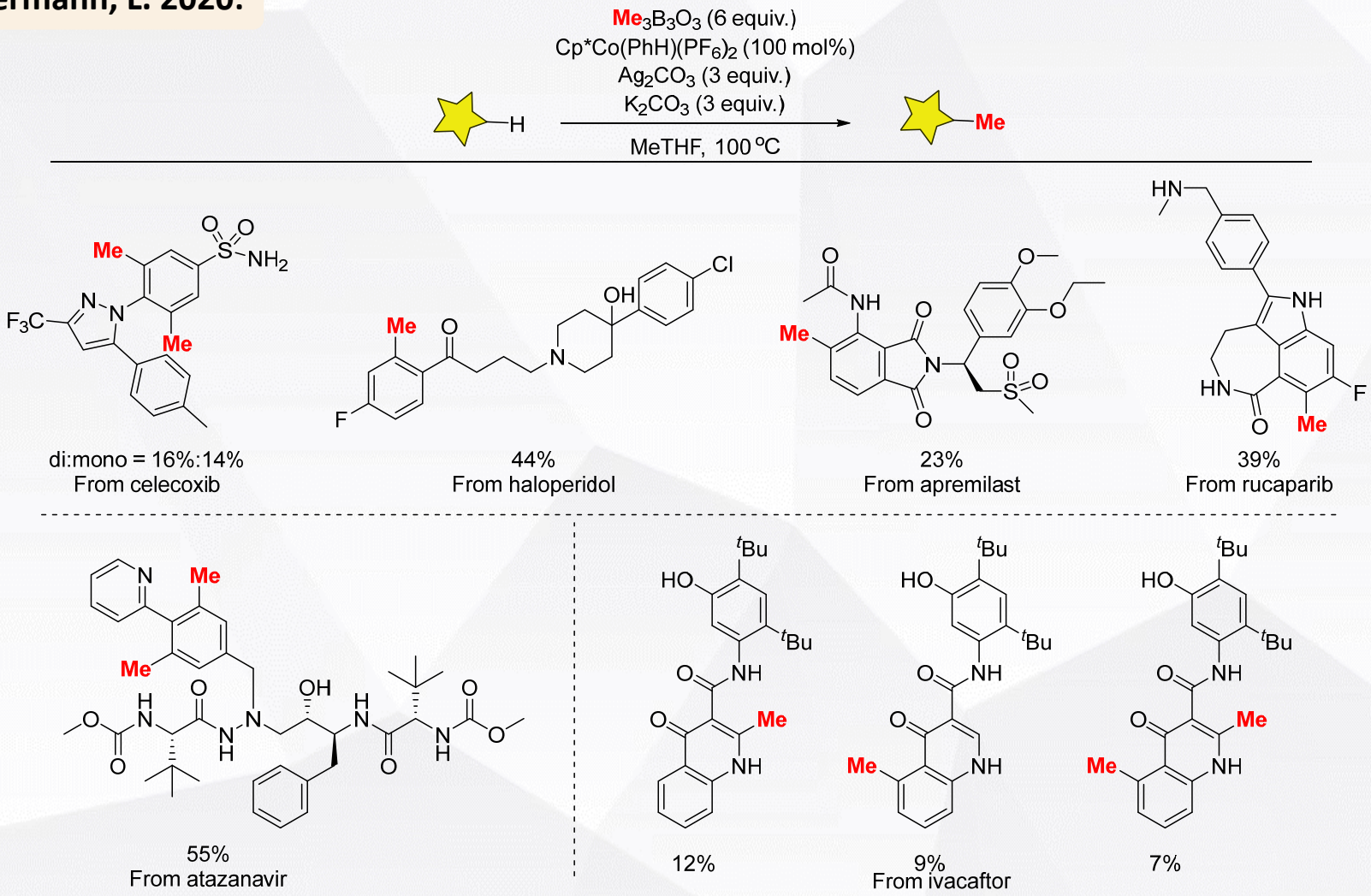
Ackermann, L.; Johansson, M. J. et al. *Nat. Chem.* **2020**, *12*, 511-519.

02

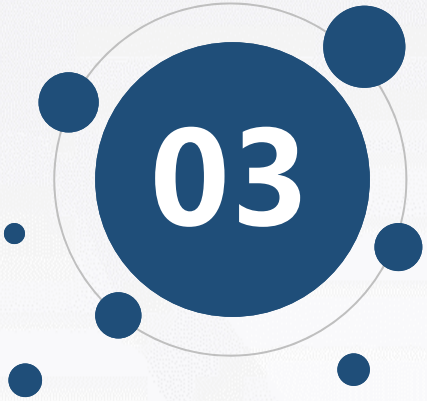
Methylation: Co

Based on C-H Activation

>> Ackermann, L. 2020:



Ackermann, L.; Johansson, M. J. et al. *Nat. Chem.* **2020**, *12*, 511-519.



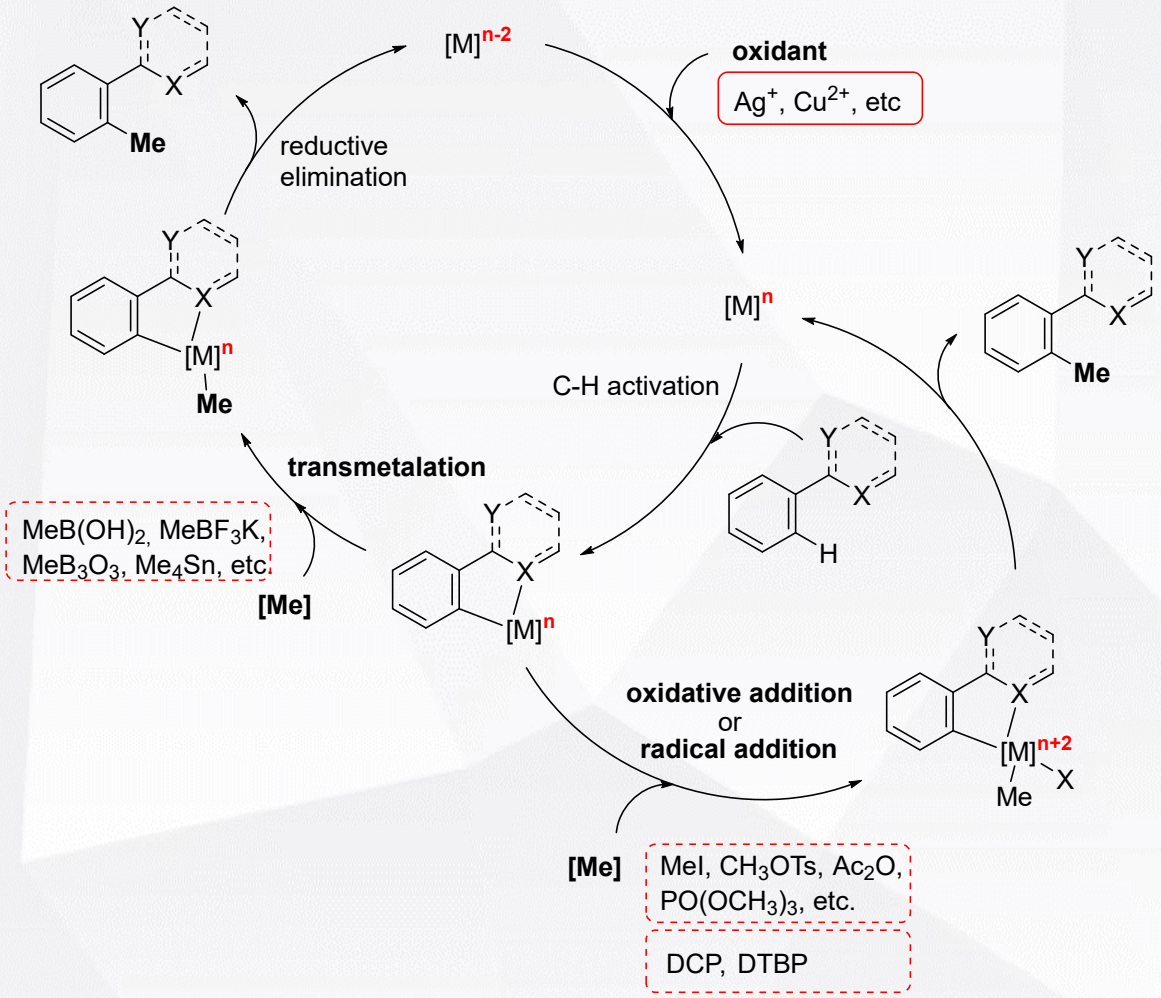
Summary & Outlook

03

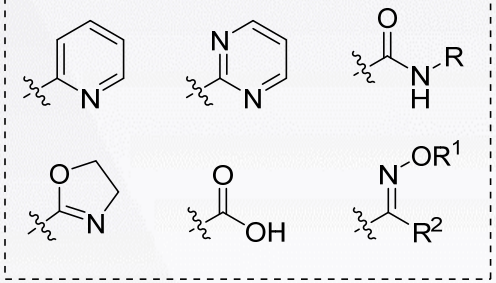
Summary

For **Precious** Metals: Pd/Rh/Ru/Ir

typical path:



DG: for examples



Advantages:

- ✓ Relatively simple DG
- ✓ No additional ligands usually
- ✓ Always mild methyl reagent

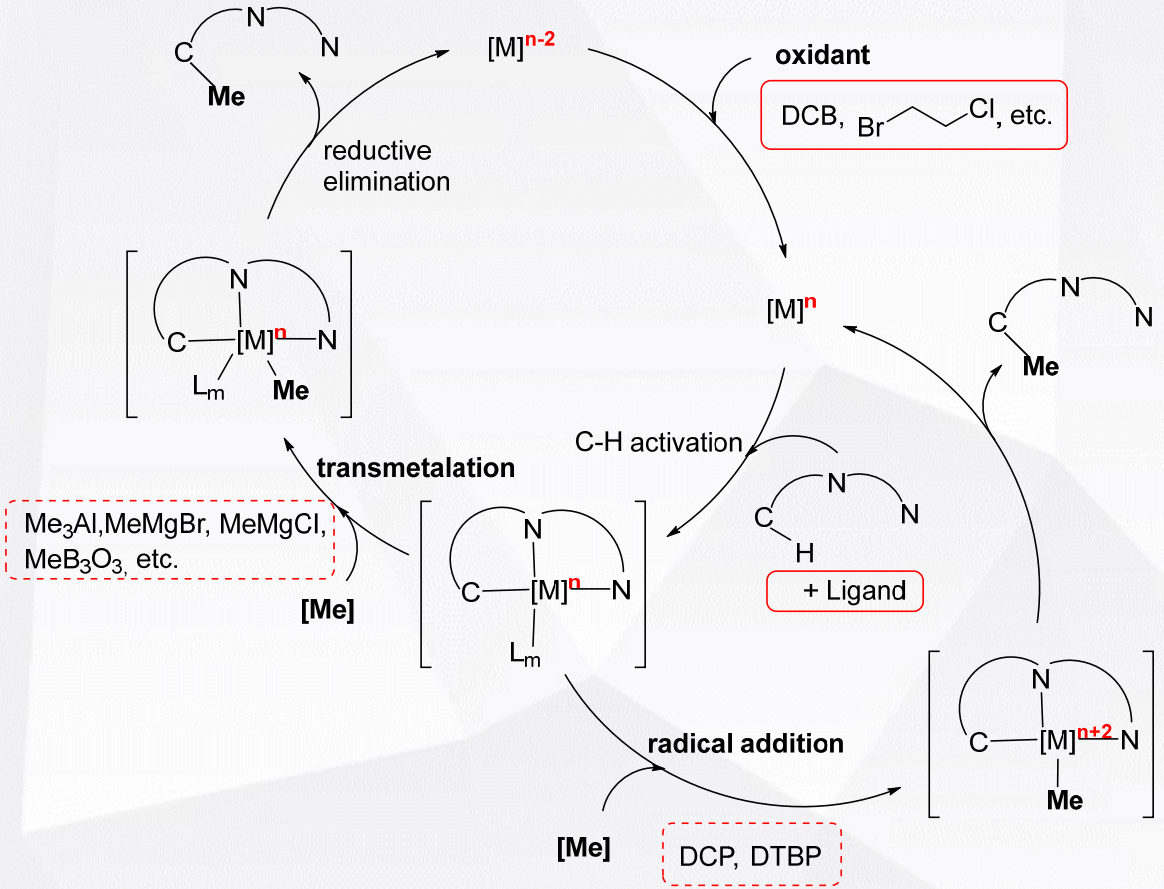
Disadvantages:

- Expensive metal catalyst
- Always equivalent metal oxidant
- Always high reaction temperature
- Additional additive for activation (such as $AgSbF_6$ for Rh)

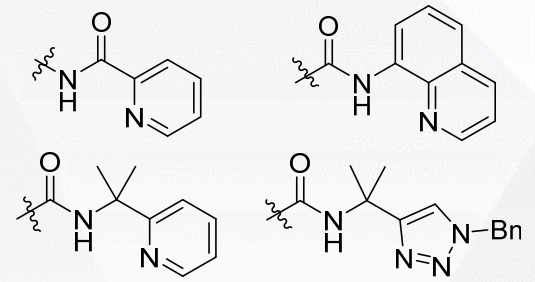
Summary

For **Cheap** Metals: Mn/Fe/Co/Ni

typical path:



DG: for examples



Ligand: for examples

dppen, dppe, TMEDA, PPh_3, Me_2N-TP, etc.

Advantages:

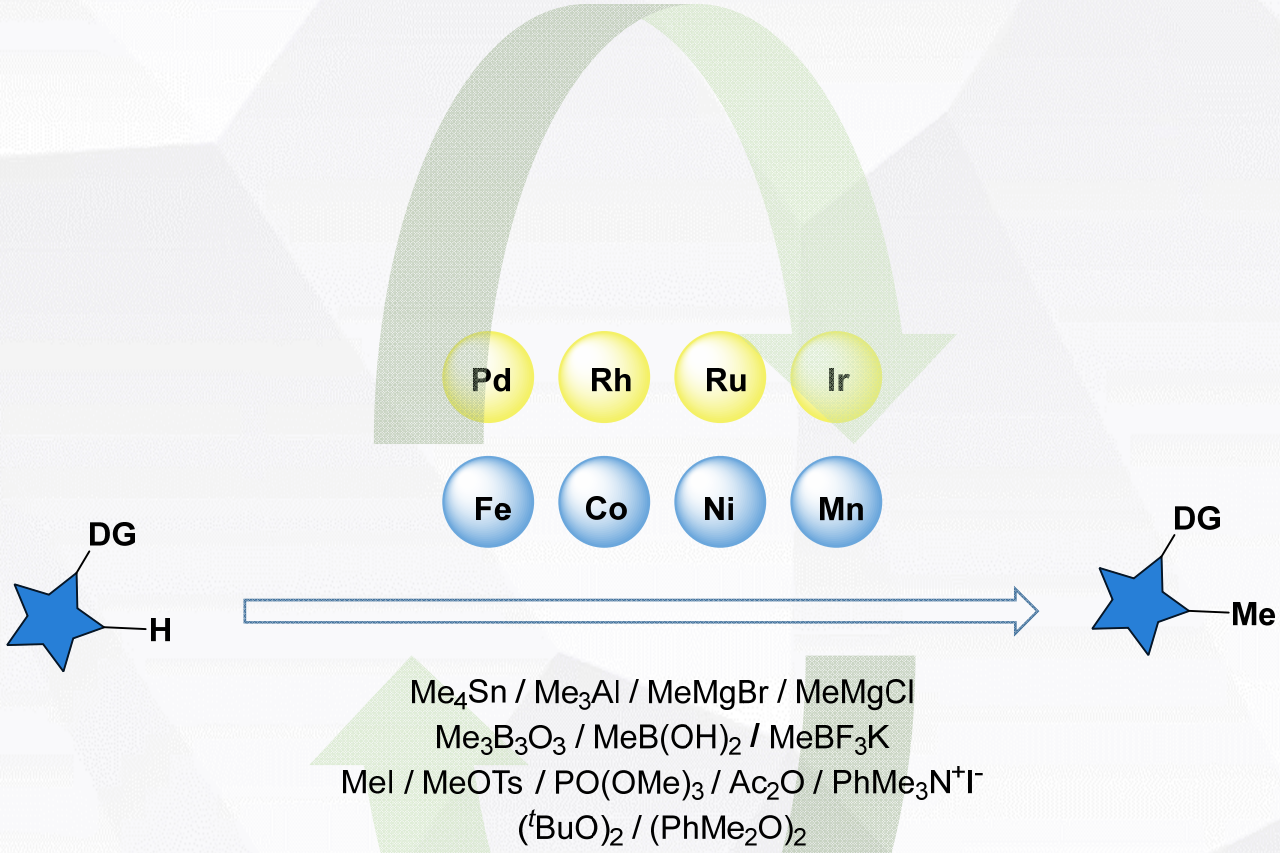
- ✓ Cheap metal catalyst
- ✓ Always mild oxidant
- ✓ Relatively low reaction temperature
- ✓ Relatively high TON (such as Fe)

Disadvantages:

- Relatively complicated DG
- Always additional ligand
- High-reactivity methyl reagent

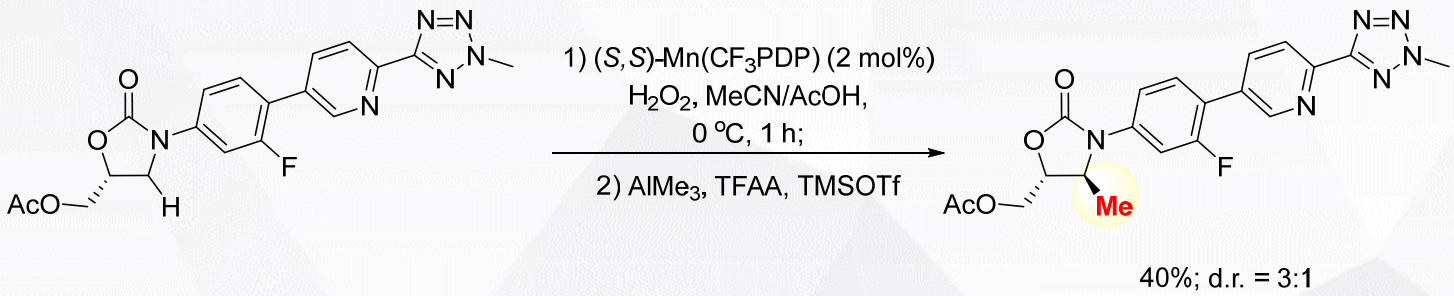
03

Summary


Pd
Rh
Ru
Ir
Fe
Co
Ni
Mn
DG
H
DG
Me
Me_4Sn / Me_3Al / MeMgBr / MeMgCl
$Me_3B_3O_3$ / $MeB(OH)_2$ / $MeBF_3K$
MeI / MeOTs / $PO(OMe)_3$ / Ac_2O / $PhMe_3N^+I^-$
$(^tBuO)_2$ / $(PhMe_2O)_2$

03 Outlook

- ✓ Understanding of the **relationship** between DGs and metals
- ✓ Conversion of DGs from "introduction" to **inherent functional group**
- ✓ Development of **methylation reagents** with high-activity and high-selectivity including CD_3, CT_3, $^{11}CH_3$, $^{14}CH_3$, etc.



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White, M. C. et al. *Nature*, **2020**, *580*, 621–627.

- ✓ Upgrade of C-H activation from C(sp^2)-H to **C(sp^3)-H** in late-stage modification
- ✓ Exploitation of **chiral** catalyst and **chiral** ligand

THANKS FOR YOUR ATTENTION