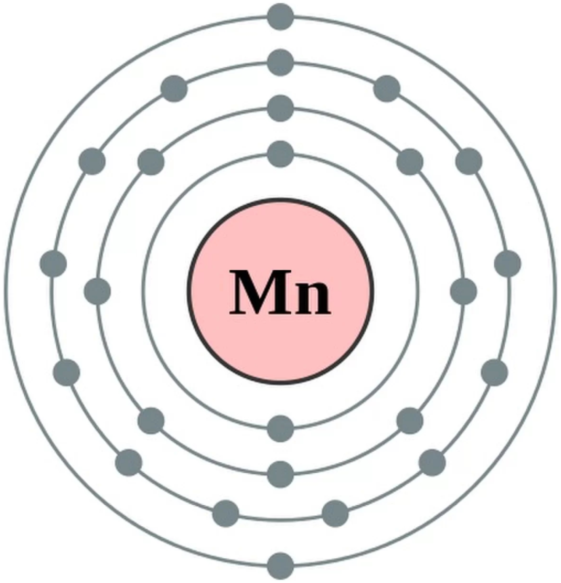
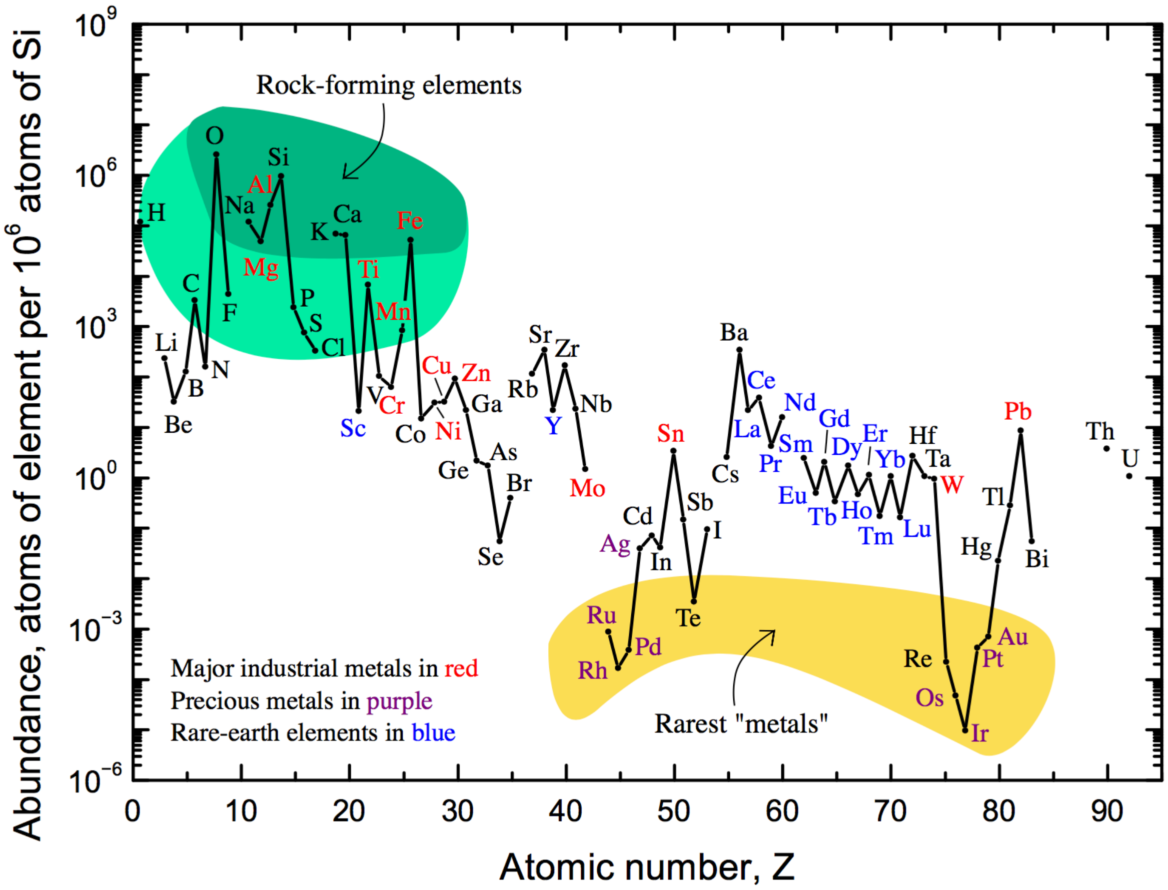
Recent Advances in Cross-Coupling by Manganese Catalysis



Xiaheng Zhang
MacMillan Group Meeting
February 27th, 2018

Why do people care about Manganese Catalysis

Manganese is the third most abundant transition metal in the Earth's crust



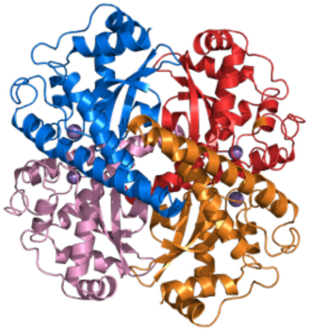
https://en.wikipedia.org/wiki/Abundance_of_the_chemical_elements

Why do people care about Manganese Catalysis

superoxide dismutase (Mn-SOD)
antioxidant enzyme
catalyzes the dismutation of
the superoxide (O_2^-) radical

Mn

VII B group
electron configuration: $3d^5 4s^2$
range of oxidation state: -3 to +7



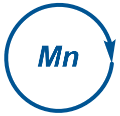
arginase
enzyme in the urea cycle
converts *L*-arginine into
L-ornithine and urea

Benefits of Manganese Catalysis

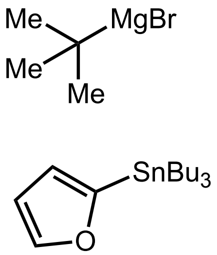
- **naturally abundant in the earth's crust**
- **low cost and low toxicity relative to other transition metals**
- **present in various metalloproteins**
- **essential element for all species (human daily intake ~ 4 mg)**

Can we discover new reactivity that is unique to manganese catalysis?

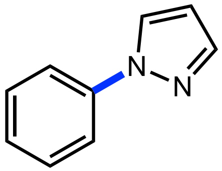
Recent Advances in Cross-Coupling by Manganese Catalysis



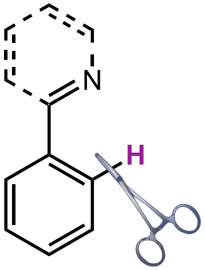
Cross-coupling for C-C bond formation



Cross-coupling for C-X bond formation



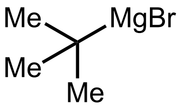
C-H activation for C-C bond formation

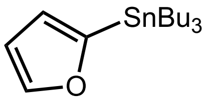


Recent Advances in Cross-Coupling by Manganese Catalysis

Mn

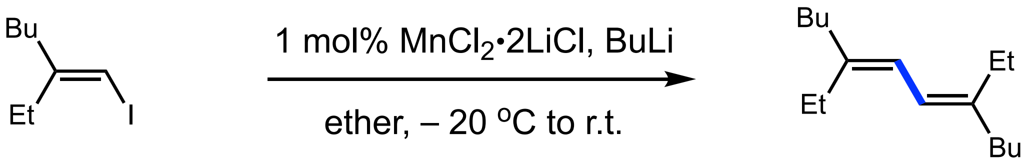
Cross-coupling for C-C bond formation

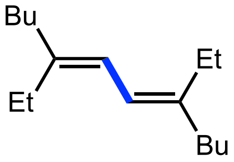




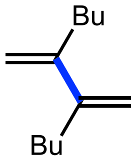
Manganese Catalyzed Cross Coupling

Cahiez: The first Mn catalyzed coupling reaction

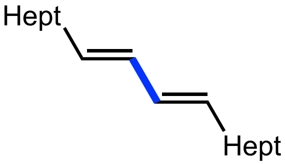




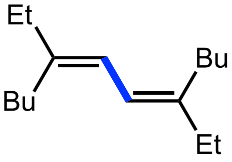
90% yield



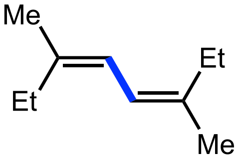
70% yield



88% yield



91% yield

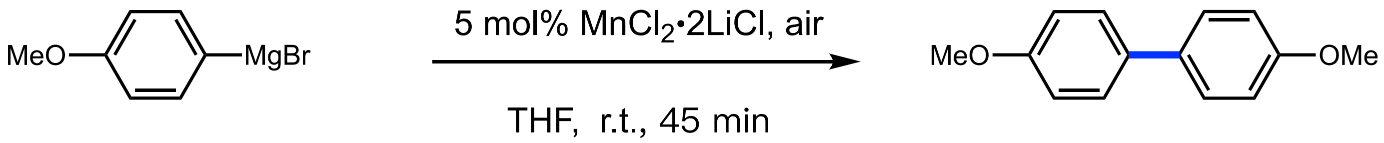


87% yield

Cahiez, G.; Bernard, D.; Normant, J. F. *J. Organomet. Chem.* **1976**, *113*, 99.

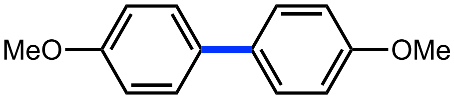
Manganese Catalyzed Homocoupling

Mn catalyzed homocoupling of RMgX with O_2 as an oxidant

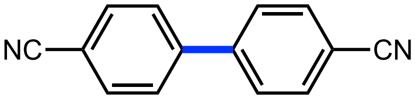


5 mol% $MnCl_2 \cdot 2LiCl$, air

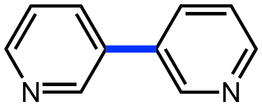
THF, r.t., 45 min



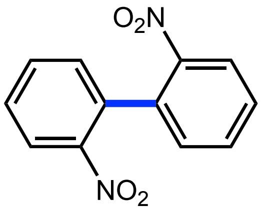
95% yield



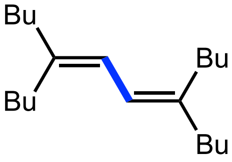
78% yield



80% yield

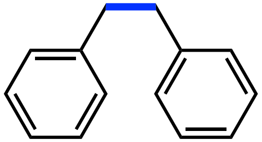


75% yield



88% yield

91% yield

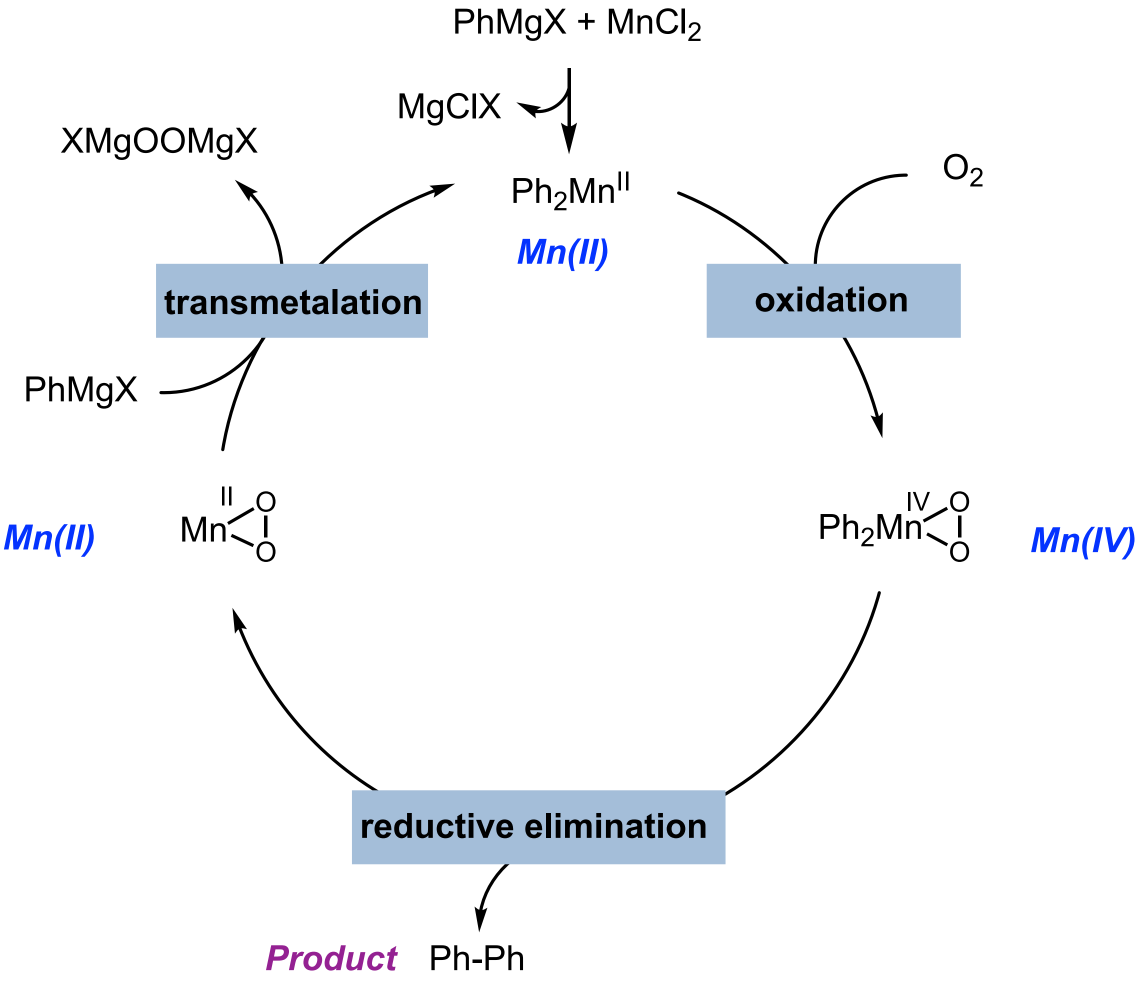


80% yield

Cahiez, G.; Moyeux, A.; Buendia, J.; Duplais, C. *J. Am. Chem. Soc.* **2007**, *129*, 13788.

Manganese Catalyzed Homocoupling

- Cahiez proposed an Mn (II)/(IV) mechanistic cycle



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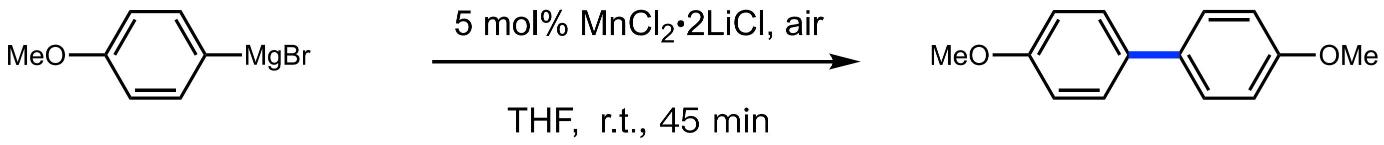
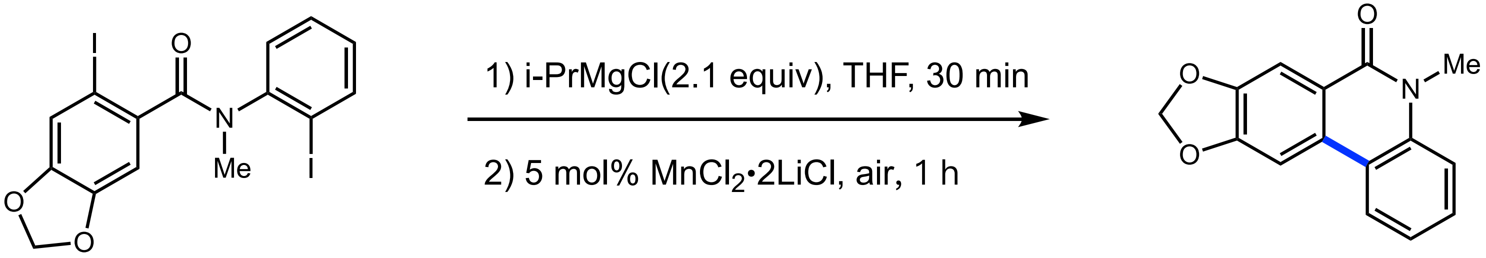
Mn catalyzed homocoupling of RMgX with O_2 as an oxidant





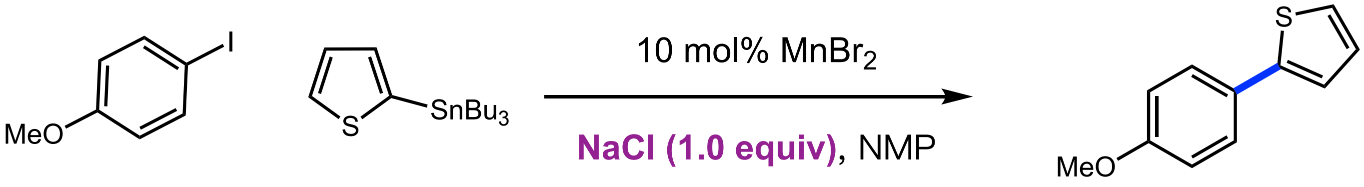
N-methylcrinasiadine, natural product

46% yield

Cahiez, G.; Moyeux, A.; Buendia, J.; Duplais, C. *J. Am. Chem. Soc.* **2007**, *129*, 13788.

Manganese Catalyzed Cross-coupling

The first Mn catalyzed cross-coupling reaction



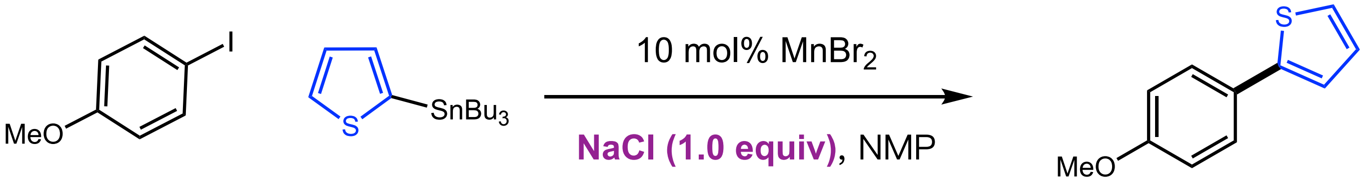
Salts	Yield	thiophene-dimer
NaCl	88%	trace
KCl	86%	trace
KF	20%	50%
LiCl	10%	35%

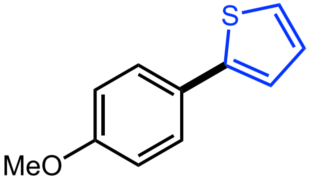
inorganic salt is essential due to the suppression of the homocoupling by-product

Kang, S.-K.; Kim, J.-S.; Choi, S.-C. *J. Org. Chem.* **1997**, *62*, 4208.

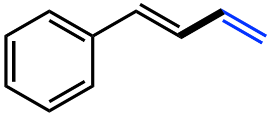
Manganese Catalyzed Cross-coupling

The first Mn catalyzed cross-coupling reaction

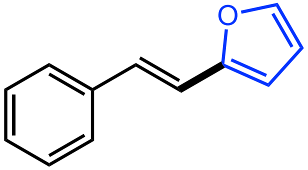




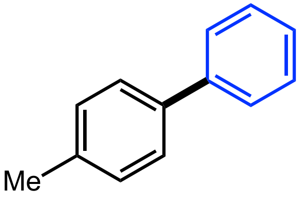
88% yield



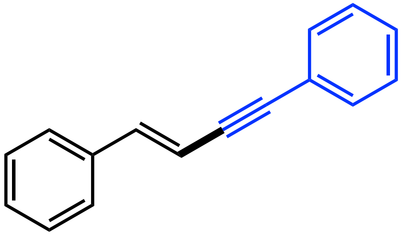
70% yield



80% yield



76% yield



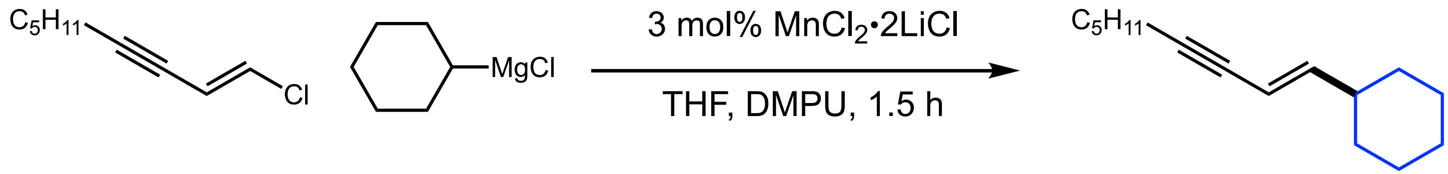
71% yield

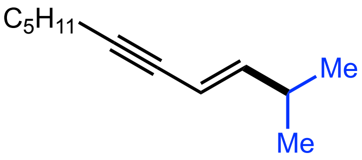
What about sp^2-sp^3 C–C bond formation ?

Kang, S.-K.; Kim, J.-S.; Choi, S.-C. *J. Org. Chem.* **1997**, *62*, 4208.

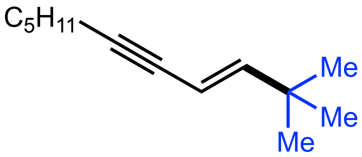
Manganese Catalyzed Cross-coupling

The first report of Mn catalyzed cross-coupling using Grignard reagent

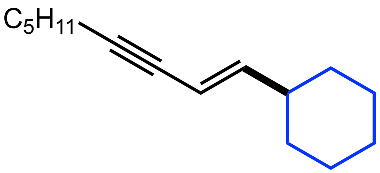




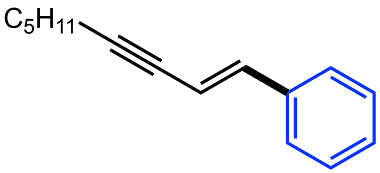
80% yield



62% yield



95% yield

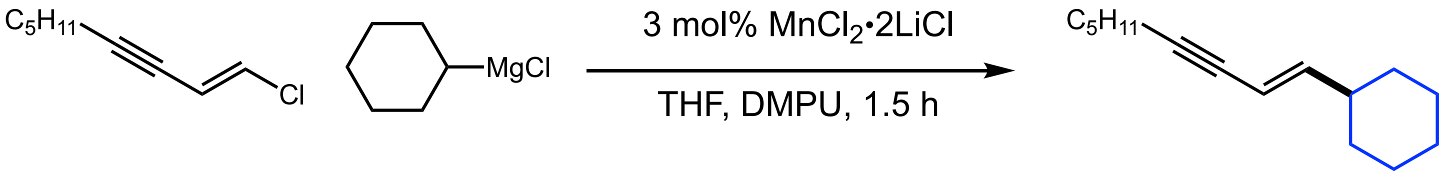


25% yield

Alami, M.; Ramiandrasoa, P.; Cahiez, G. *Synlett* **1998**, 325.

Manganese Catalyzed Cross-coupling

The first report of Mn catalyzed cross-coupling using Grignard reagent



Comparison between Mn-, Ni- and Pd-catalysis

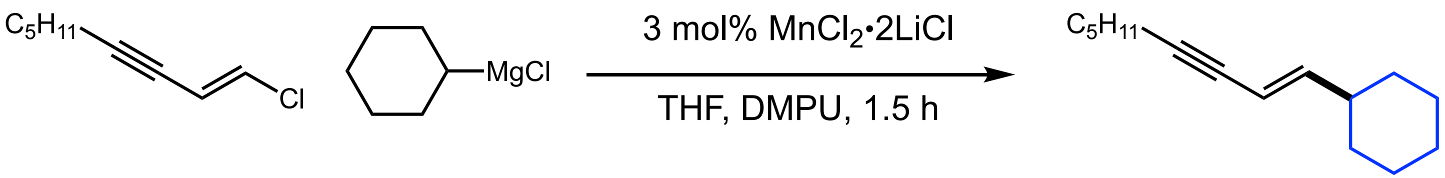
Catalyst	Yield
$PdCl_2(PPh_3)_2$	27%
$PdCl_2(dppf)$	38%
$NiCl_2(PPh_3)_2$	35%
$MnCl_2$•2LiCl	**84%**

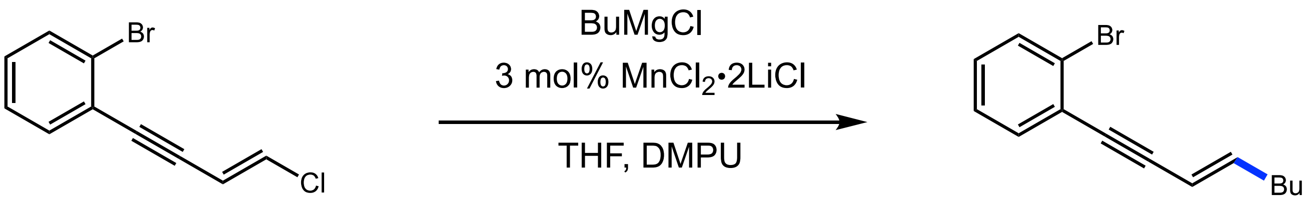
} **β elimination**

Alami, M.; Ramiandrasoa, P.; Cahiez, G. *Synlett* **1998**, 325.

Manganese Catalyzed Cross-coupling

The first report of Mn catalyzed cross-coupling using Grignard reagent





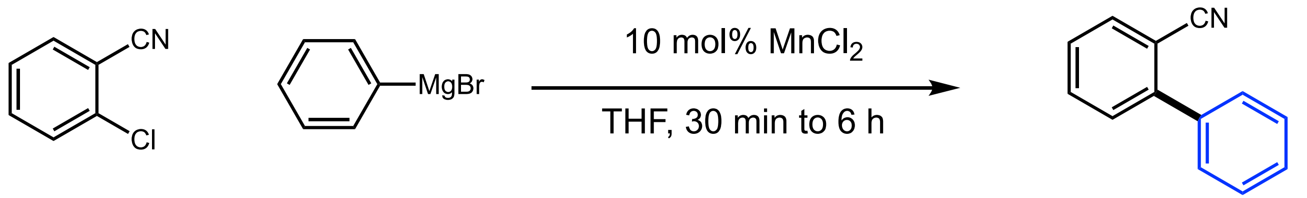
chemoselective functionalization

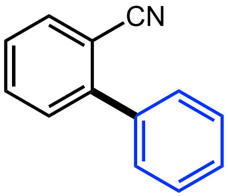
88% yield

Alami, M.; Ramiandrasoa, P.; Cahiez, G. *Synlett* **1998**, 325.

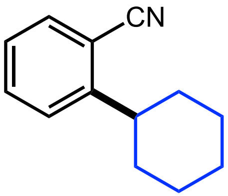
Manganese Catalyzed Cross-coupling

Mn catalyzed cross-coupling of Grignard reagents with activated aryl halides

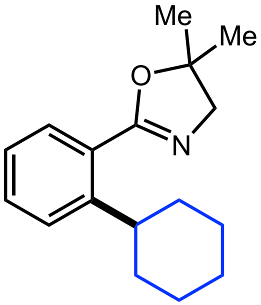




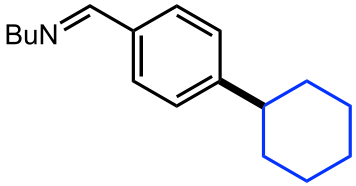
77% yield



75% yield



64% yield

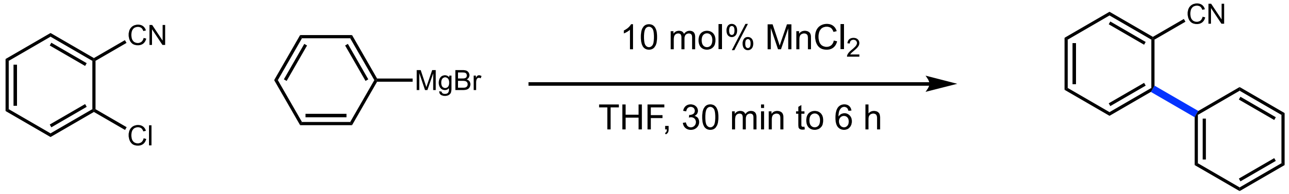


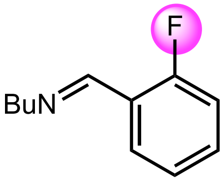
88% yield

Cahiez, G.; Lepifre, F.; Ramiandrasoa, P. *Synthesis* **1999**, 2138.

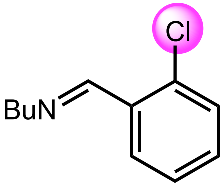
Manganese Catalyzed Cross-coupling

Mn catalyzed cross-coupling of Grignard reagents with activated aryl halides

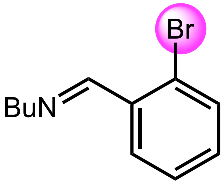




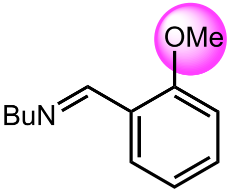
90% yield, **2 h**



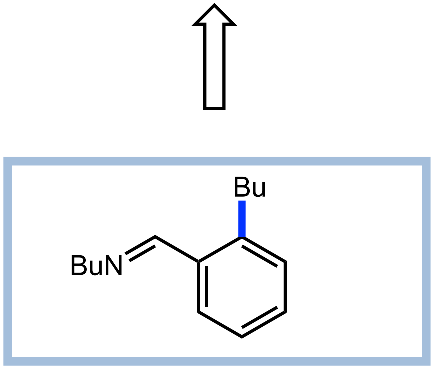
93% yield, **30 min**



92% yield, **10 min**



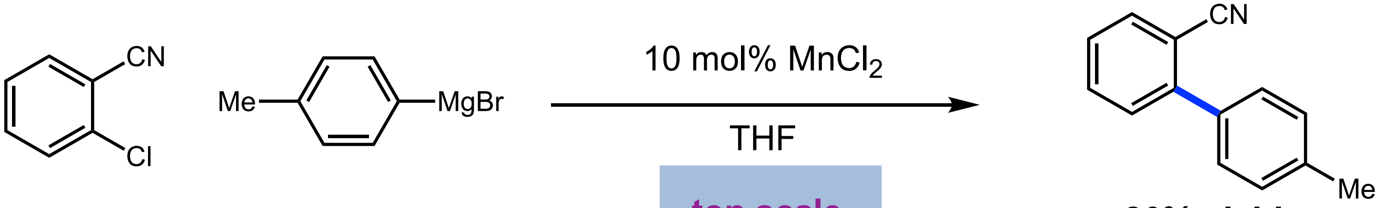
91% yield, **20 min**



Cahiez, G.; Lepifre, F.; Ramiandrasoa, P. *Synthesis* **1999**, 2138.

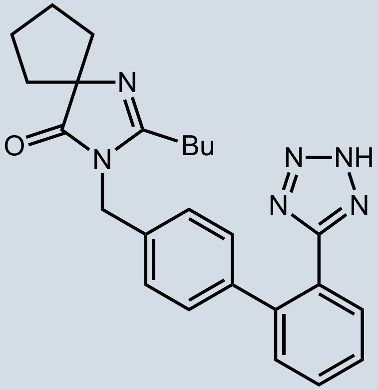
Manganese Catalyzed Cross-coupling

Application to the pharmaceutical compound synthesis



ton scale

80% yield

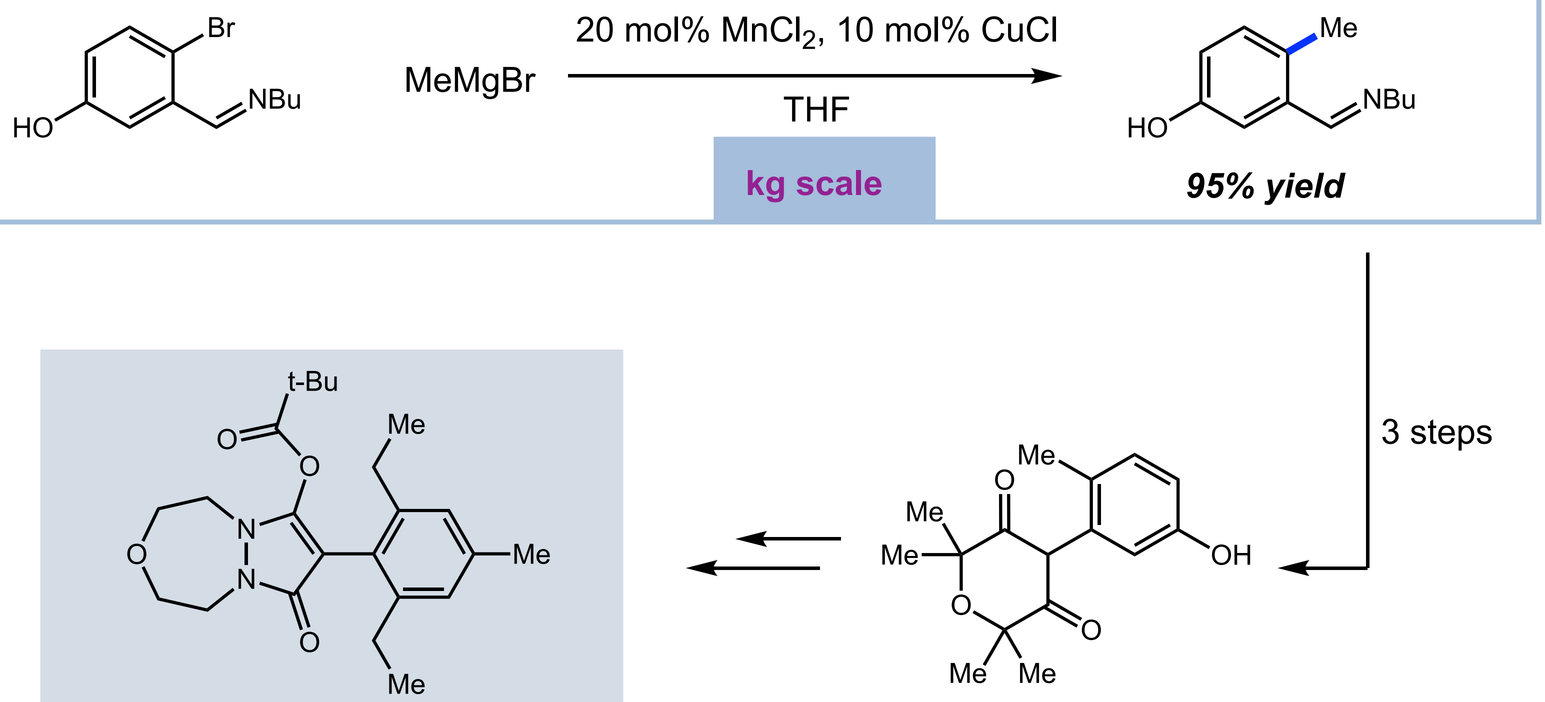


Irbesartan, an antihypertensive drug from **Sanofi-Aventis**

Cahiez, G.; Lepifre, F.; Ramiandrasoa, P. *Synthesis* **1999**, 2138.

Manganese Catalyzed Cross-coupling

Application to the pharmaceutical compound synthesis

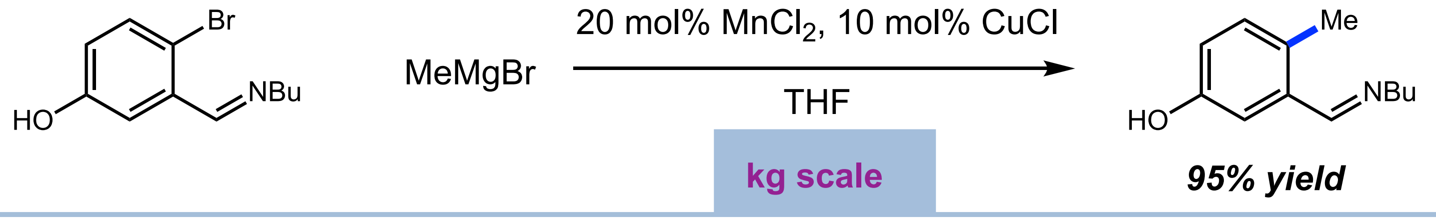


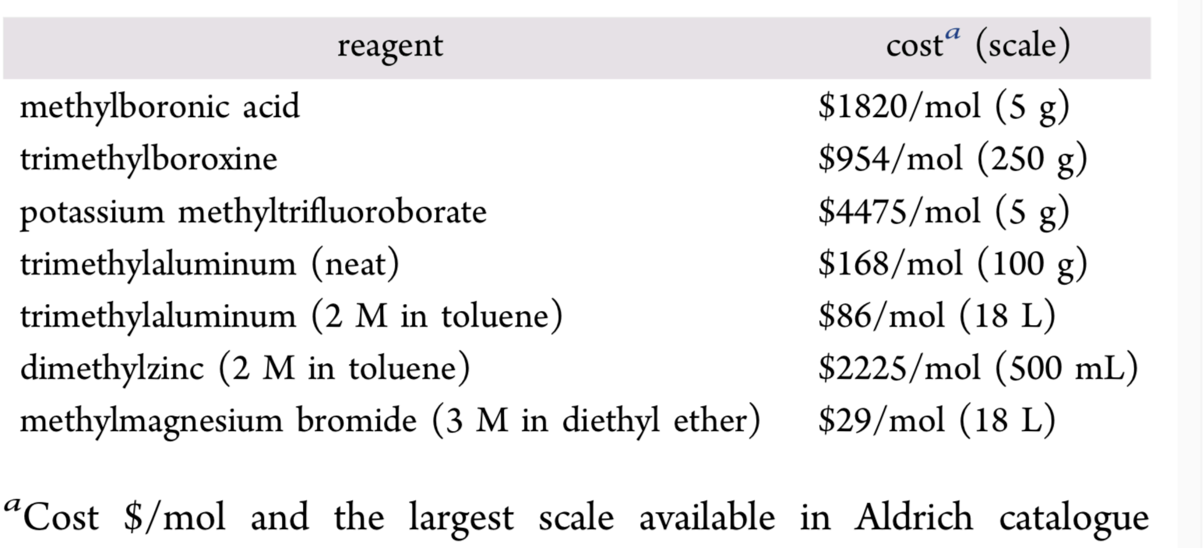
Pinoxaden, an herbicide from **Syngenta**

Smejkal, T. *et al*. *Org*. *Process Res*. *Dev*. **2017**, *21*, 1625.

Manganese Catalyzed Cross-coupling

Application to the pharmaceutical compound synthesis



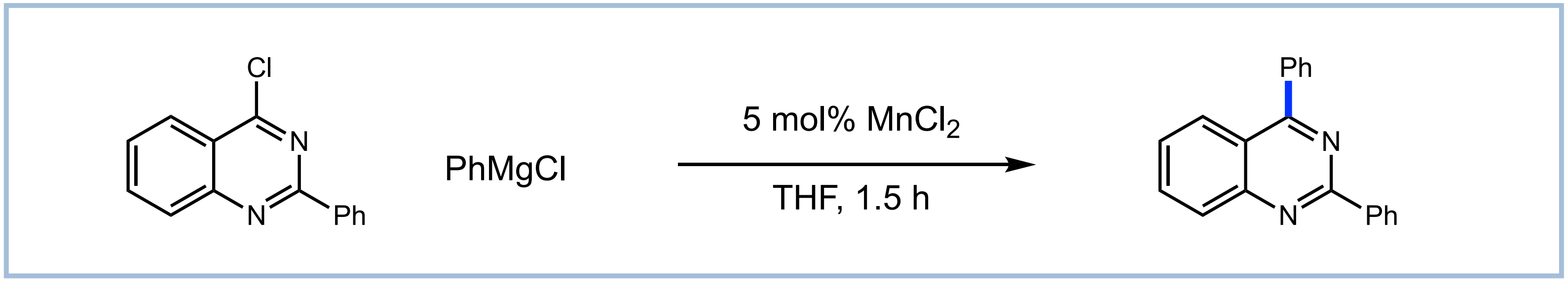


reagent	cost[a] (scale)
methylboronic acid	\$1820/mol (5 g)
trimethylboroxine	\$954/mol (250 g)
potassium methyltrifluoroborate	\$4475/mol (5 g)
trimethylaluminum (neat)	\$168/mol (100 g)
trimethylaluminum (2 M in toluene)	\$86/mol (18 L)
dimethylzinc (2 M in toluene)	\$2225/mol (500 mL)
methylmagnesium bromide (3 M in diethyl ether)	\$29/mol (18 L)

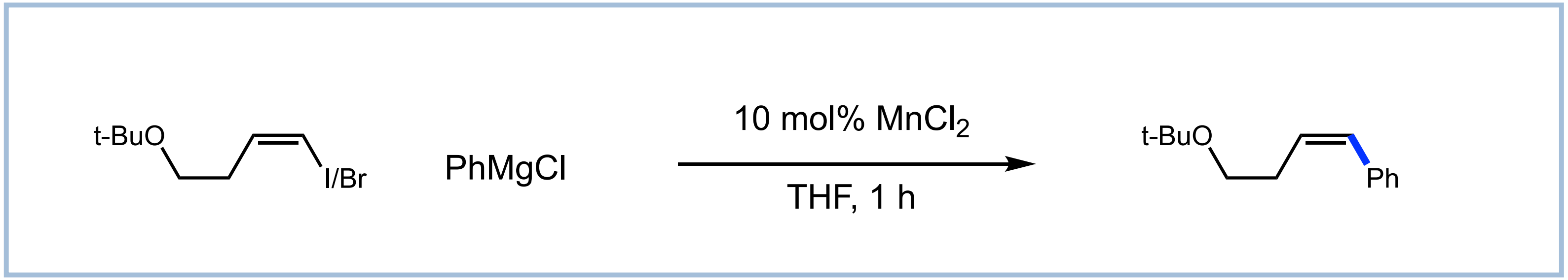
[a] Cost \$/mol and the largest scale available in Aldrich catalogue

Smejkal, T. *et al*. *Org*. *Process Res*. *Dev*. **2017**, *21*, 1625.

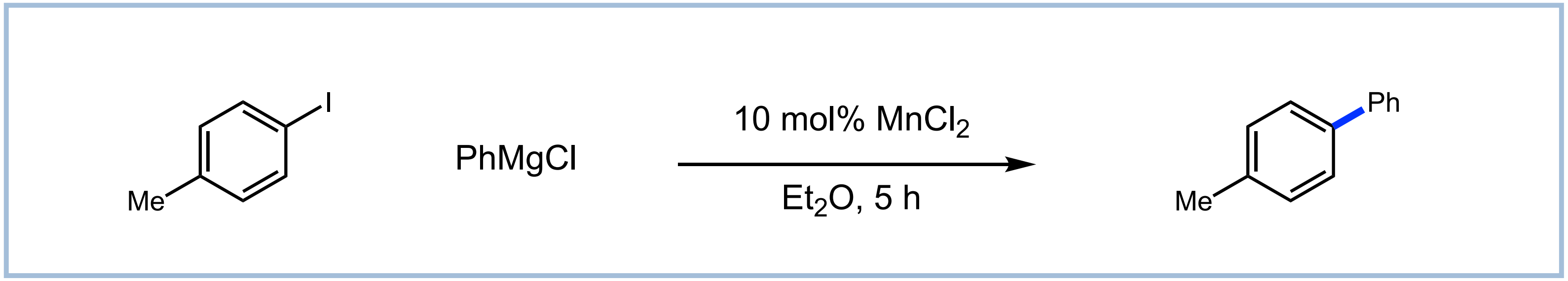
Development of Manganese Catalyzed Cross-coupling



Rueping, M.; Ieawsuwan, W. *Synlett* **2007**, 247.



Cahiez, G.; Gager, O.; Lecomte, F. *Org. Lett.* **2008**, *10*, 5255.



Madsen, R. *et al. Eur. J. Org. Chem.* **2017**, 5269.

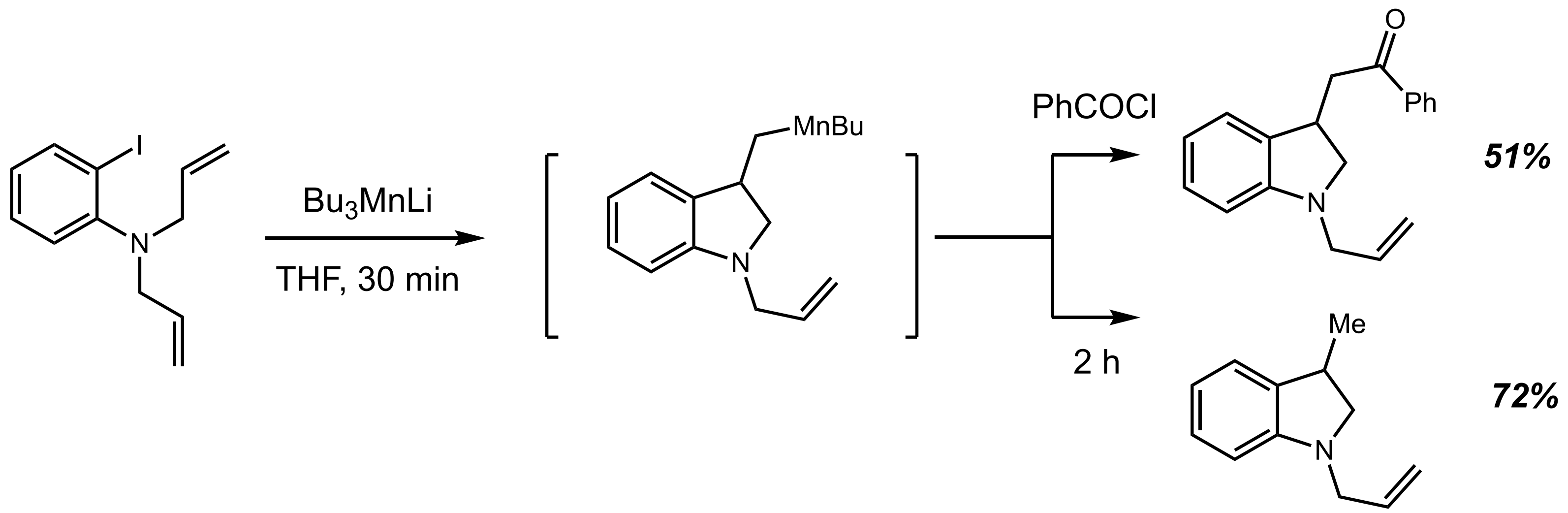
Manganese Catalyzed Cross-coupling

- Typical characteristic of manganese catalysis comparing to other organometallic catalysis

- Reaction doesn’t need ligand to facilitate the elimination step.
- Most of the coupling reactions share very similar condtion. ($MnCl_2$ and THF solvent)
- Reaction is very fast (10 min ~ 1 h) compared to other transition metals.
- Not sensitive to the steric hindrance.

Manganese Catalyzed Cross-coupling

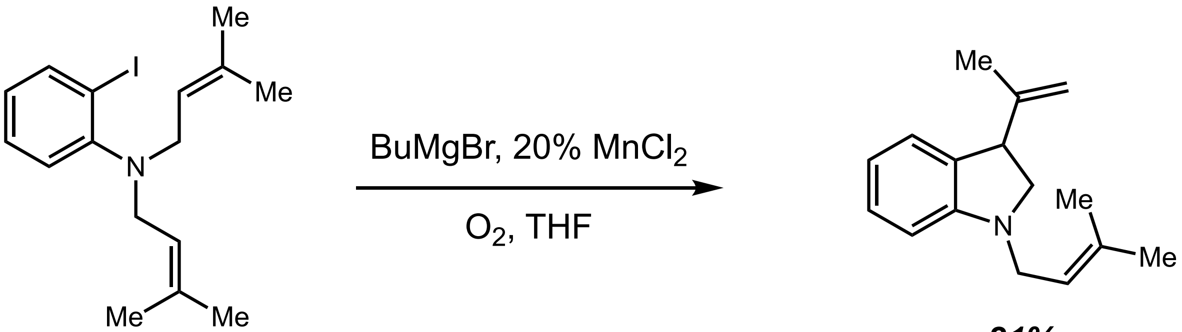
■ Mechanism Insight of Manganese Catalysis



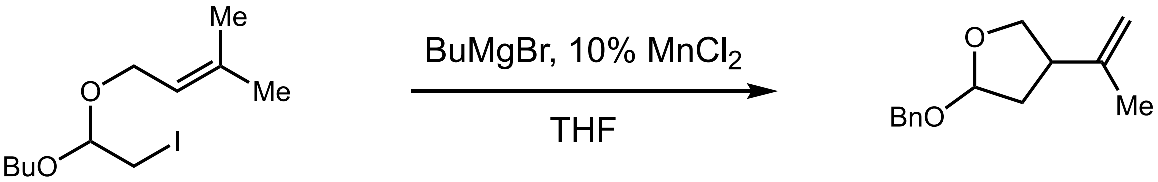
Nakao, J.; Inoue, R.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1997**, *62*, 1910.
. Oshima, K. *J. Organomet. Chem.* **1999**, *575*, 1.
.

Manganese Catalyzed Cross-coupling

■ Mechanism Insight of Manganese Catalysis



81%



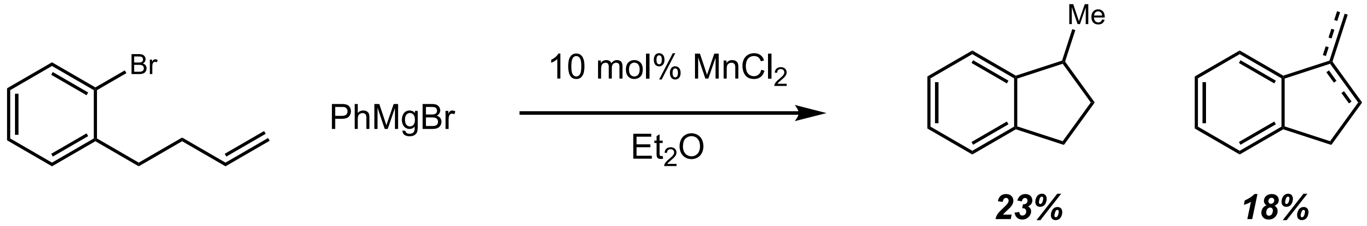
80%

Nakao, J.; Inoue, R.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1997**, *62*, 1910.
. Oshima, K. *J. Organomet. Chem.* **1999**, *575*, 1.
.

Manganese Catalyzed Cross-coupling

■ Proposed mechanism for manganese Catalyzed cross-coupling

Aryl radical trapping

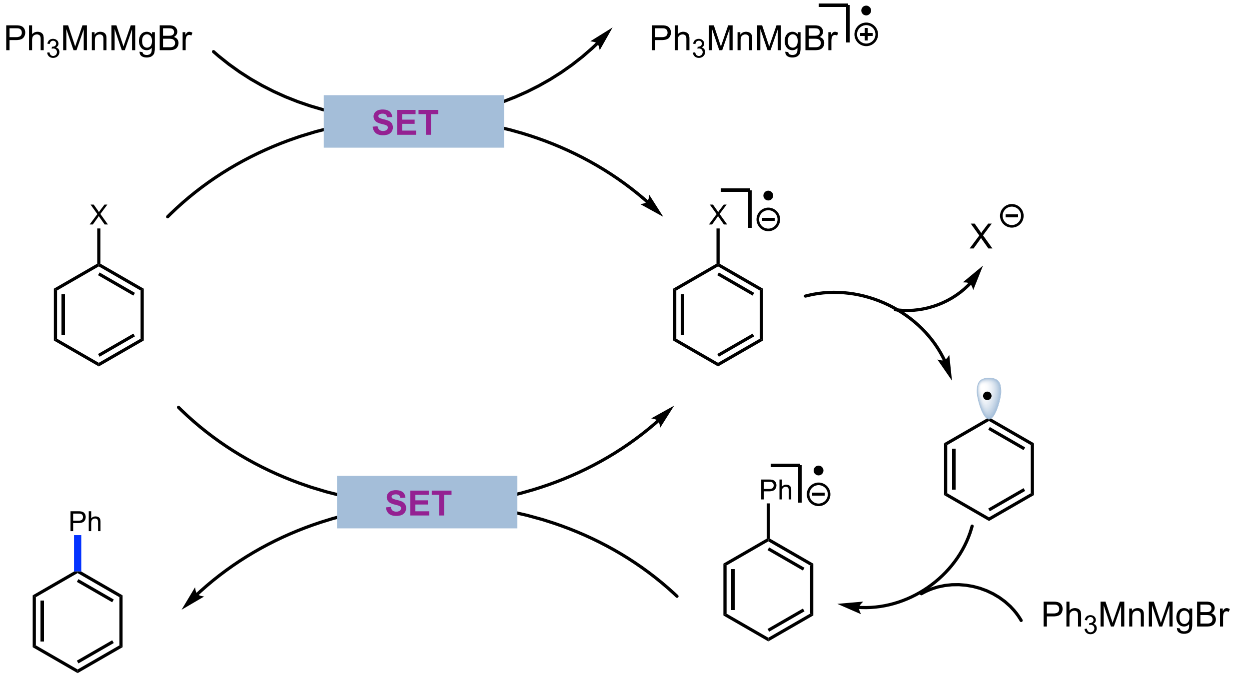


cyclization suggests intermediacy of radicals

Madsen, R. *et al*. *Eur. J. Org. Chem.* **2017**, 5269.

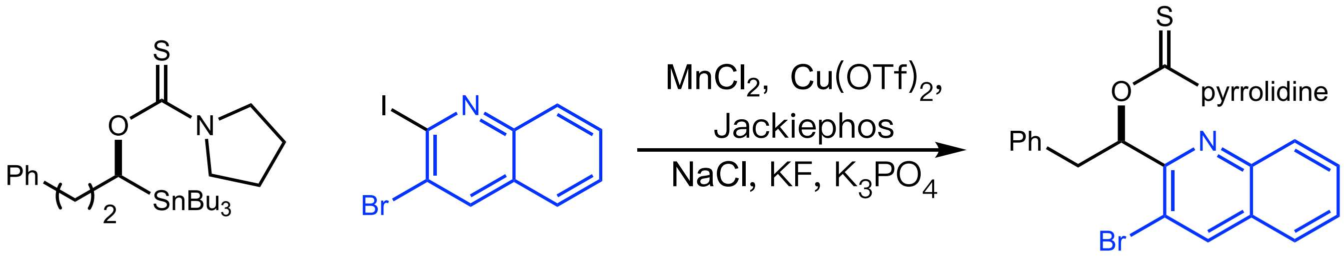
Manganese Catalyzed Cross-coupling

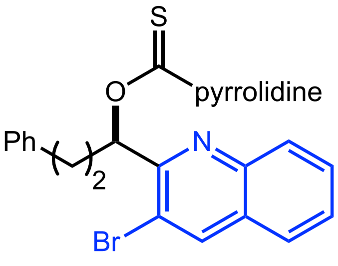
■ Proposed mechanism for manganese Catalyzed cross-coupling



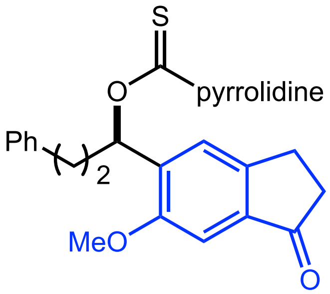
Madsen, R. *et al*. *Eur. J. Org. Chem*. **2017**, 5269.

Manganese Catalyzed Cross-coupling

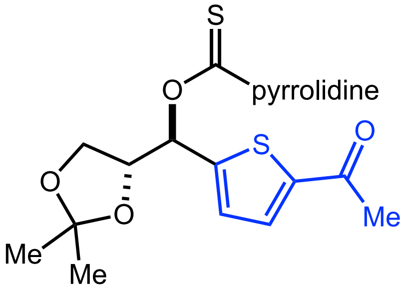




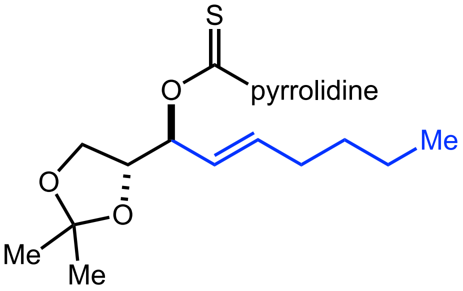
68% yield



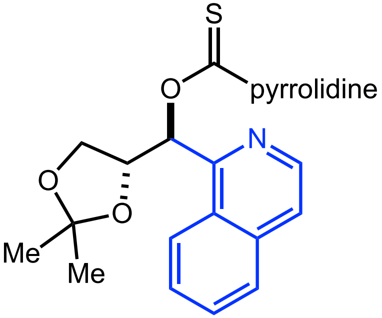
69% yield



55% yield



68% yield

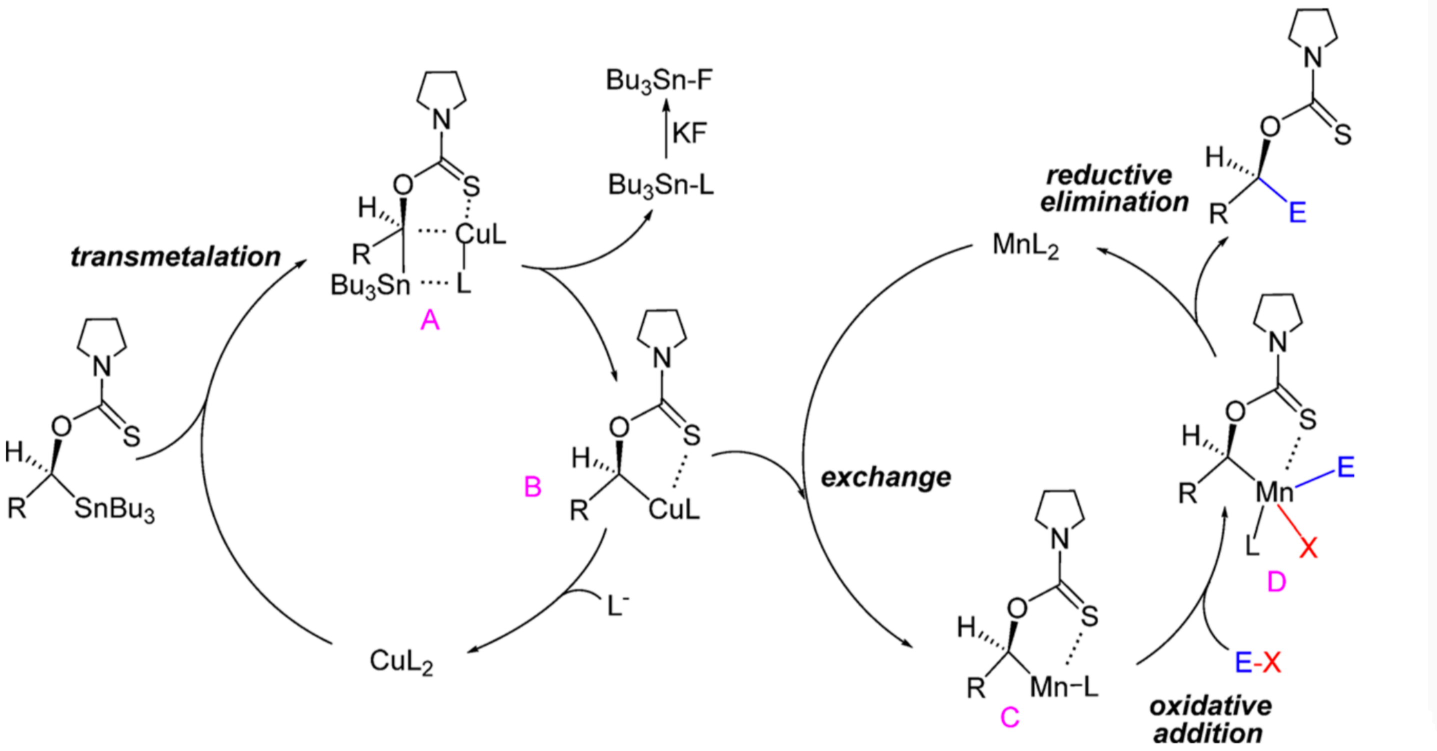


63% yield

Falck, J. R. *et al*. *J. Am. Chem. Soc*., **2007**, *129*, 790.
Dakarapu, R. Falck, J. R. *J. Org. Chem*., **2018**, *83*, 1241.

Manganese Catalyzed Cross-coupling

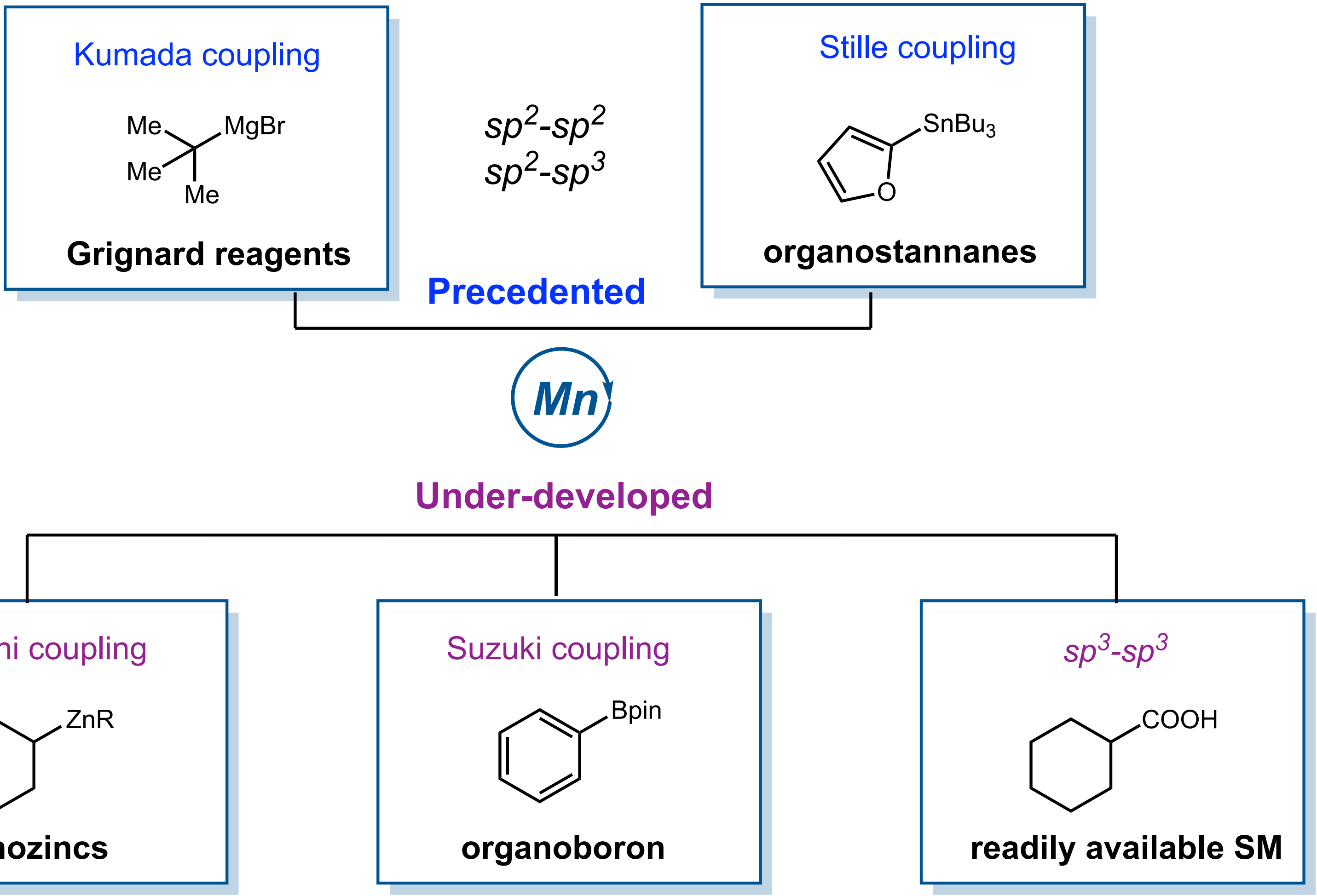
■ Proposed mechanism for Mn/Cu-cocatalyzed cross-coupling



Falck, J. R. *et al*. *J*. *Am*. *Chem*. *Soc*., **2007**, *129*, 790.
Dakarapu, R. Falck, J. R. *J*. *Org*. *Chem*., **2018**, *83*, 1241.

Manganese Catalyzed Cross-coupling

■ Brief summary of manganese catalyzed C-C bond formation



Kumada coupling

Grignard reagents

sp^2-sp^2
sp^2-sp^3

Stille coupling

organostannanes

Precedented

Under-developed

Negishi coupling

organozincs

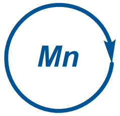
Suzuki coupling

organoboron

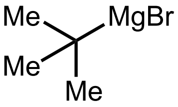
sp^3-sp^3

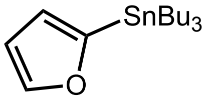
readily available SM

Recent Advances in Cross-Coupling by Manganese Catalysis

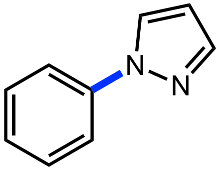


Cross-coupling for C-C bond formation



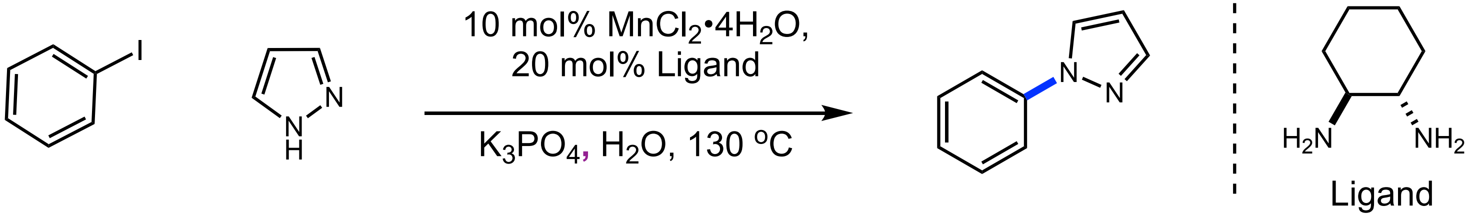


Cross-coupling for C-X bond formation



Manganese Catalyzed C-N Bond Formation

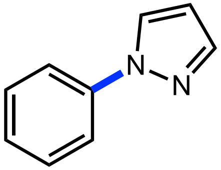
The first Mn catalyzed C-N coupling



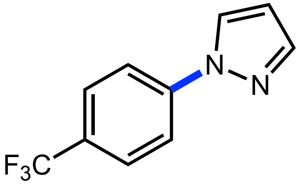
10 mol% $MnCl_2\cdot4H_2O$,
20 mol% Ligand

K_3PO_4, H_2O, 130 °C

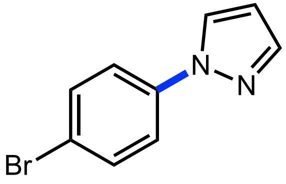
Ligand



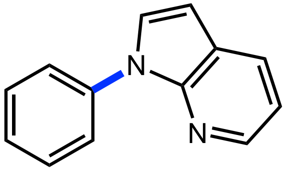
78% yield



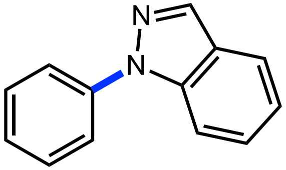
70% yield



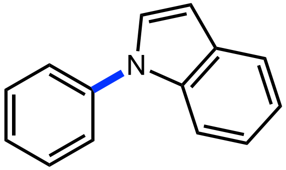
75% yield



87% yield



90% yield



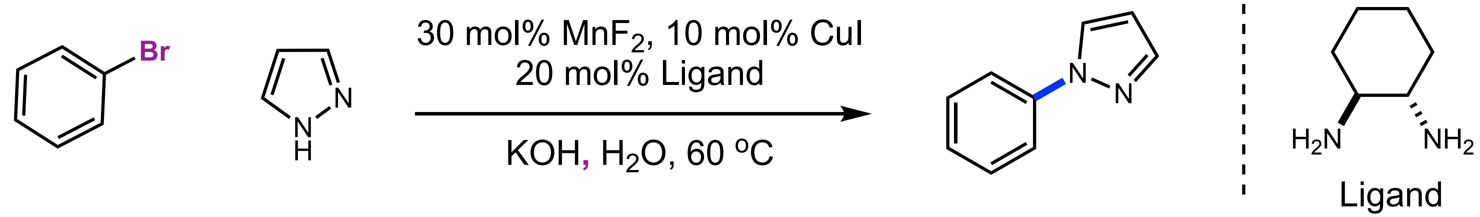
25% yield

limitations

Y.-C. Teo, F.-F. Yong, C.-Y. Poh, Y.-K. Yan, G.-L. Chua, *Chem. Commun.* **2009**, 6258.

Manganese Catalyzed C-N Bond Formation

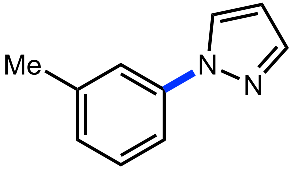
Mn/Cu bimetallic catalyzed C-N coupling



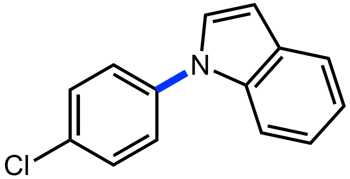
30 mol% MnF_2, 10 mol% CuI
20 mol% Ligand

KOH, H_2O, 60 °C

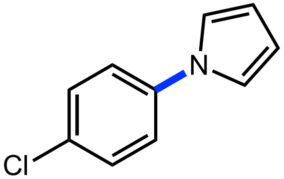
Ligand



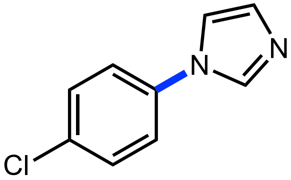
84% yield



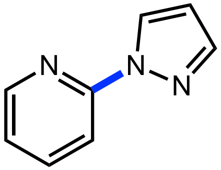
82% yield



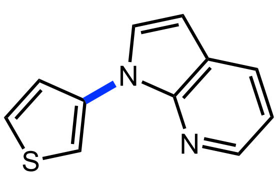
62% yield



65% yield



94% yield

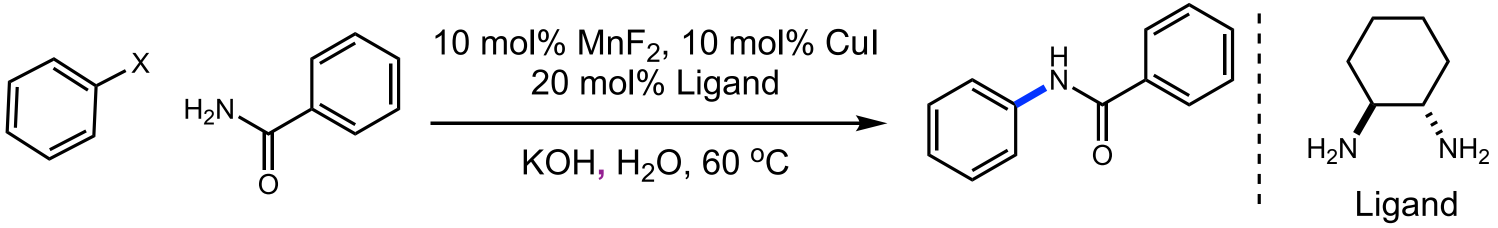


92% yield

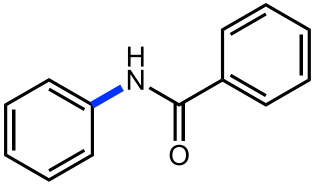
Y.-C. Teo, F.-F. Yong, G. S. Lim. *Tetrahedron Lett*. **2011**, *52*, 7171.

Manganese Catalyzed C-N Bond Formation

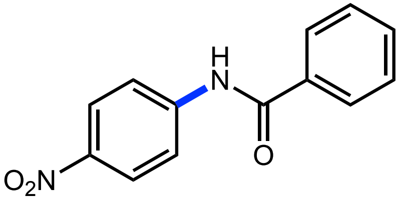
Mn/Cu bimetallic catalyzed C-N coupling in water



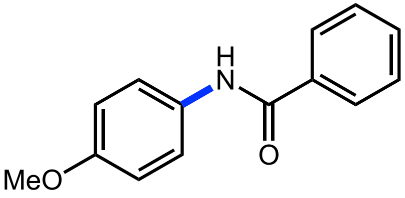
Amides



92% yield

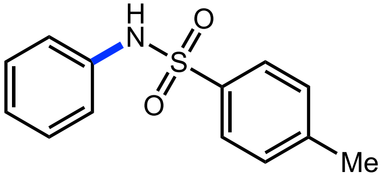


82% yield

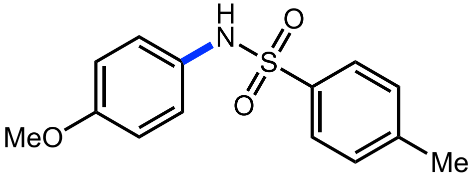


71% yield

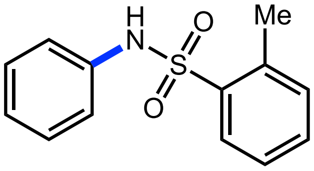
Sulfonamides



97% yield



93% yield

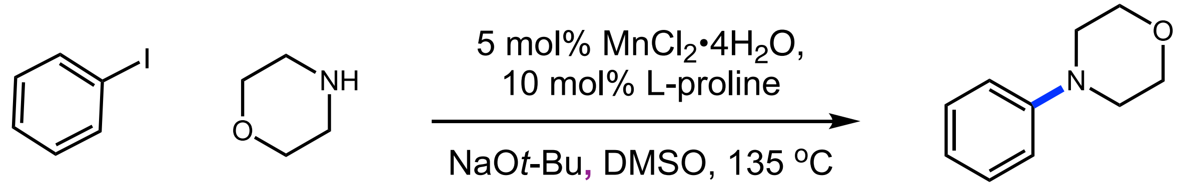


89% yield

Y.-C. Teo *et al*. *Eur. J. Org. Chem*. **2013**, 515.

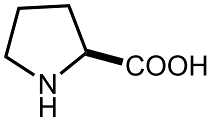
Manganese Catalyzed C-N Bond Formation

Mn catalyzed C-N coupling with aliphatic amines

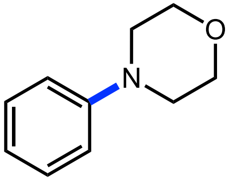


5 mol% $MnCl_2 \cdot 4H_2O$,
10 mol% L-proline

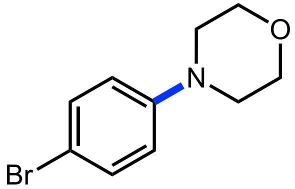
NaO*t*-Bu, DMSO, 135 °C



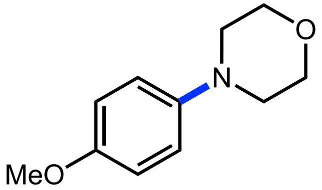
Ligand



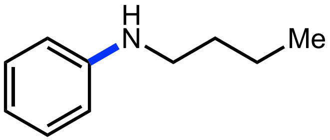
72% yield



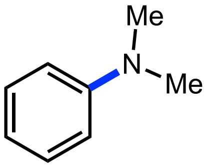
70% yield



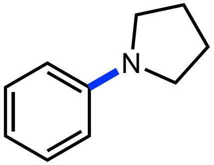
60% yield



50% yield



40% yield



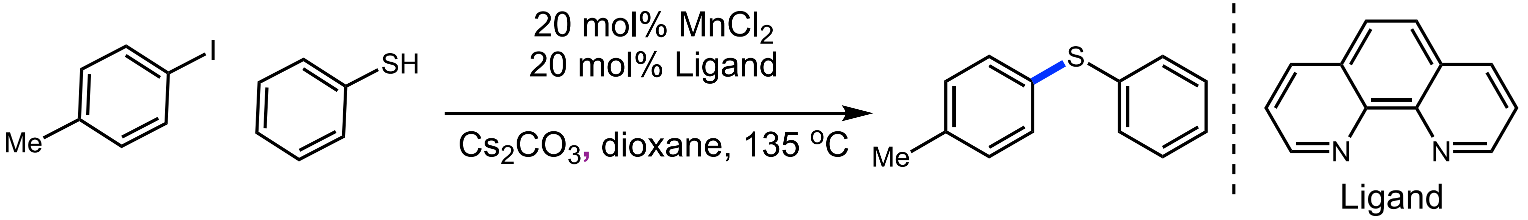
80% yield

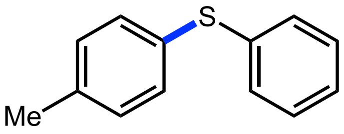
reaction mechanism is still unclear for C-N coupling

F.-F. Yong, Y.-C. Teo, *Tetrahedron Lett*. **2010**, *51*, 3910.

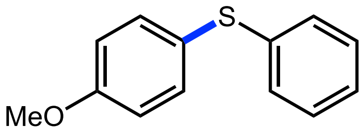
Manganese Catalyzed C-S Bond Formation

The only example of Mn catalyzed C-S coupling

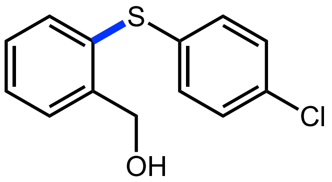




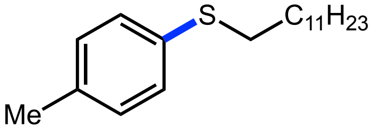
99% yield



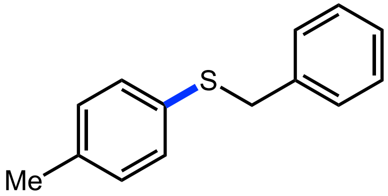
99% yield



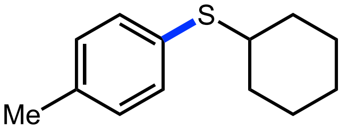
76% yield



81% yield



64% yield

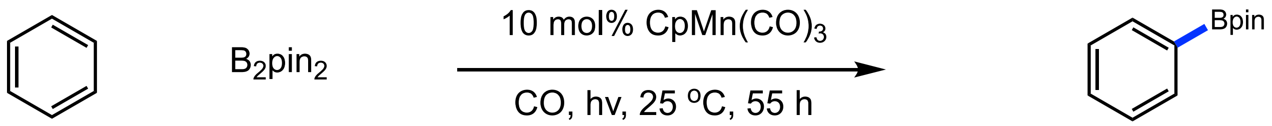


63% yield

T.-J. Liu, C.-L. Yi, C.-C. Chan, C.-F. Lee, *Chem. Asian J.* **2013**, *8*, 1029.

Manganese Catalyzed C-B Bond Formation

The first Mn catalyzed C-H borylation



10 mol% $CpMn(CO)_3$

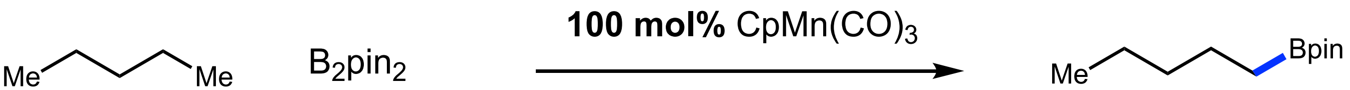
CO, hv, 25 ^oC, 55 h

mercury lamp

solvent

76% yield

Mn promoted C-H borylation



100 mol% $CpMn(CO)_3$

CO, hv, 25 ^oC, 55 h

mercury lamp

solvent

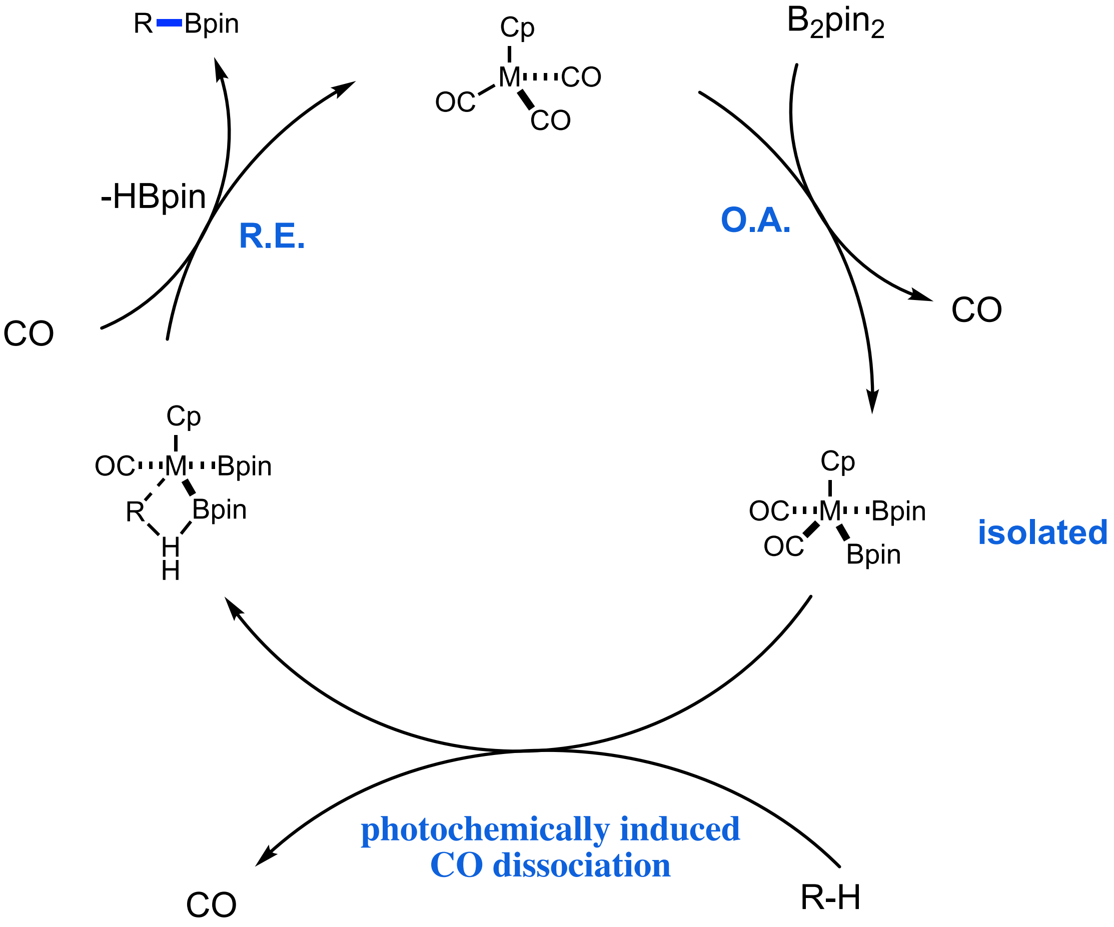
35% yield

limited substrate scope

Chen, H.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **1999**, *38*, 3391;

Manganese Catalyzed C-B Bond Formation

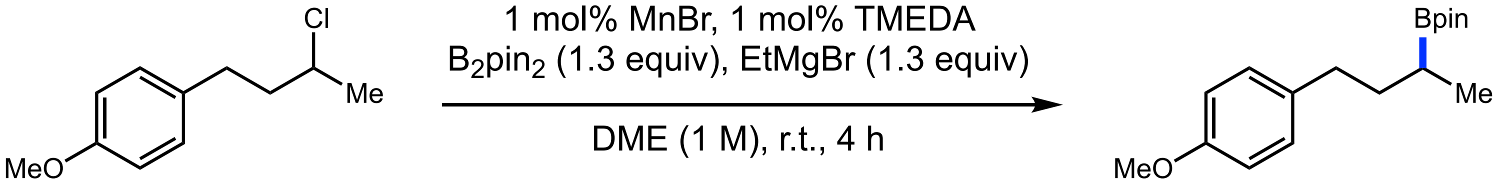
■ Proposed mechanism for the photochemical promoted C-H borylation



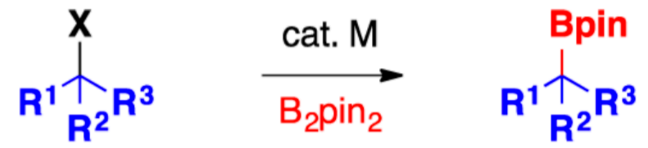
Chen, H.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **1999**, *38*, 3391;

Manganese Catalyzed C-B Bond Formation

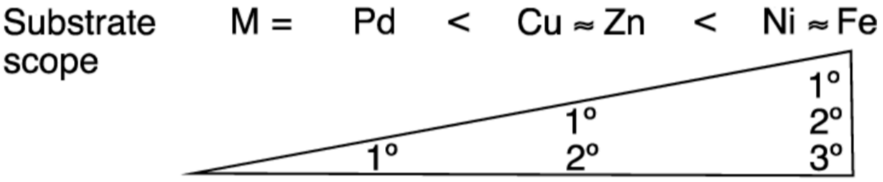
The first Mn catalyzed borylation of unactivated alkyl chloride



96% yield



X = I and Br



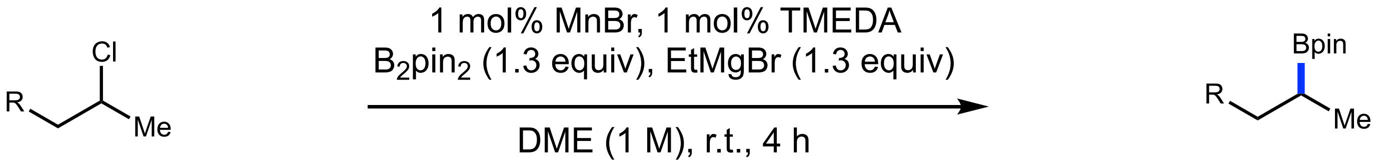
(only works for alkyl Bromide)

Alkyl chlorides remain rare

unique reactivity of Mn

Atack, T. C.; Cook, S. P. *J. Am. Chem. Soc.* **2016**, *138*, 6139.

Manganese Catalyzed C-B Bond Formation

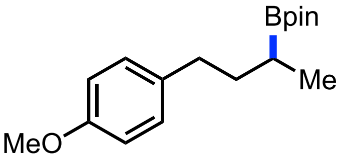


1 mol% MnBr, 1 mol% TMEDA
B_2pin_2 (1.3 equiv), EtMgBr (1.3 equiv)

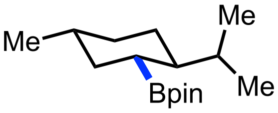
DME (1 M), r.t., 4 h

alkyl chloride

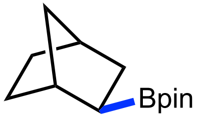
borylated product



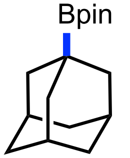
(Cl, ***88% yield***)
(Br, ***91% yield***)
(I, ***68% yield***)



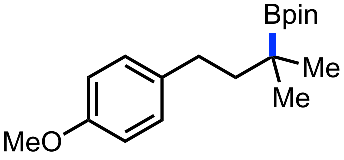
78% yield



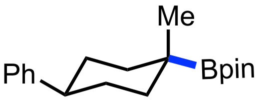
83% yield



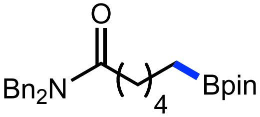
83% yield



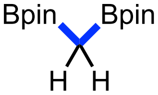
71% yield



65% yield



58% yield



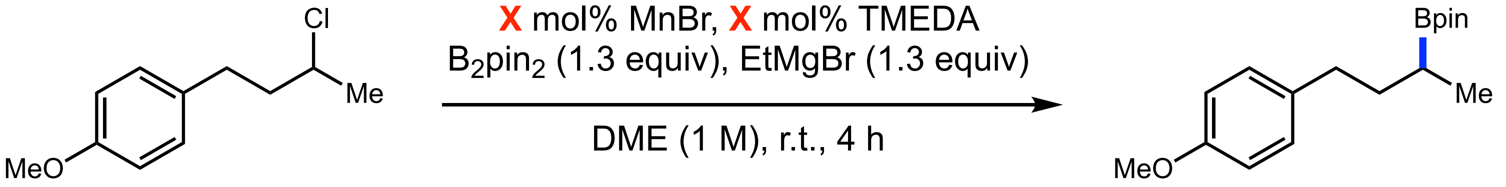
64% yield

(from **CH_2Cl_2**)

Atack, T. C.; Cook, S. P. *J. Am. Chem. Soc.* **2016**, *138*, 6139.

Manganese Catalyzed C-B Bond Formation

Effect of catalyst loading



X mol% MnBr, X mol% TMEDA

B_2pin_2 (1.3 equiv), EtMgBr (1.3 equiv)

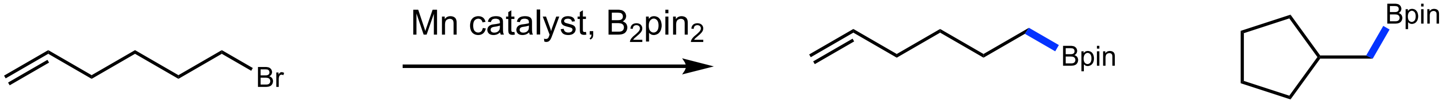
DME (1 M), r.t., 4 h

entry	Mn/TMEDA %	time	yield[a]
1[b]	0.1%	24 h	80%
2	1%	4 h	88%
3	5%	0.5 h	78%

Atack, T. C.; Cook, S. P. *J. Am. Chem. Soc.* **2016**, *138*, 6139.

Manganese Catalyzed C-B Bond Formation

Mechanism studies for the reaction



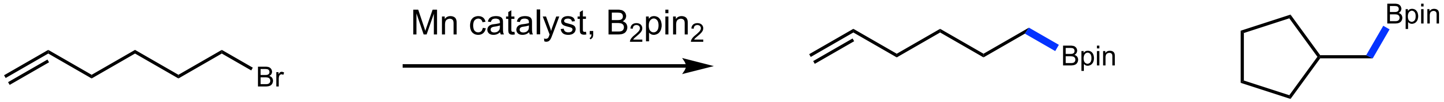
0.5 M, 0 °C	*79% yield*	*0% yield*
0.5 M, r.t.	*50% yield*	*16% yield*
0.1 M, 65 °C	*2% yield*	*37% yield*

0.5 M, 0 °C	*20% yield*	*51% yield*
1.0 M, 22 °C	*8% yield*	*83% yield*

Atack, T. C.; Cook, S. P. *J. Am. Chem. Soc.* **2016**, *138*, 6139.

Manganese Catalyzed C-B Bond Formation

Mechanism studies for the reaction



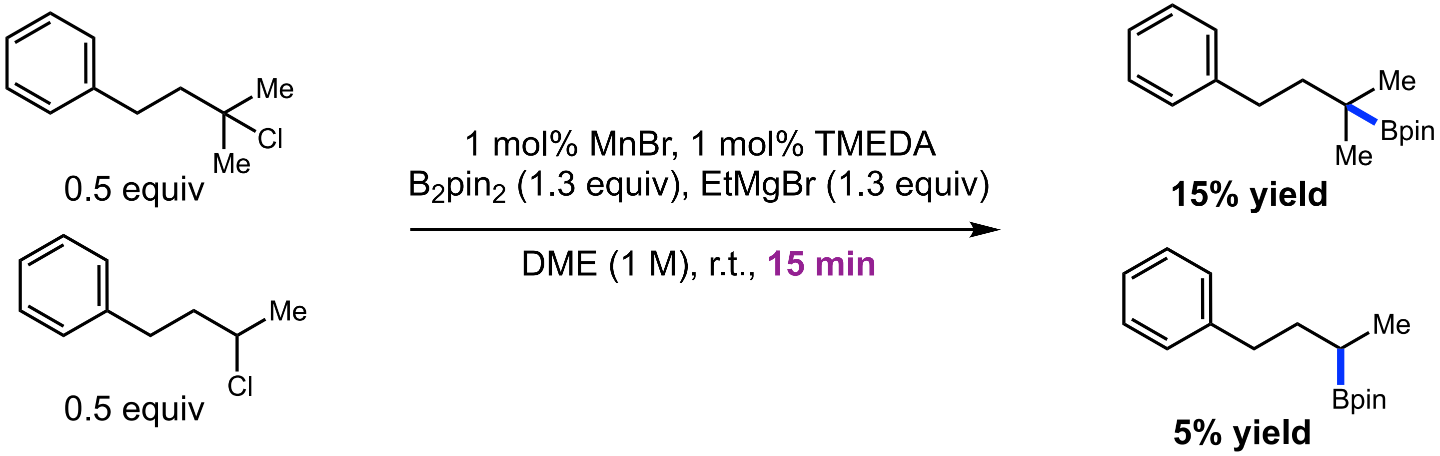
0.5 M, 0 °C	***79% yield***	***0% yield***
0.5 M, r.t.	***50% yield***	***16% yield***
0.1 M, 65 °C	***2% yield***	***37% yield***

- ***Results suggest alkyl radicals are involved from the alkyl halides***
- ***Reducing the temperature to 0 °C produced direct borylation product as the sole product, suggesting the rate of radical recombination with Mn is faster than that of 5-exo ring closure.***
- ***The first report on the use of temperarture to effect a switch in selectivity in radical-based transiton metal chemistry.***

Atack, T. C.; Cook, S. P. *J. Am. Chem. Soc.* **2016**, *138*, 6139.

Manganese Catalyzed C-B Bond Formation

■ Mechanism studies for the reaction

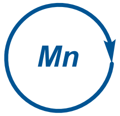


preference for alkyl chloride activation **1° < 2° < 3° (k_{rel} = 1:2.5:4.5)**

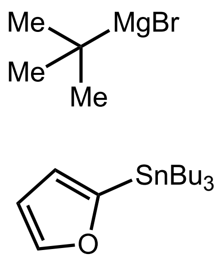
supporting the intermediacy of alkyl radicals formation is involved in the turnover-limiting step

Atack, T. C.; Cook, S. P. *J. Am. Chem. Soc*. **2016**, *138*, 6139.

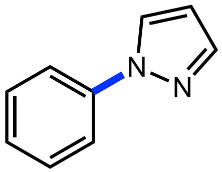
Recent Advances in Cross-Coupling by Manganese Catalysis



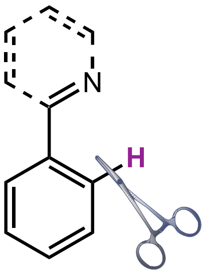
Cross-coupling for C-C bond formation



Cross-coupling for C-X bond formation

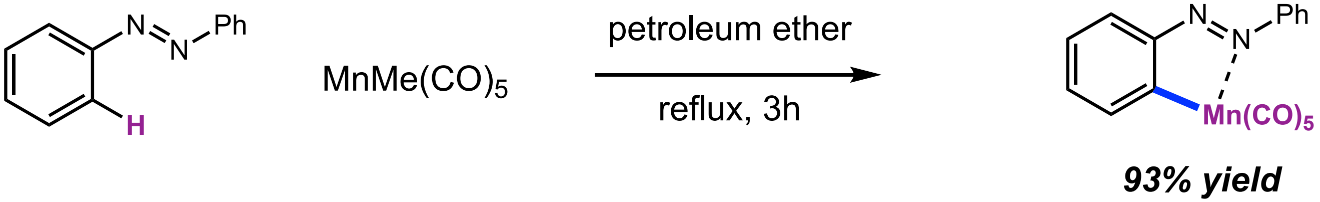


C-H activation for C-C bond formation

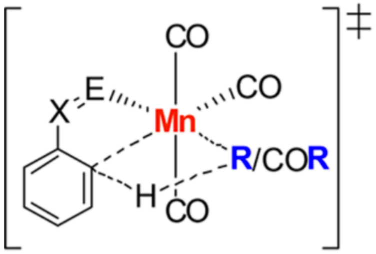


Manganese Catalyzed C-C bond formation via C-H activation

The first stoichiometric Mn promoted C-H activation



Stoichiometric Cyclomanganation



$MnR(CO)_5$

R = Me, CH_2Ph, etc.

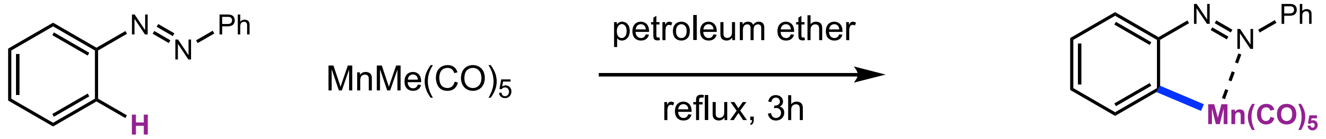
- ***via σ-bond metathesis***
- ***difficult to regenerate the active catalyst***

the development of Mn catalyzed C−H activation protocols remained nearly dormant in the following 40 years…

Bruce, M. I.; Iqbal, M. Z.; Stone, F. G. A. *J. Chem. Soc. A* **1970**, 3204.

Manganese Catalyzed C-C bond formation via C-H activation

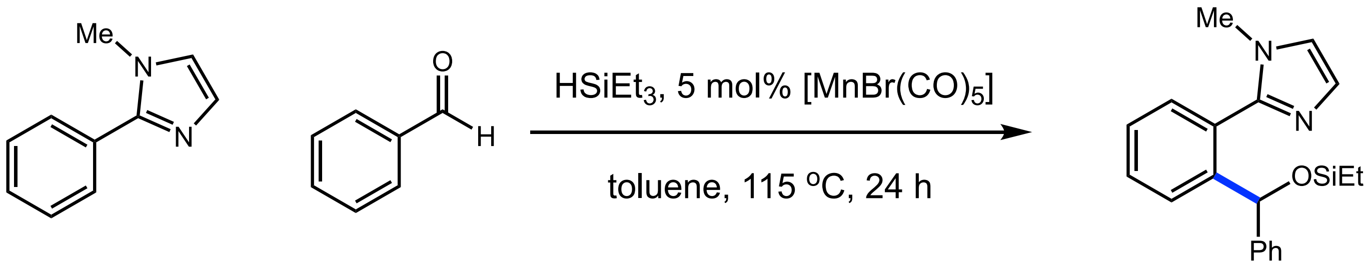
The first stoichiometric Mn promoted C-H activation



93% yield

Bruce, M. I.; Iqbal, M. Z.; Stone, F. G. A. *J. Chem. Soc. A* **1970**, 3204.

The first Mn catalyzed C-H activation for C-C bond formation

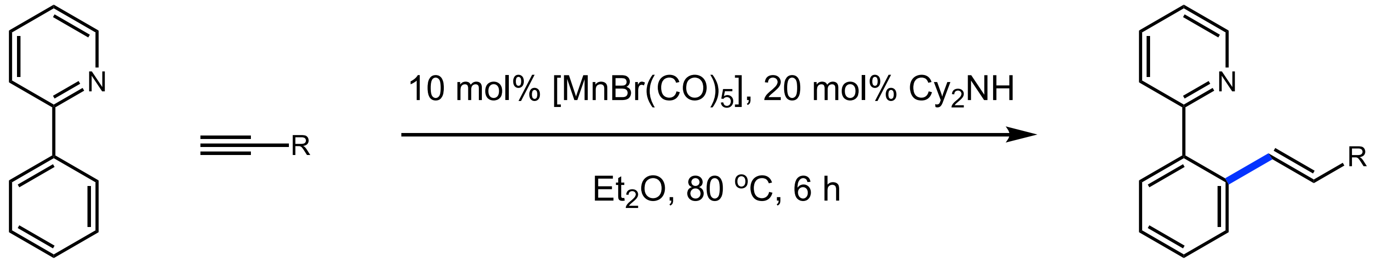


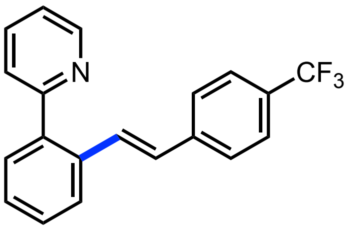
48-87% yield, 7 examples

Kuninobu, Y.; Nishina, T.; Takeuchi, T.; Takai, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 6518.

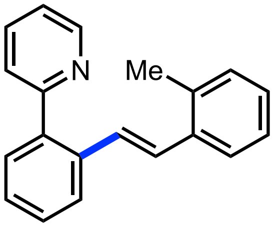
Manganese Catalyzed C-C bond formation via C-H activation

Mn catalyzed C-H alkenylation

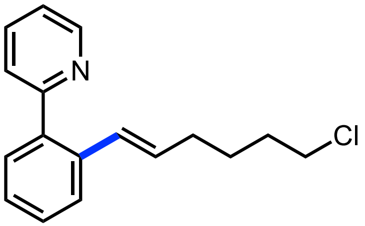




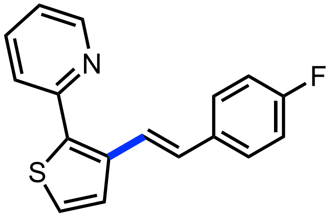
71% yield



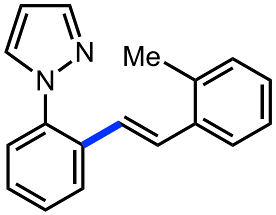
80% yield



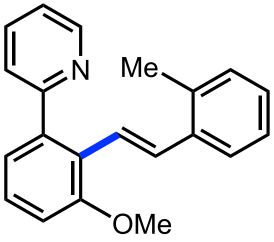
68% yield



51% yield



77% yield

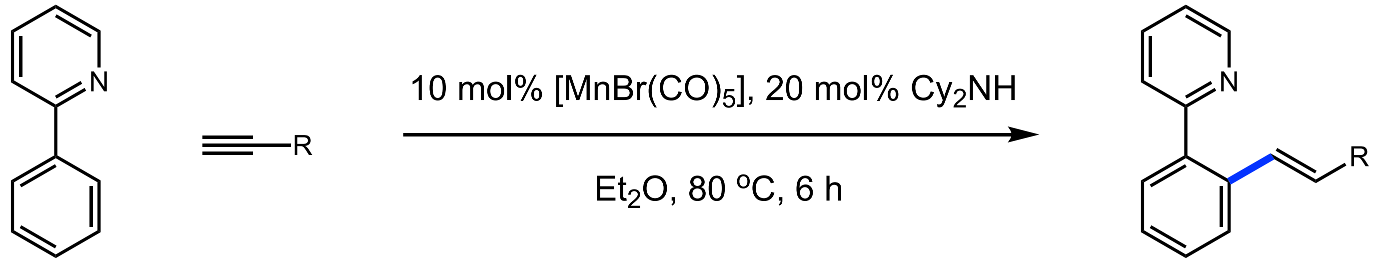


67% yield

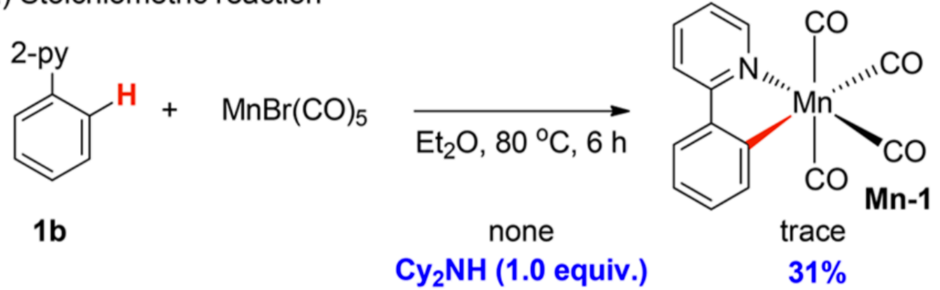
Zhou, B.; Chen, H.; Wang, C. *J. Am. Chem. Soc.* **2013**, *135*, 1264.

Manganese Catalyzed C-C bond formation via C-H activation

Mn catalyzed C-H alkenylation

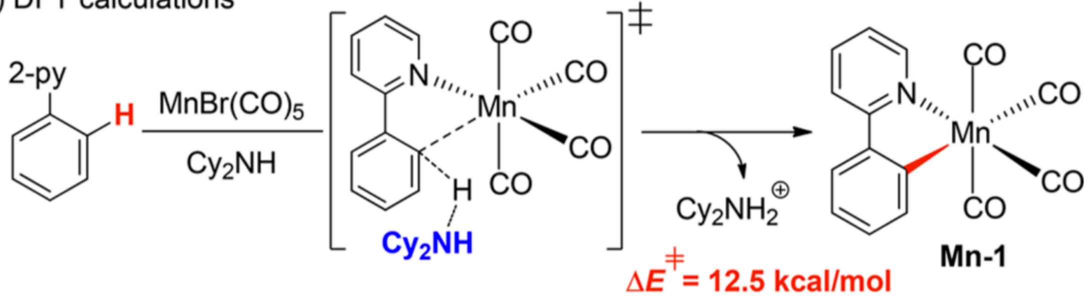


a) Stoichiometric reaction



the catalytic base is the key to success of this transformation

b) DFT calculations

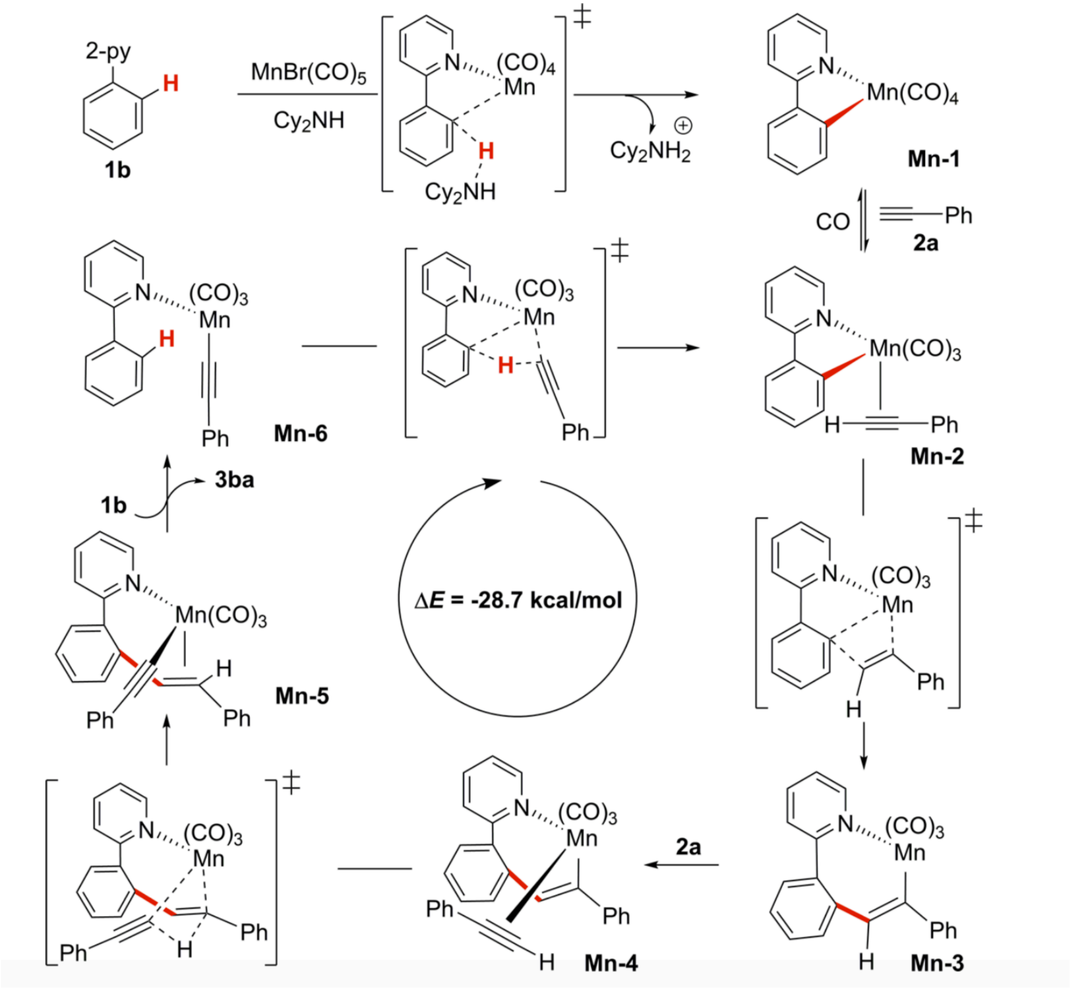


exothermic step

Zhou, B.; Chen, H.; Wang, C. *J. Am. Chem. Soc.* **2013**, *135*, 1264.

Manganese Catalyzed C-C bond formation via C-H activation

■ Proposed mechanism for Mn catalyzed C-H alkenylation

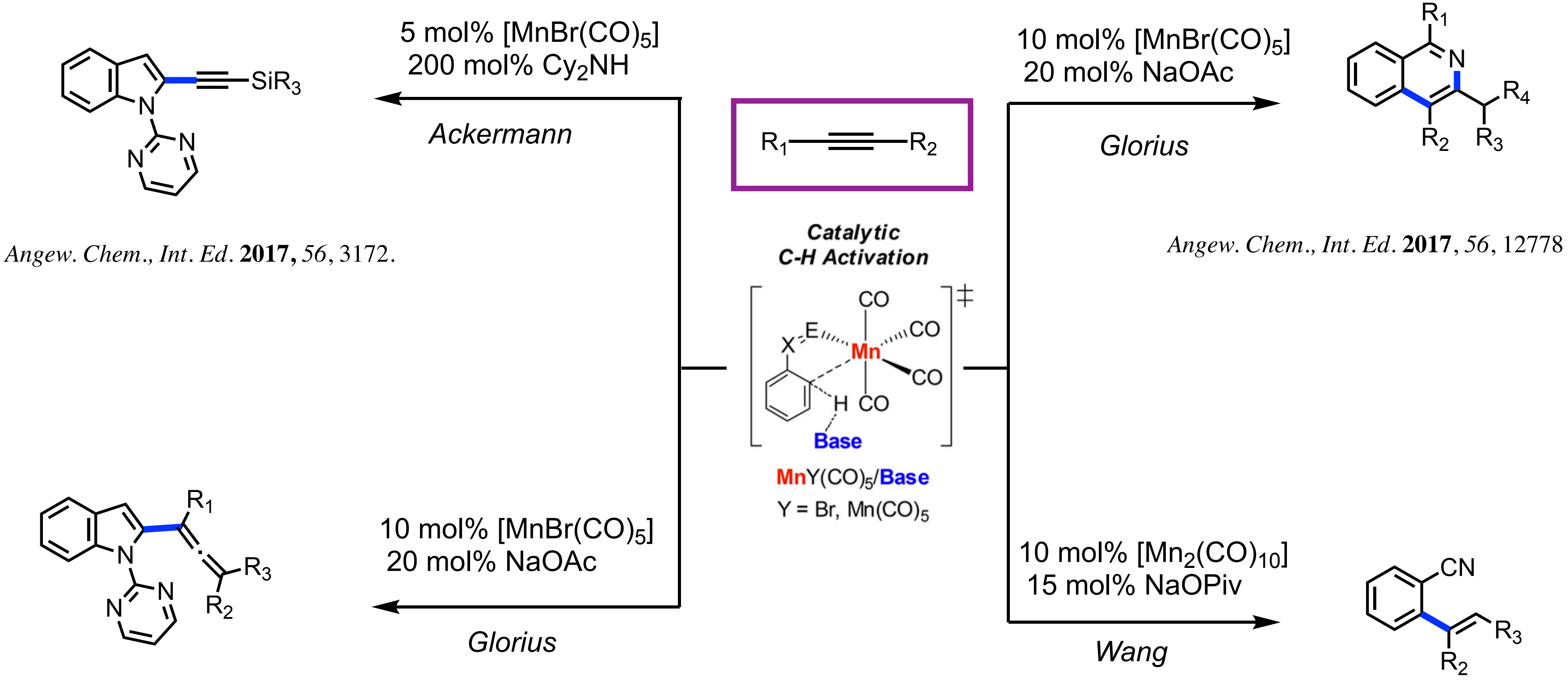


Zhou, B.; Chen, H.; Wang, C. *J. Am. Chem. Soc.* **2013**, *135*, 1264.

Manganese Catalyzed C-C bond formation via C-H activation

■ C-H activation coupling with alkyne derivatives by using Mn/base systems

selected examples



5 mol% [$MnBr(CO)_5$]
200 mol% Cy_2NH

Ackermann

Angew. Chem., Int. Ed. **2017,** *56*, 3172.

10 mol% [$MnBr(CO)_5$]
20 mol% NaOAc

Glorius

Angew. Chem., Int. Ed. **2017**, *56*, 12778

Catalytic
C-H Activation

Mn$Y(CO)_5$/**Base**
Y = Br, $Mn(CO)_5$

10 mol% [$MnBr(CO)_5$]
20 mol% NaOAc

Glorius

Angew. Chem., Int. Ed. **2017**, *56*, 6660

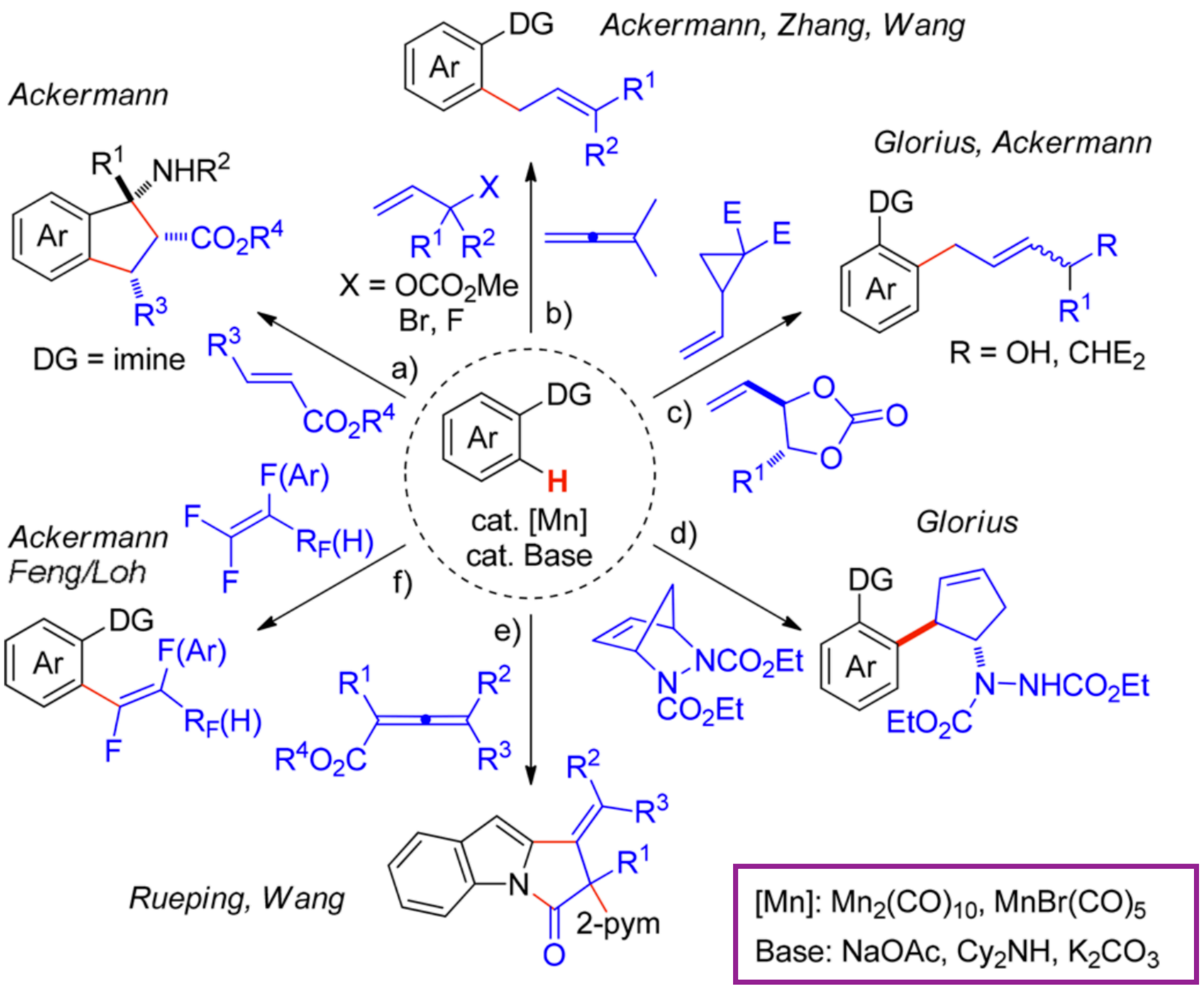
10 mol% [$Mn_2(CO)_{10}$]
15 mol% NaOPiv

Wang

Adv. Synth. Catal. **2016**, *358*, 2436.

Manganese Catalyzed C-C bond formation via C-H activation

C-H activation coupling with olefins by using Mn/base systems



[Mn]: $Mn_2(CO)_{10}$, $MnBr(CO)_5$

Base: NaOAc, Cy_2NH, K_2CO_3

selected examples

Chem. Commun. **2014**, *50*, 14558.

Angew. Chem., Int. Ed. **2016**, *55*, 7747.

Chem. Commun. **2017**, *53*, 8731.

ACS Catal. **2017**, *7*, 4209.

Org. Lett. **2017**, *19*, 3159.

Chem. Sci. **2017**, *8*, 3379.

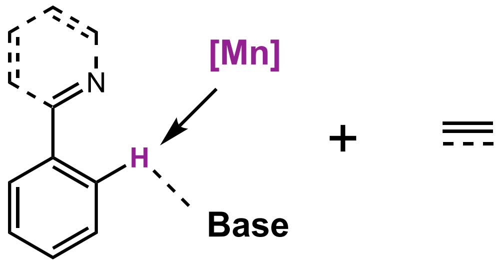
Angew. Chem., Int. Ed. **2017**, *56*, 6339.

Angew. Chem., Int. Ed. **2017**, *56*, 9935.

Angew. Chem., Int. Ed. **2017**, *56*, 9939.

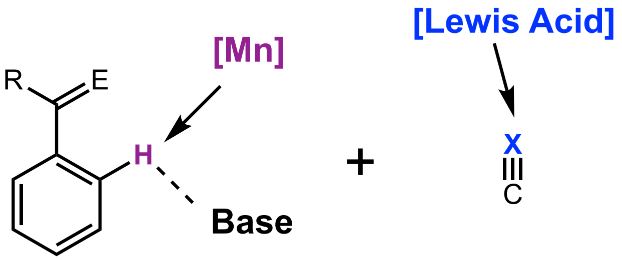
Manganese Catalyzed C-C bond formation via C-H activation

Mn/Base System



- *strong N-directing groups required*
- *addition to less polarized C-C multiple bonds*
- *limited substrate scope*

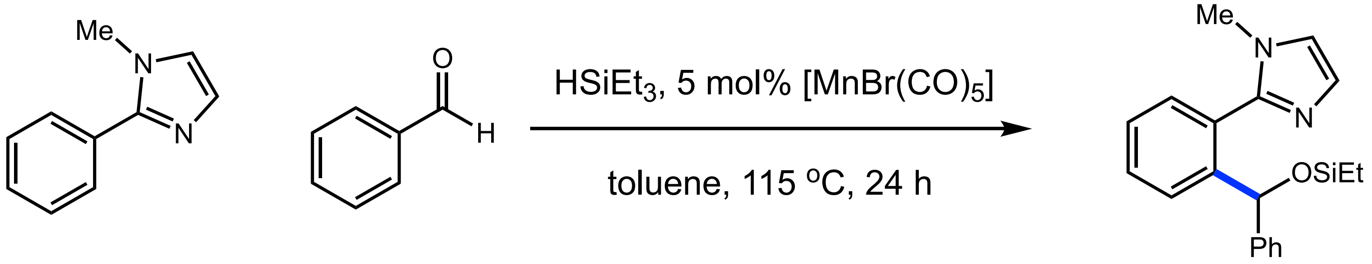
Mn/Lewis Acid System



- *E can be weak O- or N-directing groups*
- *addition to more polarized C-X multiple bonds*
- *extended substrate scope*

Manganese Catalyzed C-C bond formation via C-H activation

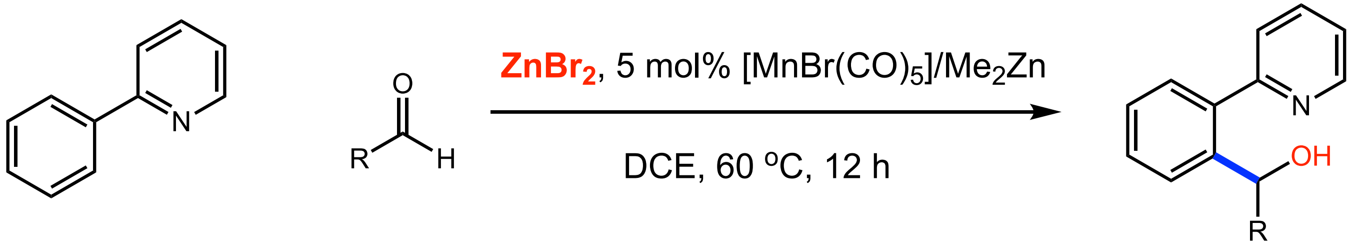
The first Mn catalyzed C-H activation



48-87% yield, 7 examples

Kuninobu, Y.; Nishina, T.; Takeuchi, T.; Takai, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 6518.

The methodology was expanded by using a Lewis acid

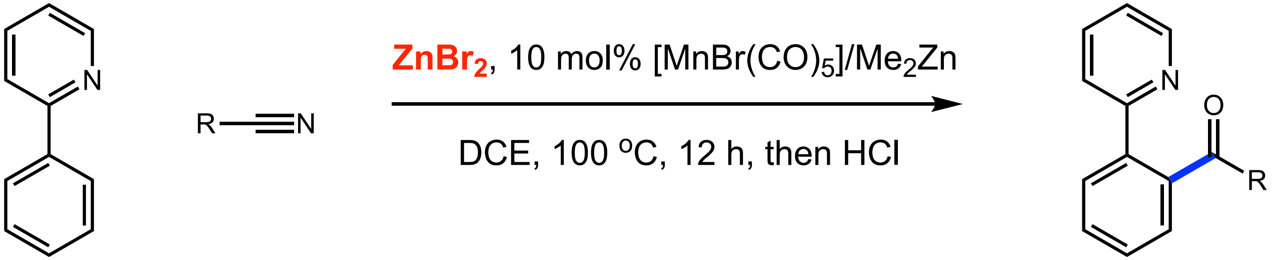


38-95% yield, 101 examples

Zhou, B.; Hu, Y.; Wang, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 13659.

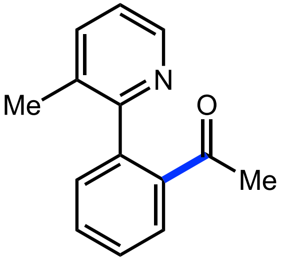
Manganese Catalyzed C-C bond formation via C-H activation

Mn catalyzed C-H addition to nitriles



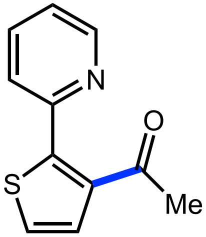
$ZnBr_2$, 10 mol% $[MnBr(CO)_5]/Me_2Zn$

DCE, 100 °C, 12 h, then HCl

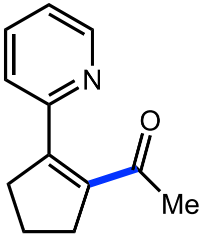


(with MeCN)

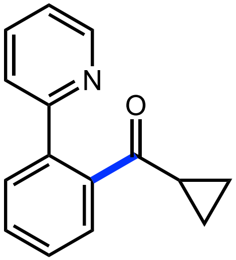
70% yield



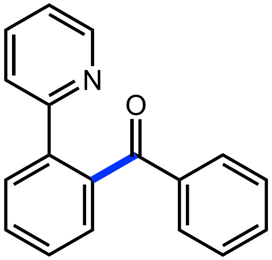
88% yield



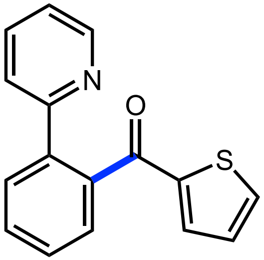
88% yield



50% yield



77% yield

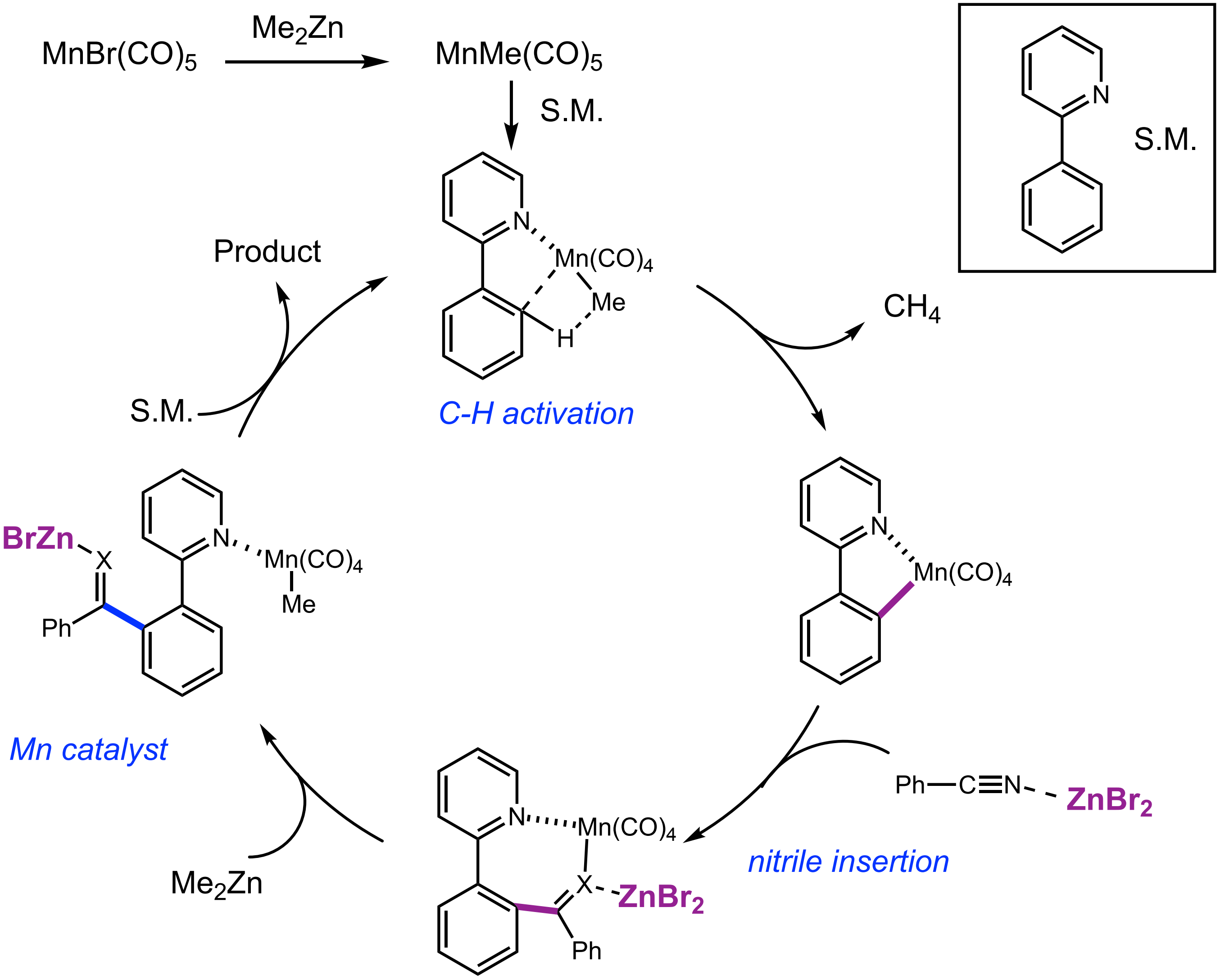


78% yield

Zhou, B.; Hu, Y.; Wang, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 13659.

Manganese Catalyzed C-C bond formation via C-H activation

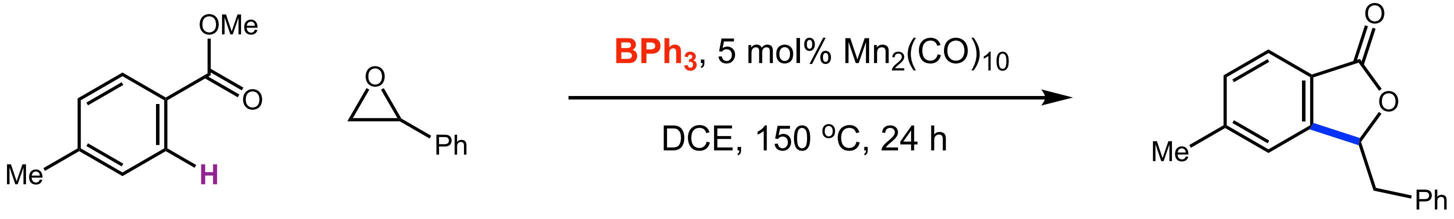
■ Proposed mechanism for Mn catalyzed C-H addition to nitriles/aldehyde



Manganese Catalyzed C-C bond formation via C-H activation

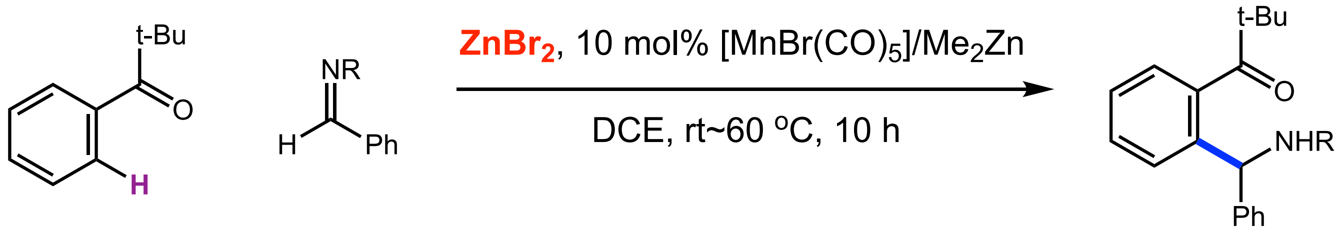
selected exapmles

Mn catalyzed C-H activation with the aid of acids



Sueki, S.; Wang, Z.; Kuninobu, Y. *Org. Lett.* **2016**, *18*, 304.

Mn catalyzed C-H activation with the aid of acids

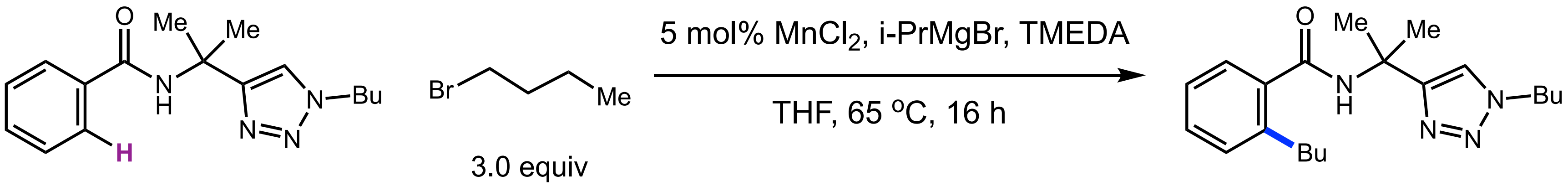


Zhou, B.; Hu, Y.; Liu, T.; Wang, C. *Nat. Commun.* **2017**, *8*, 1169.

What about combining with more challenging alkyl halides for the sp^2-sp^3 cross-coupling?

Manganese Catalyzed C-C bond formation via C-H activation

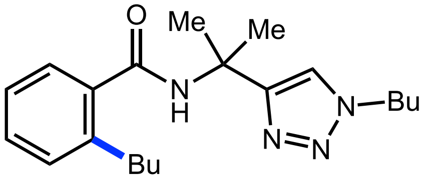
Mn catalyzed C-H alkylations with alkyl halides



5 mol% $MnCl_2$, i-PrMgBr, TMEDA

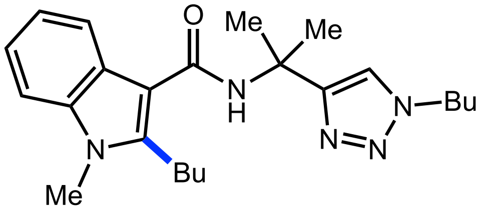
THF, 65 °C, 16 h

3.0 equiv

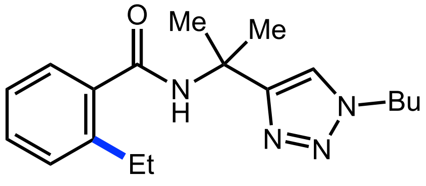


82% yield

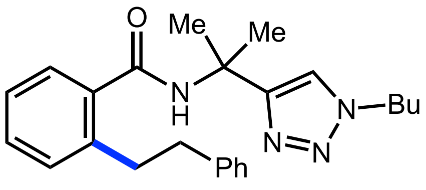
with phosphine ligand 50% yield



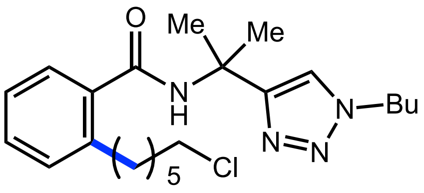
59% yield



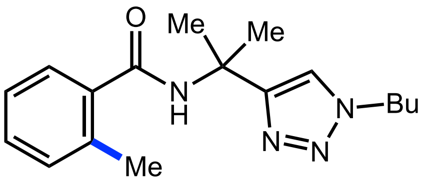
71% yield



62% yield



78% yield



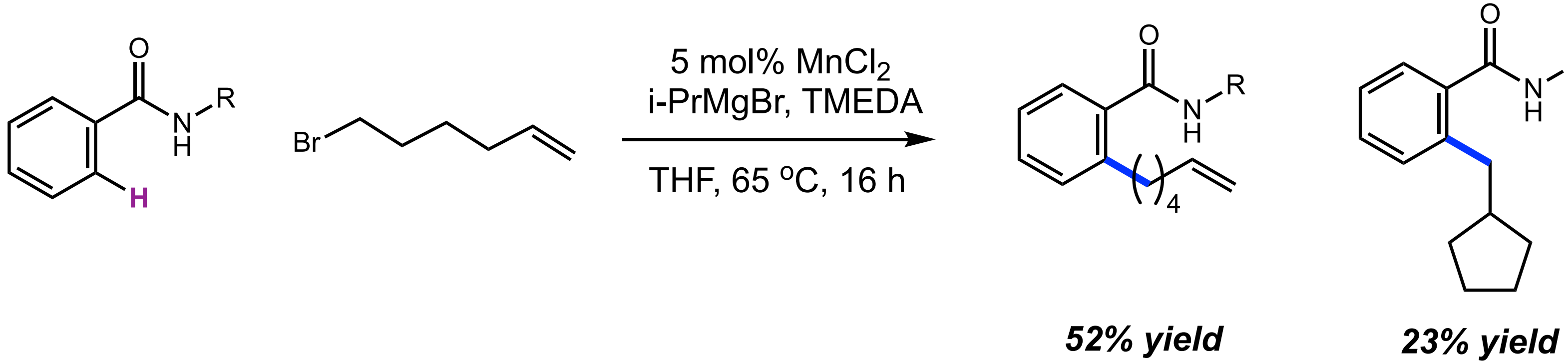
87% yield

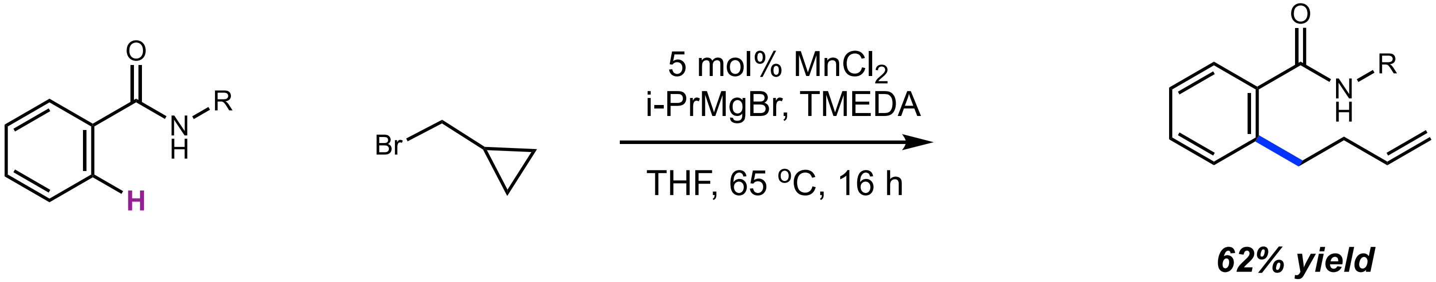
with MeMgBr (7.0 equiv)

Liu, W.; Cera, G.; Oliveira, J. C. A.; Shen, Z.; Ackermann, L. *Chem. - Eur. J.* **2017**, *23*, 11524.

Manganese Catalyzed C-C bond formation via C-H activation

Radical Clock experiment

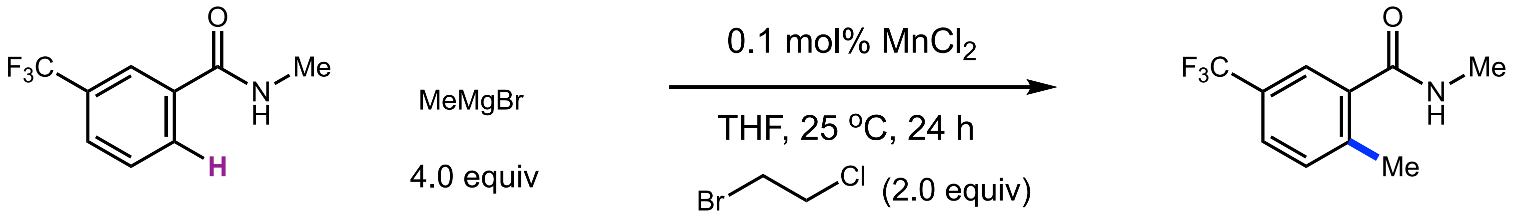


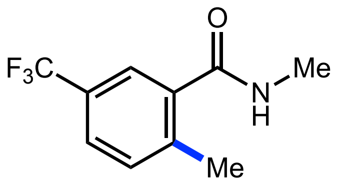


Liu, W.; Cera, G.; Oliveira, J. C. A.; Shen, Z.; Ackermann, L. *Chem*. - *Eur. J*. **2017**, *23*, 11524.

Manganese Catalyzed C-C bond formation via C-H activation

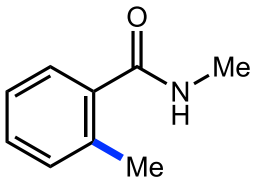
Mn catalyzed directed C-H methylation



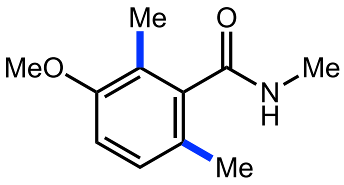


90% yield

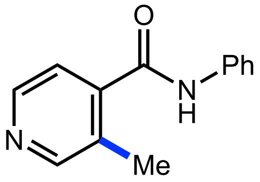
without 1-bromo-2-chloroethane, 0% yield



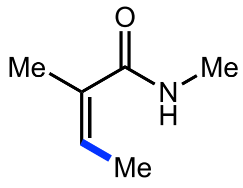
98% yield



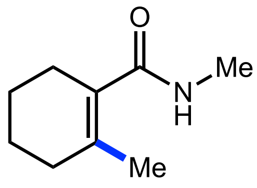
84% yield (di:mono 1.3/1)



79% yield



65% yield

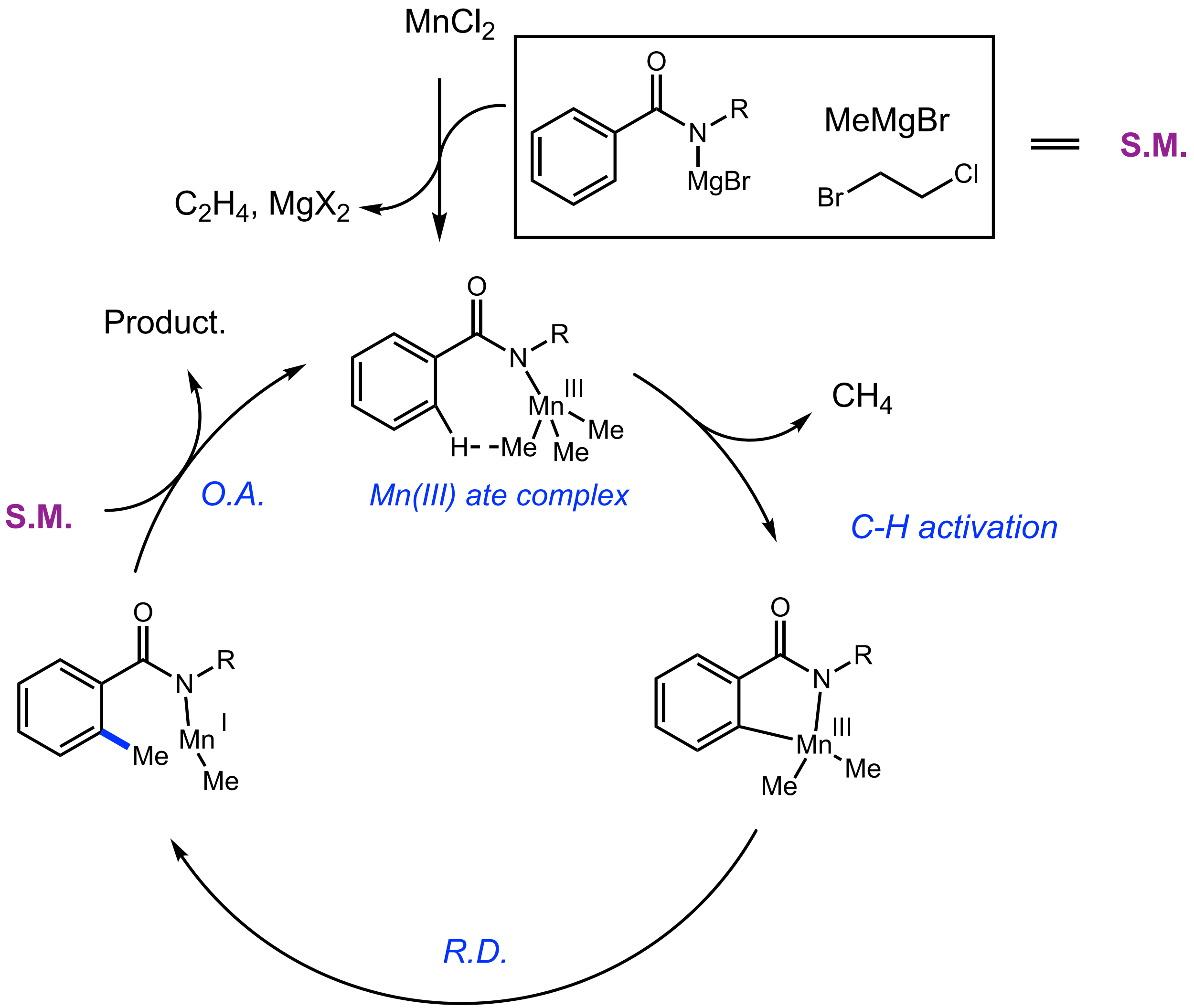


88% yield

Sato, T.; Yoshida, T.; Al Mamari, H. H.; Ilies, L.; Nakamura, E. *Org. Lett.* **2017**, *19*, 5458.

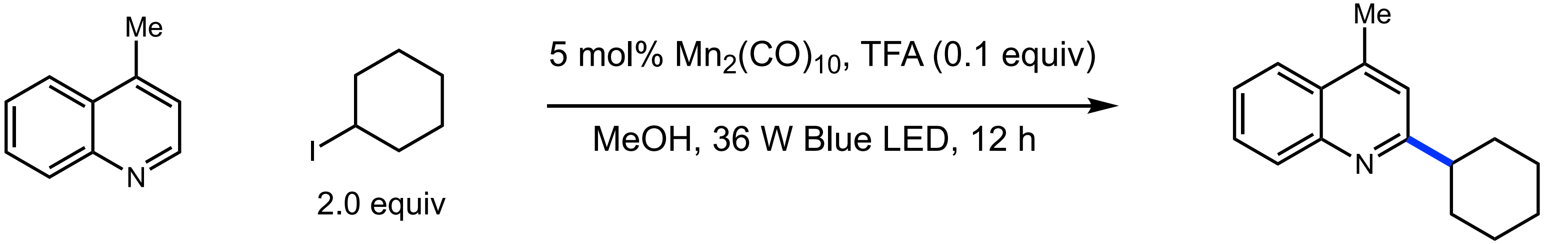
Manganese Catalyzed C-C bond formation via C-H activation

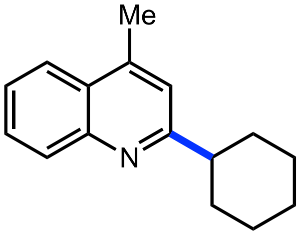
■ Proposed mechanism for Mn catalyzed C-H methylation



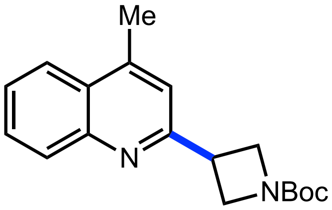
Manganese Catalyzed C-C bond formation via C-H activation

Mn catalyzed C-H alkylations with alkyl halides via photoredox

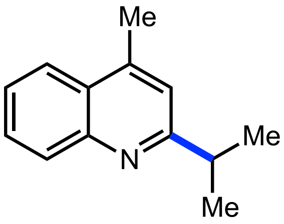




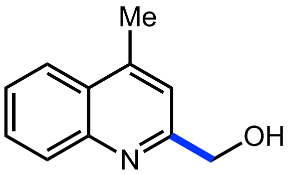
98% yield



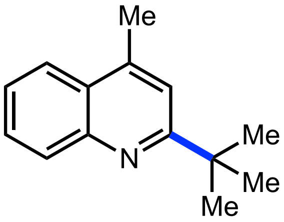
67% yield



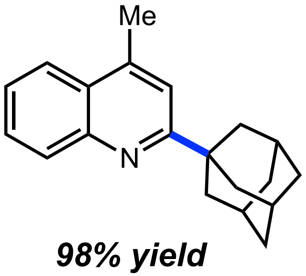
76% yield



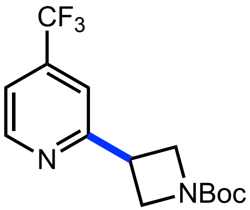
33% yield



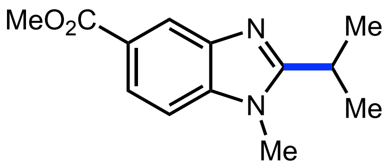
62% yield



98% yield



44% yield

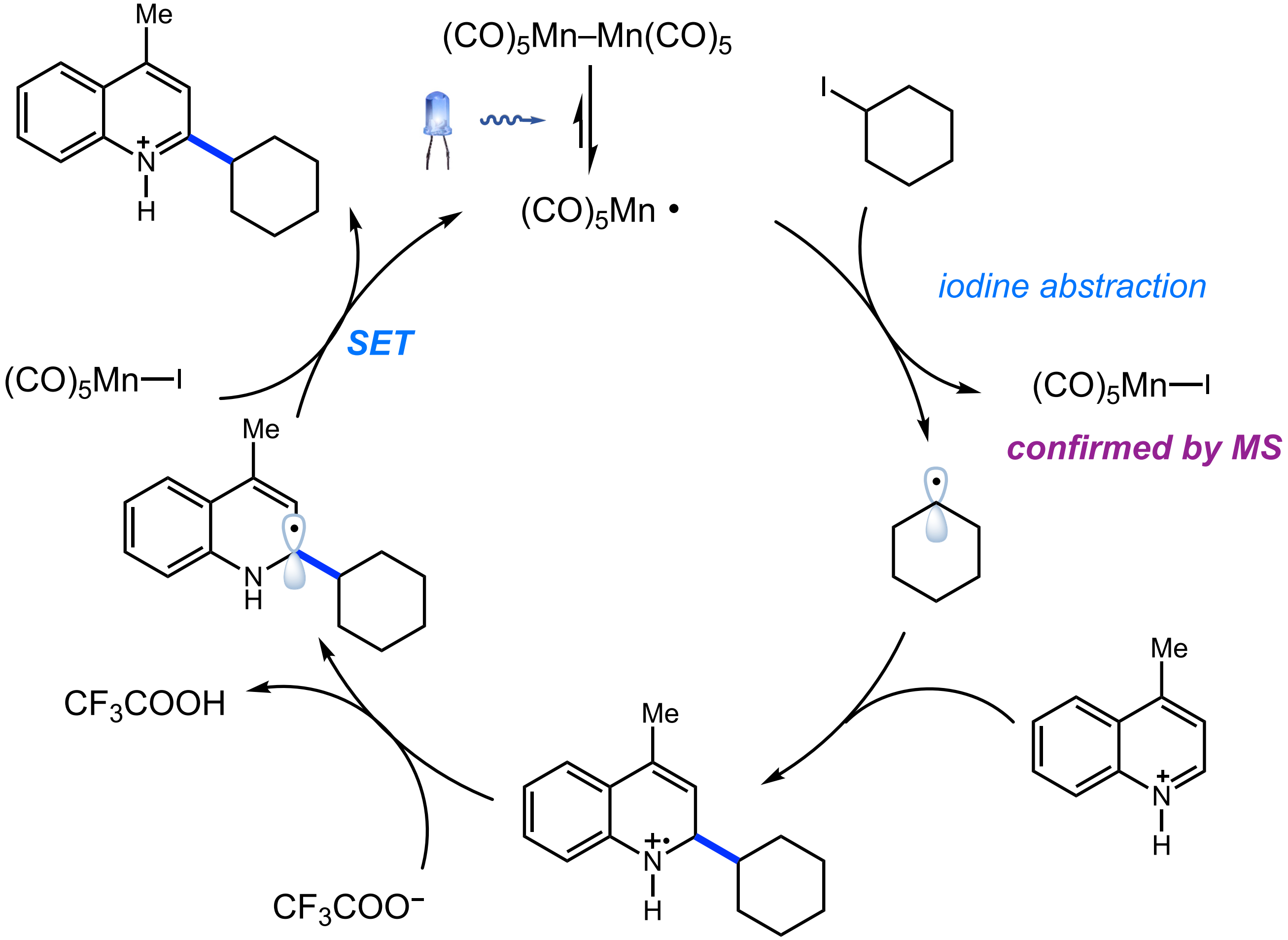


60% yield

Fadeyi, O. O. *et al*. *Angew. Chem. Int. Ed.* **2017**, *56*, 15309.

Manganese Catalyzed C-C bond formation via C-H activation

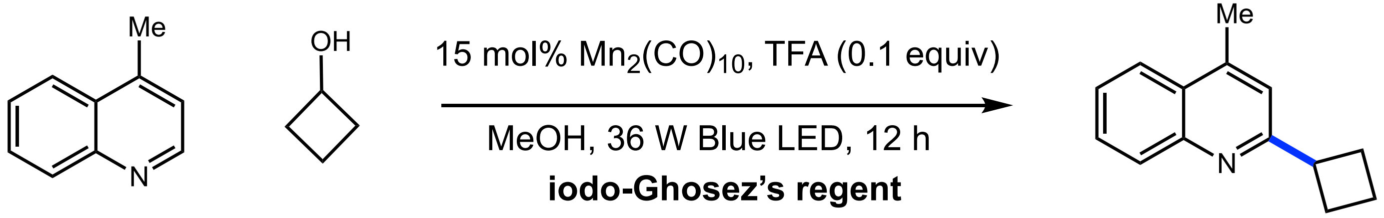
■ Proposed mechanism



Fadeyi, O. O. *et al*. *Angew. Chem. Int. Ed.* **2017**, *56*, 15309.

Manganese Catalyzed C-C bond formation via C-H activation

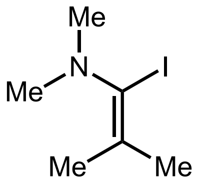
Mn catalyzed C-H alkylations with alcohols via photoredox



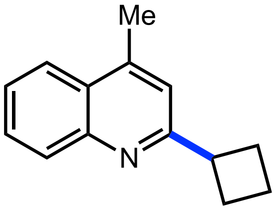
15 mol% $Mn_2(CO)_{10}$, TFA (0.1 equiv)

MeOH, 36 W Blue LED, 12 h

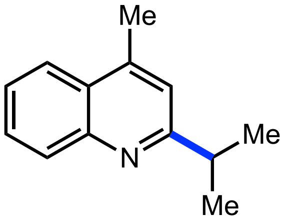
iodo-Ghosez's regent



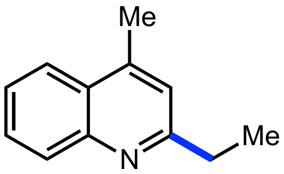
iodo-Ghosez's regent



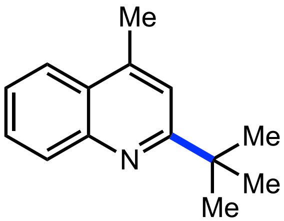
42% yield



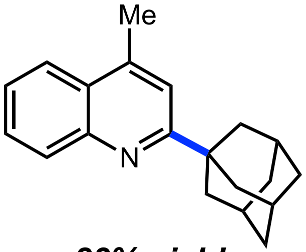
75% yield



40% yield



41% yield

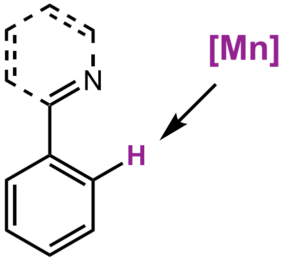


83% yield

Fadeyi, O. O. *et al*. *Angew. Chem. Int. Ed.* **2017**, *56*, 15309.

Manganese Catalyzed C-C bond formation via C-H activation

- Brief summary of manganese catalyzed C-H activation for C-C bond formation



Coupling parters

$C\equiv C$	$C=C$	$C=O$	$C=N$	$C\equiv N$	$R-X$
alkyne	*alkene*	*ketone*	*imine*	*nitrile*	*alkyl halide*

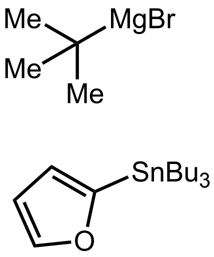
- ***obstacles remain***:

  1. Mn redox chemistry is still unclear, rare examples of redox-based catalysis by Mn;
  2. no enantioselective C-H transformation;
  3. unprecedented and unique catalic reactivity need to be explored, e.g. C-X bond formation

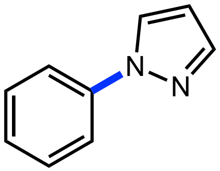
Summary

Mn

Cross-coupling for C-C bond formation



Cross-coupling for C-X bond formation



C-H activation for C-C bond formation