C–H activation of aliphatic amines without unnecessary mask

2017.11.25
M2 Takaya Togo

Outline

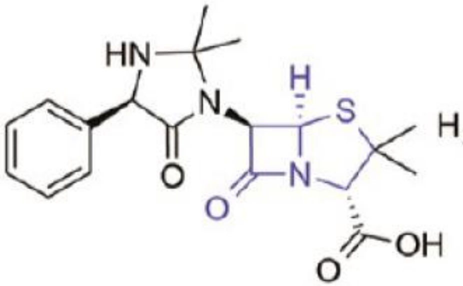
1.Introduction

2.Free amines as DG

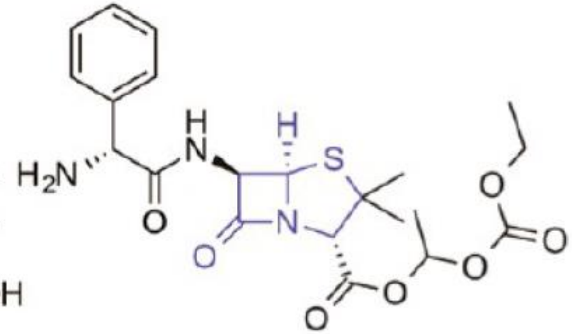
- Discovery of new activation mode
- Mechanistic studies
- Application of the reaction mode

3. In situ installed and removed DG

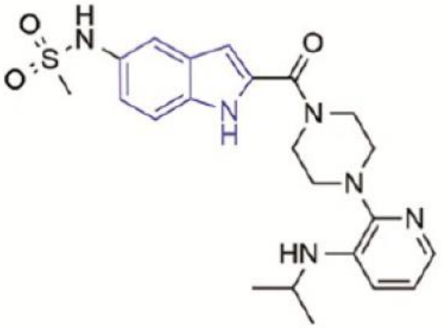
Importance of amine compounds



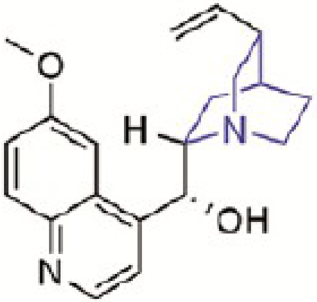
Hetacillin



Bacampicillin



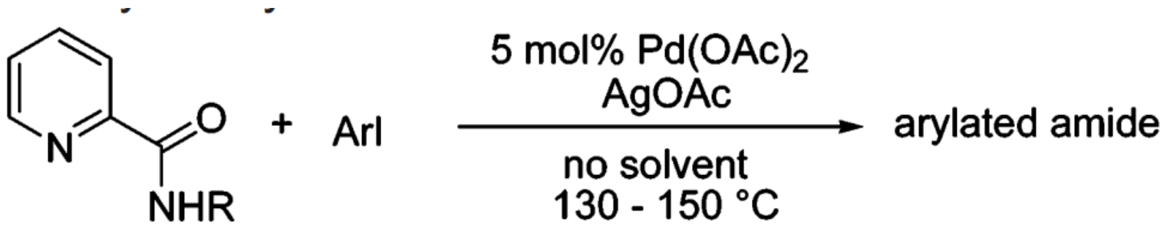
Delavirdine

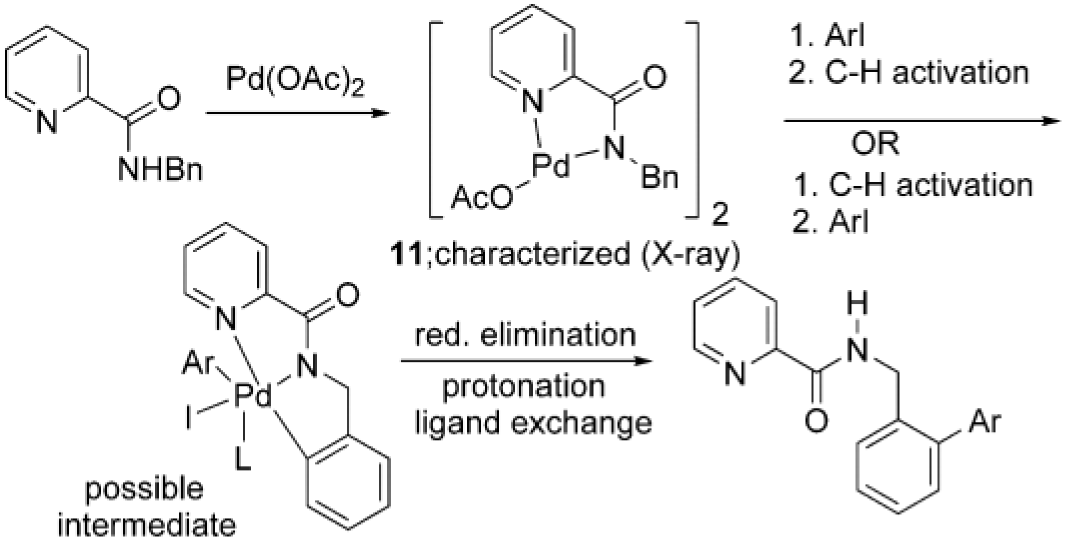


Quinine

Njardarson, J.-T. *etal* . *J. Med. Chem*. **2014**, *57*, 10257

Precedent

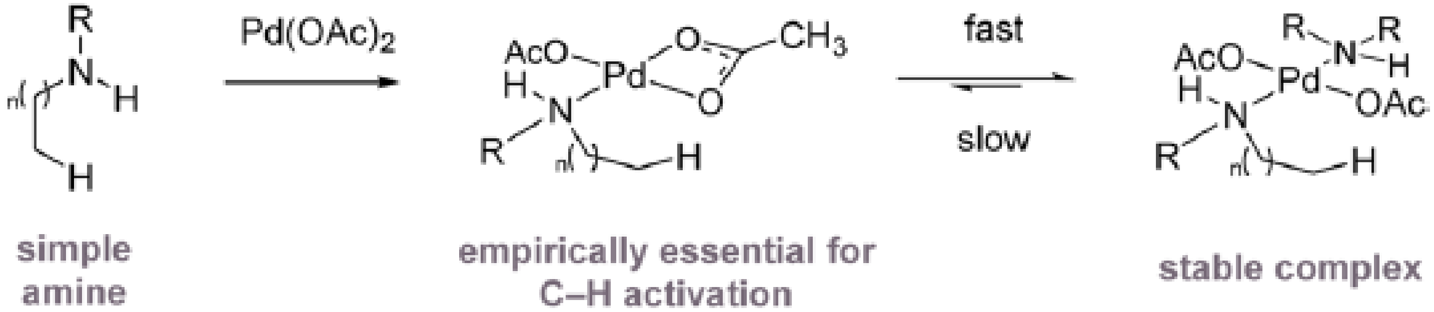




C–H activation on aliphatic amines requires their derivatization with **directing groups** .

Daugulis, O. *et al.* *J. Am. Chem. Soc*. **2005**, *127*, 13154

Problem of C-H activation of amine compounds



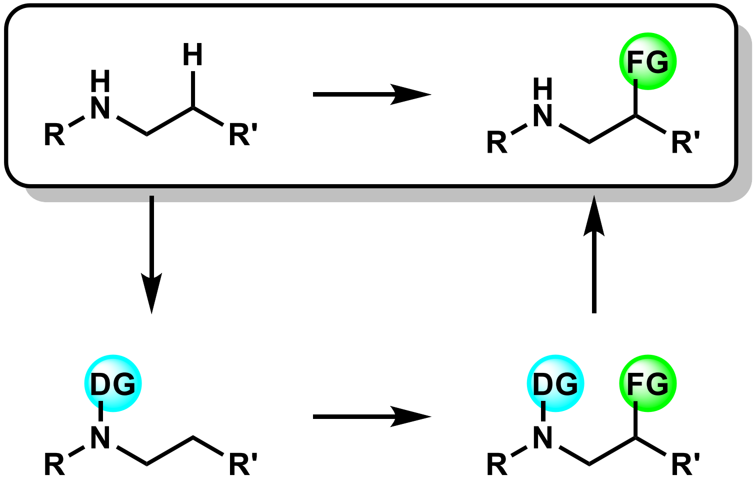
(a) Reaction of amines with palladium(II) acetate

Bis amine complex is more stable than mono amine complex.

The reaction doesn’t proceed well.

Yatsimirsky, A. - K. *et al J. Chem. Soc., Dalton Trans*. **1985**, 2629.

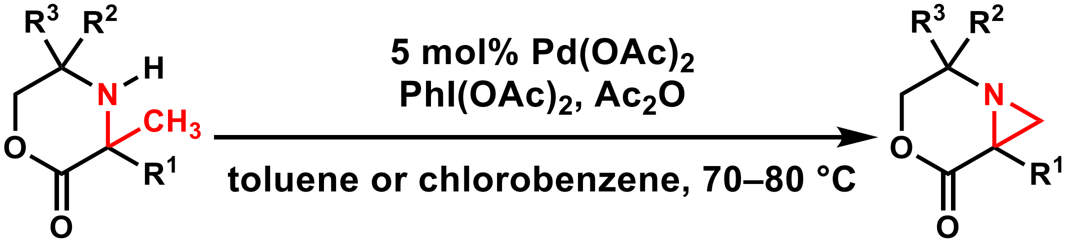
Goal of C-H activation of amine compounds



C-H functionalization of amines directly

Synthesis of amine derivatives easily

2.Free amines as DG



Prof. Matthew J. Gaunt

Recent report

1. *Nature* **2014**, *510*, 129

Palladium-catalysed C–H activation of aliphatic amines to give strained nitrogen heterocycles

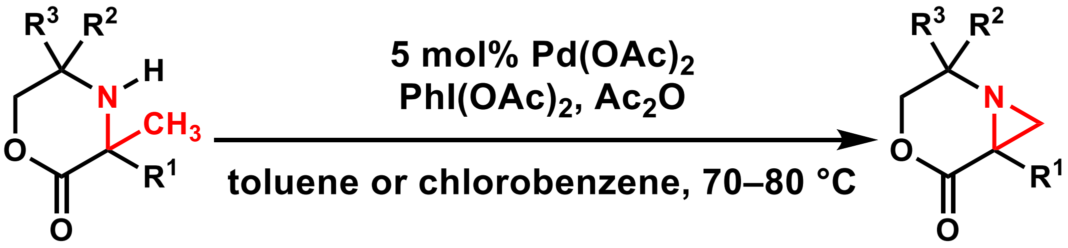
2. *J. Am. Chem. Soc*. **2015**, *137*, 10632

Mechanistic Insights into the Palladium-Catalyzed Aziridination of Aliphatic Amines by C–H Activation

3. *Angew. Chem. Int. Ed*. **2015**, *54*, 15840

Ligand-Enabled Catalytic C[BOND]H Arylation of Aliphatic Amines by a Four-Membered-Ring Cyclopalladation Pathway

Discovery of new activation mode

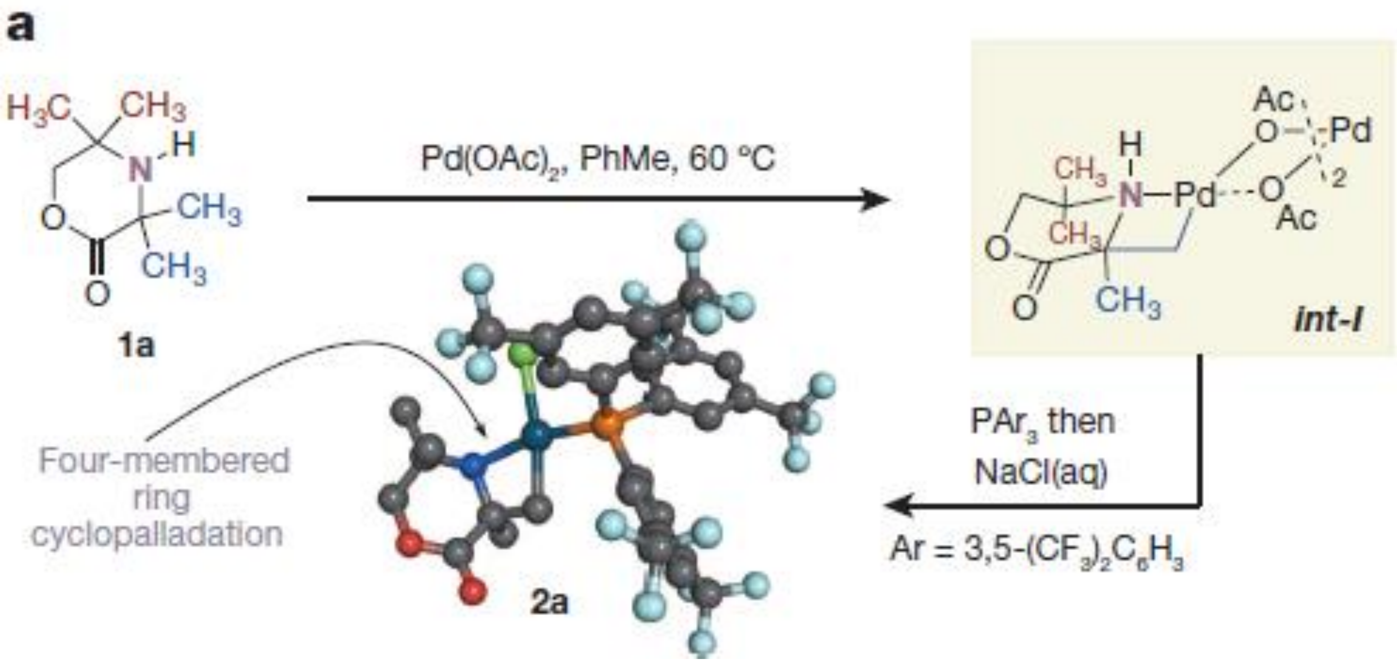


Content

They developed a new palladium-catalysed C-H bond activation mode without any DG.

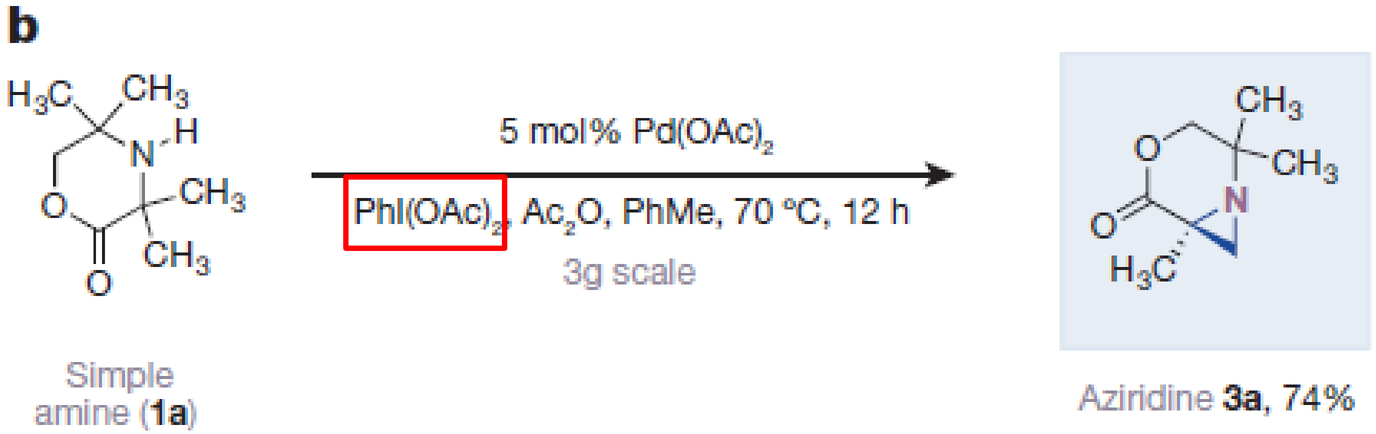
Gaunt, M. - J. *et al.* *Nature* **2014**, *510*, 129

Four-membered-ring cyclopalladation

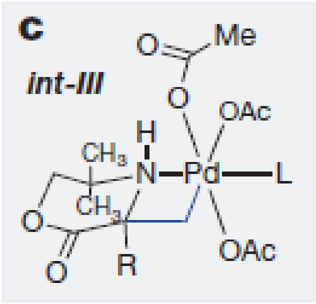


Amine-directed four-membered-ring cyclopalladation determined by single-crystal X-ray diffraction

C-H functionalization



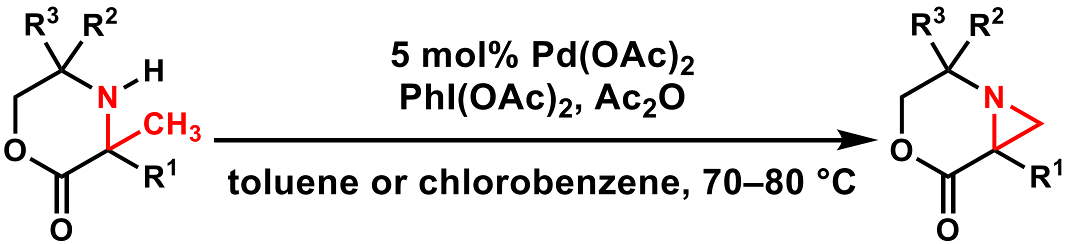
Mild chemical oxidants allow access to C–H functionalization pathways.

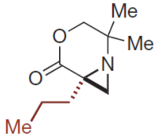


Putative Pd(IV) intermediate

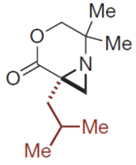
Sanford, M. -S. *et al. Nature* **2012**, *484*, 177

Scope of the reaction

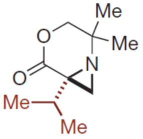




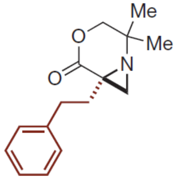
3c, 80%



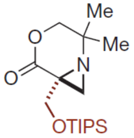
3d, 81%



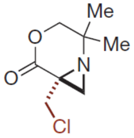
3e, 80%



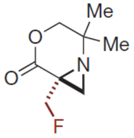
3f, 52%



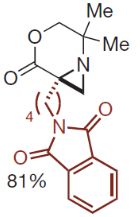
3g, 73% (3 g scale)



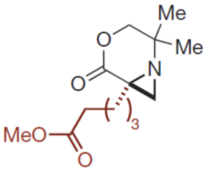
3h, 44%



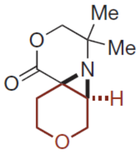
3i, 56%



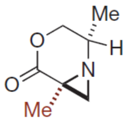
3j, 81%



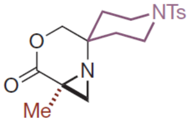
3k, 77%



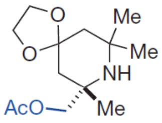
3l, 36%



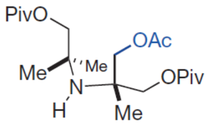
3m, 0%



3n, 73%



5, 40%



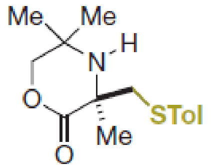
6, 60%

Uses of aziridines

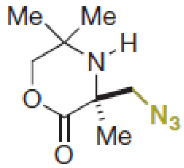
Aziridine (**3**)

Complex amine (**4**)

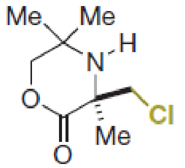
c



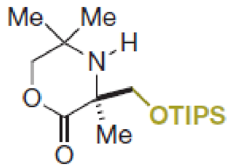
4a, 77%



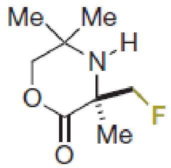
4b, 73%



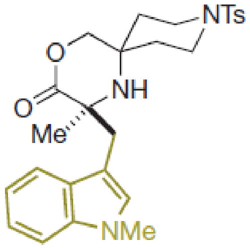
4c, 84%



4d, 67%

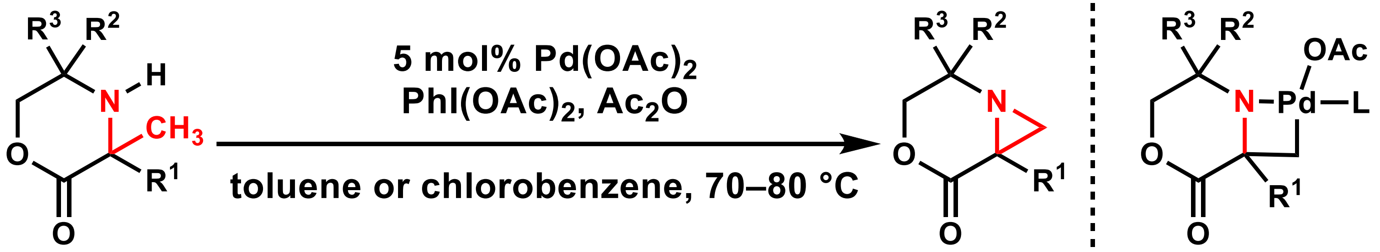


4e, 78%



4f, 74%

Mechanistic studies

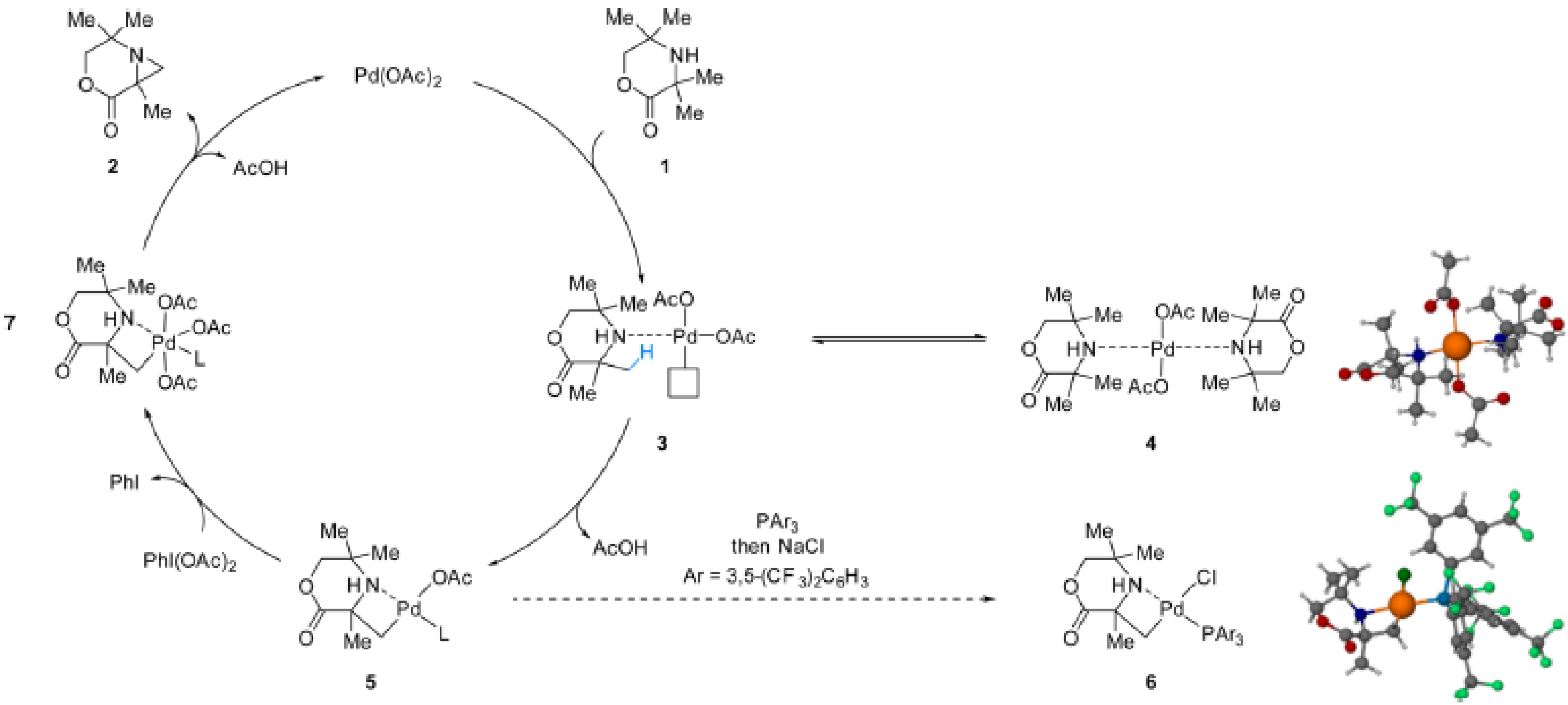


Content

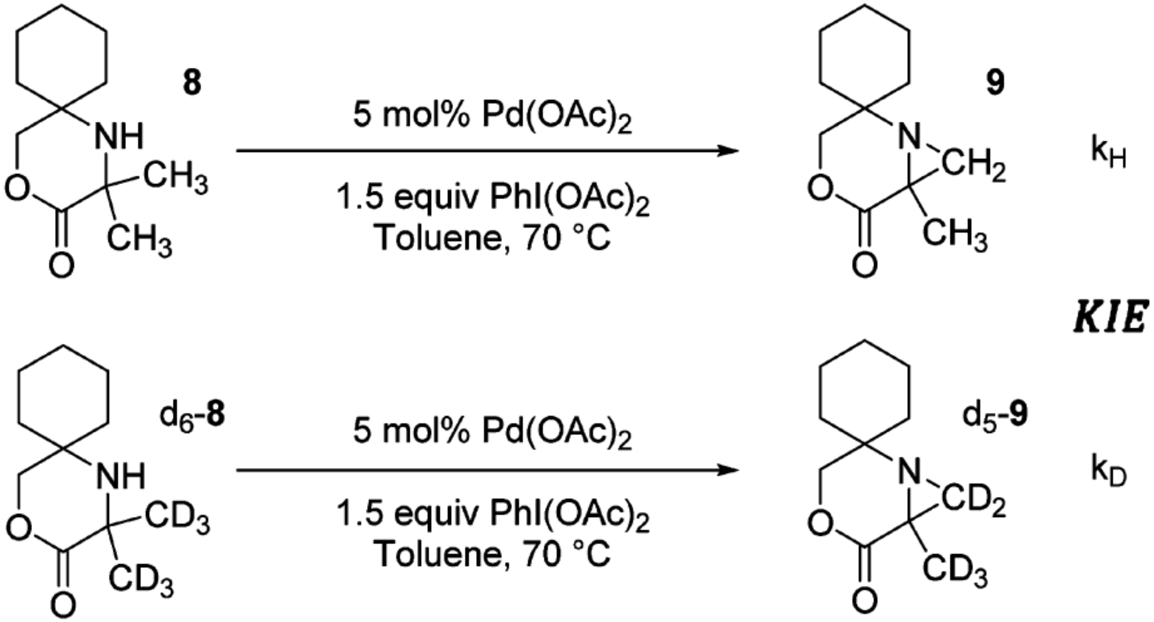
- ✔ Mechanistic studies in detail
- ✔ Device for accelerating the reaction
- ✔ Insights into the regioselectivity and the chemoselectivity

Gaunt, M. - J. *et al. J. Am. Chem. Soc.* **2015**, *137*, 10632

Proposed mechanism based on our previous study



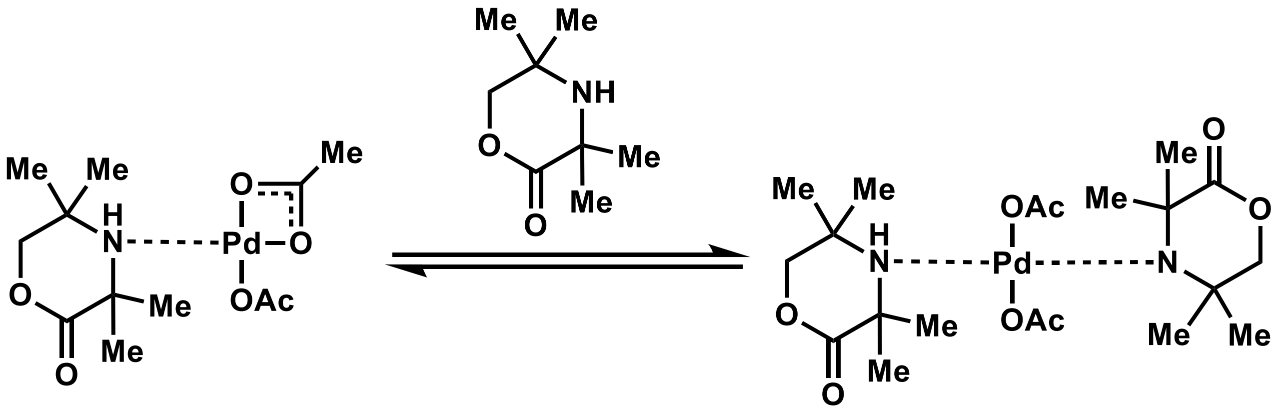
Measurement of the KIE



$$KIE = \frac{k_H}{k_D} = 3.8$$

C−H bond cleavage occurs as part of the TOLS.

Reaction profiles of two sterically different amines

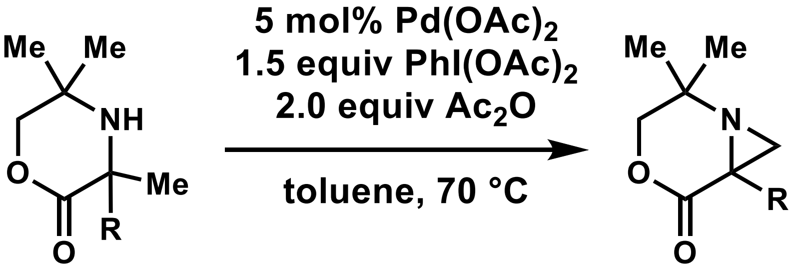


monocoordinated species
active

bis-amine complex
inactive

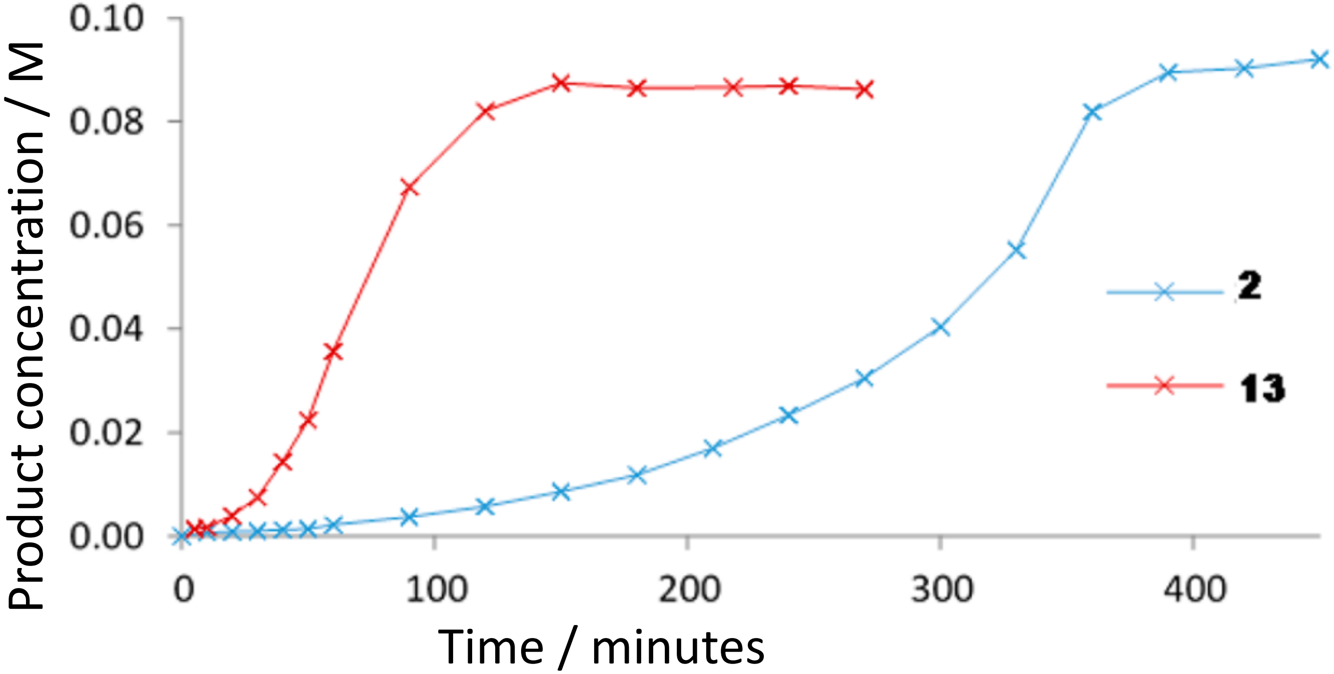
Yatsimirsky, A. - K. *et al J. Chem. Soc., Dalton Trans*. **1985**, 2629.

Reaction profiles of two sterically different amines

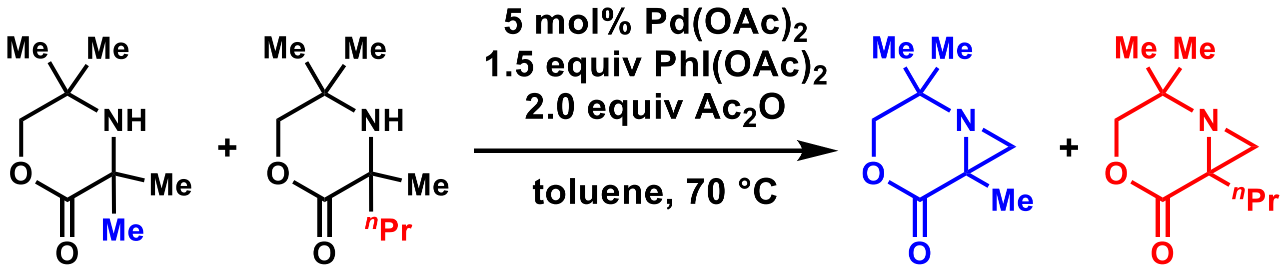


R = Me 2
R = ^{n}Pr 13

R = Me 2
R = ^{n}Pr 13



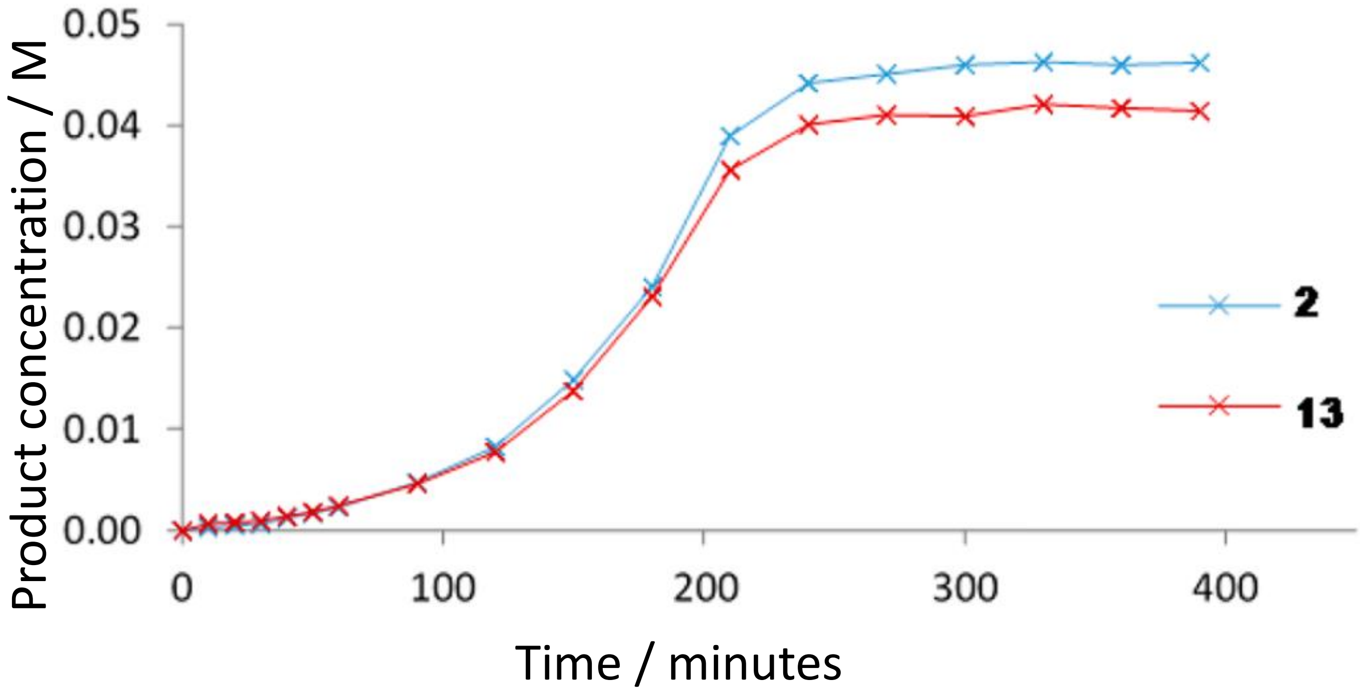
Alteration of the mono-/bis-amine equilibrium



5 mol% $Pd(OAc)_2$
1.5 equiv $PhI(OAc)_2$
2.0 equiv Ac_2O

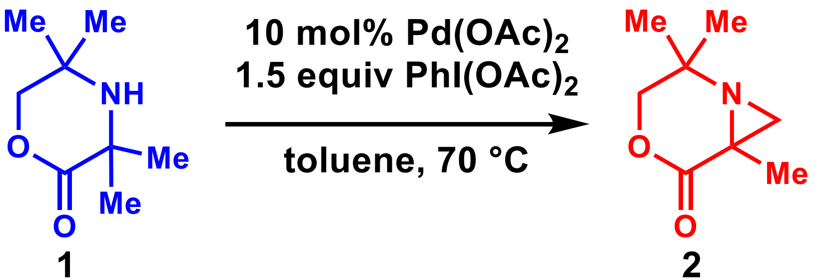
toluene, 70 °C

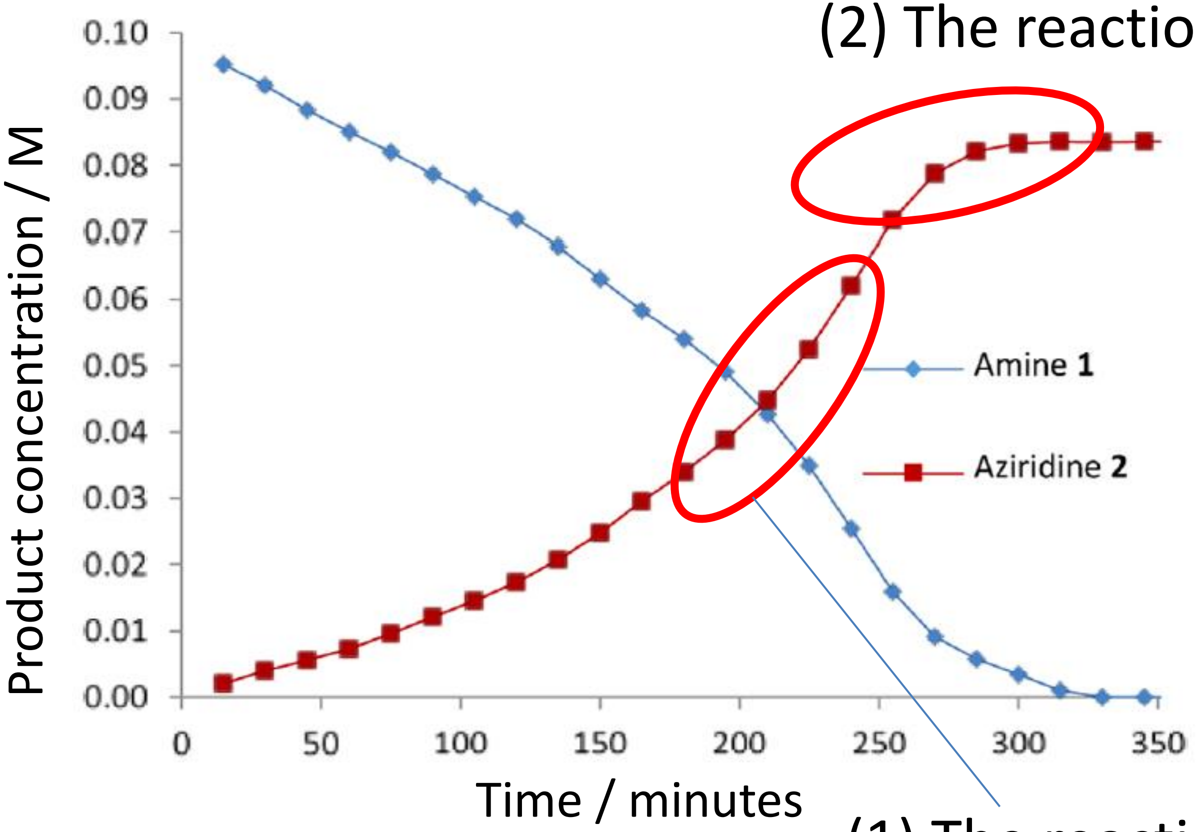
0.5 equiv 0.5 equiv **2** **13**



Both species reacted at the same rate.

Kinetic Studies





(2) The reaction rate decreases.

(1) The reaction rate increases.

(1) Why does the reaction rate increase?

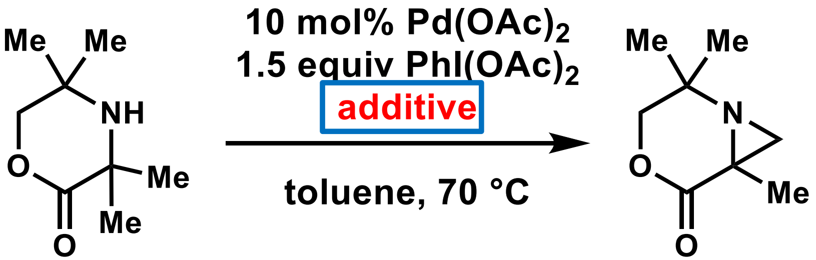
Standard reaction

$$\begin{array}{ccccccccccc} \mathbf{1} & + & \mathrm{PhI(OAc)_2} & \xrightarrow{\begin{array}{c}\text{0.1 equiv}\\ \mathrm{Pd(OAc)_2}\end{array}} & \mathbf{2} & + & \mathrm{PhI(OAc)_2} & + & \mathrm{PhI} & + & \mathrm{AcOH} \\ \text{1.0 equiv} & & \text{1.5 equiv} & & \text{1.0 equiv} & & \text{0.5 equiv} & & \text{1.0 equiv} & & \text{2.0 equiv} \end{array}$$

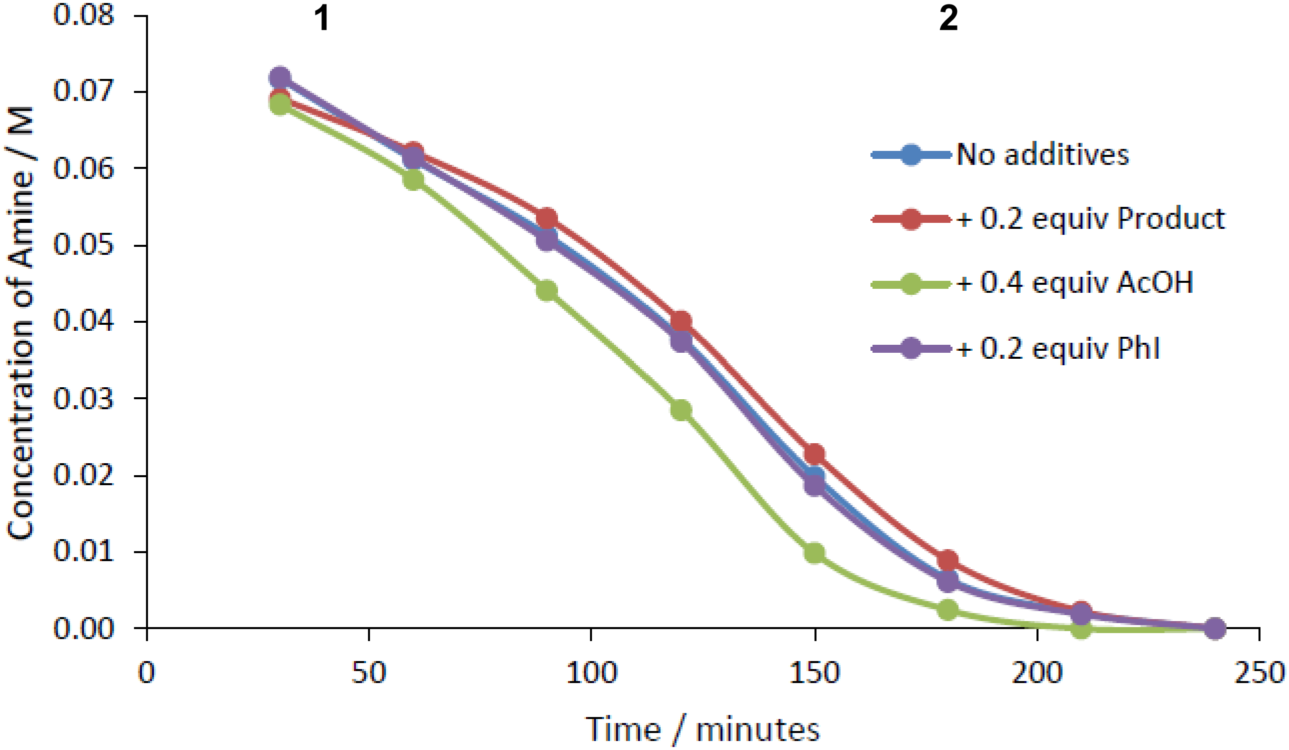
Hypothesis

(by-)product catalyzes the reaction?
→ Which (by-)product is important for the reaction?

Which (by-)product is important for the reaction?

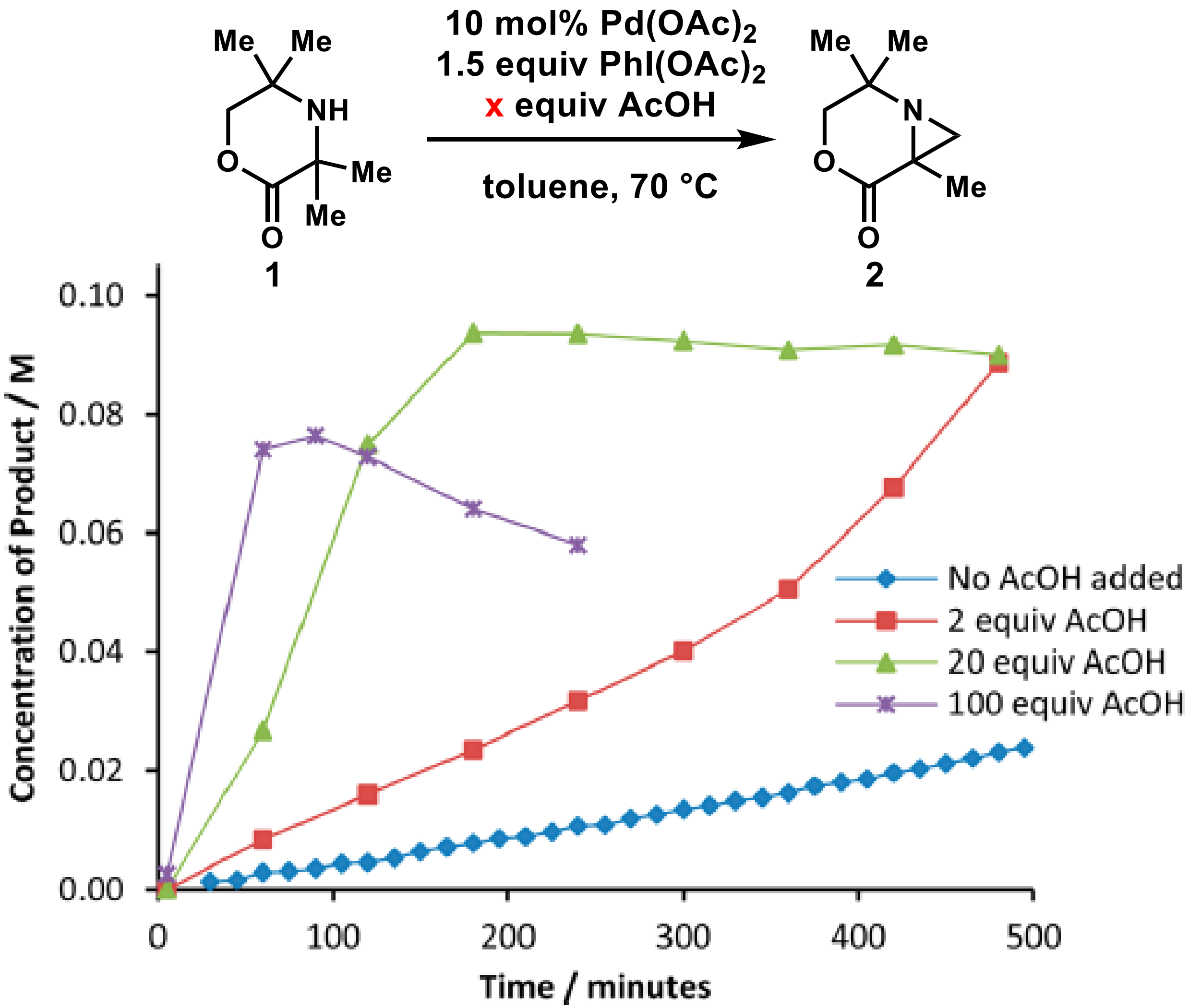


1 2



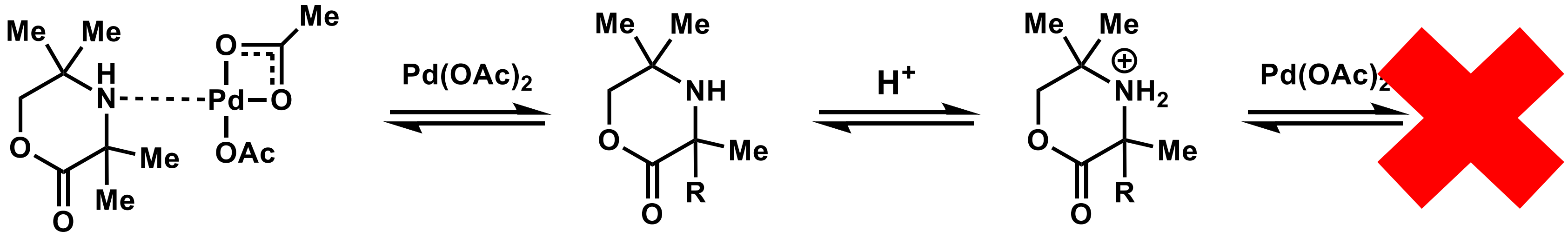
When AcOH was added to the reaction, a marginal increase was observed

Concentration of AcOH



The optimal amount of AcOH loading was found to be 20 equiv.

Putative role of acid

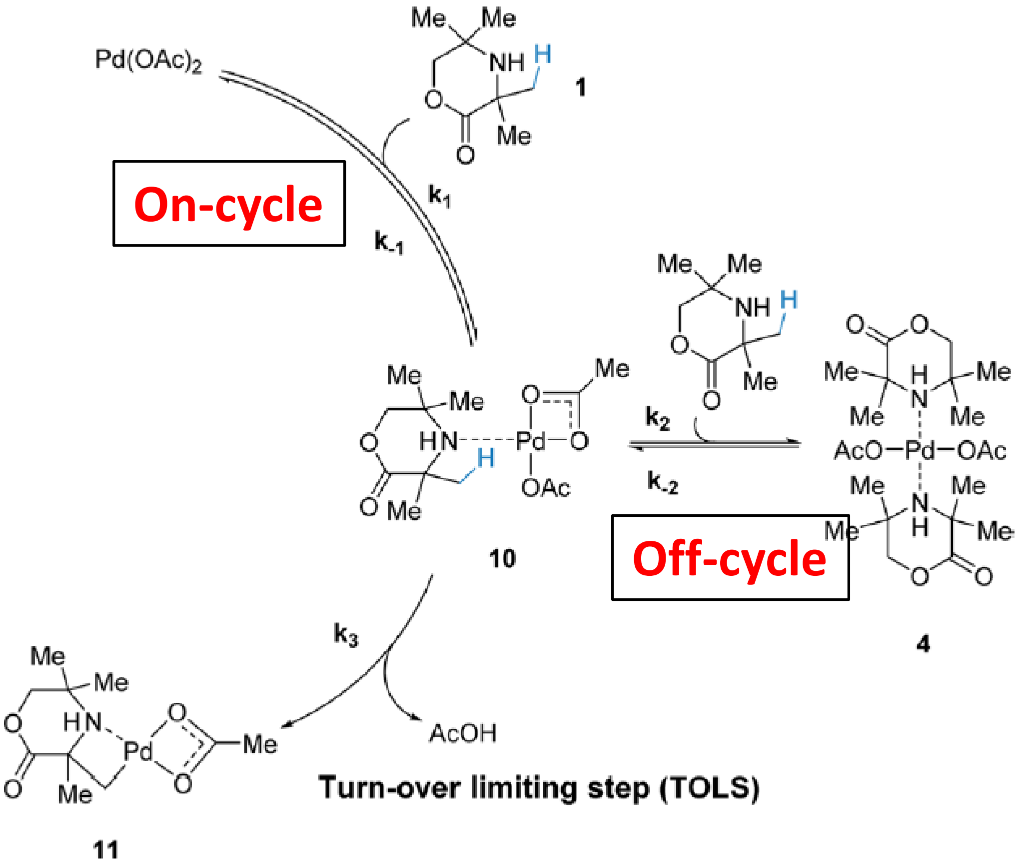


✔The presence of acid set up an equilibrium between the protonated and free based amine.

✔Other acids were also found to give rate acceleration.

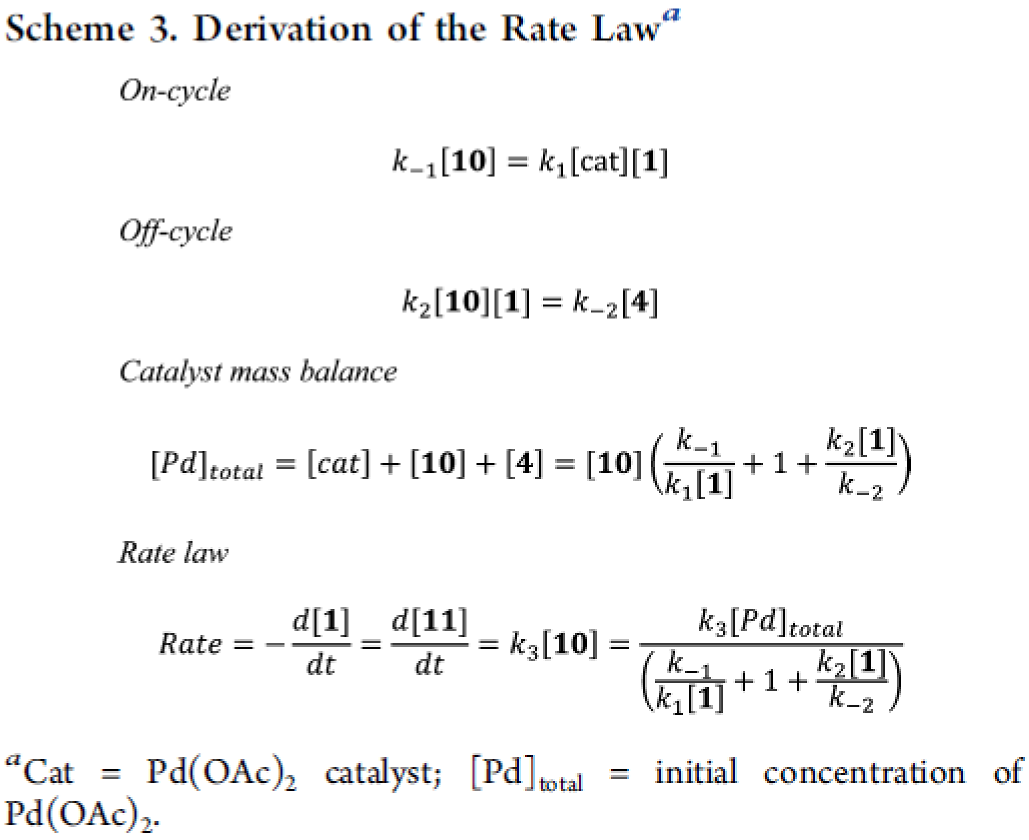
Shi, Z. *et al. J. Am. Chem. Soc*. **2007**, *129*, 7666

(2) Why does the reaction rate decrease at the end?



A mathematical description allow the qualitative insights.

Initial rate of the reaction



Scheme 3. Derivation of the Rate Law[a]

On-cycle

$$k_{-1}[\mathbf{10}] = k_1[\text{cat}][\mathbf{1}]$$

Off-cycle

$$k_2[\mathbf{10}][\mathbf{1}] = k_{-2}[\mathbf{4}]$$

Catalyst mass balance

$$[Pd]_{total} = [cat] + [\mathbf{10}] + [\mathbf{4}] = [\mathbf{10}]\left(\frac{k_{-1}}{k_1[\mathbf{1}]} + 1 + \frac{k_2[\mathbf{1}]}{k_{-2}}\right)$$

Rate law

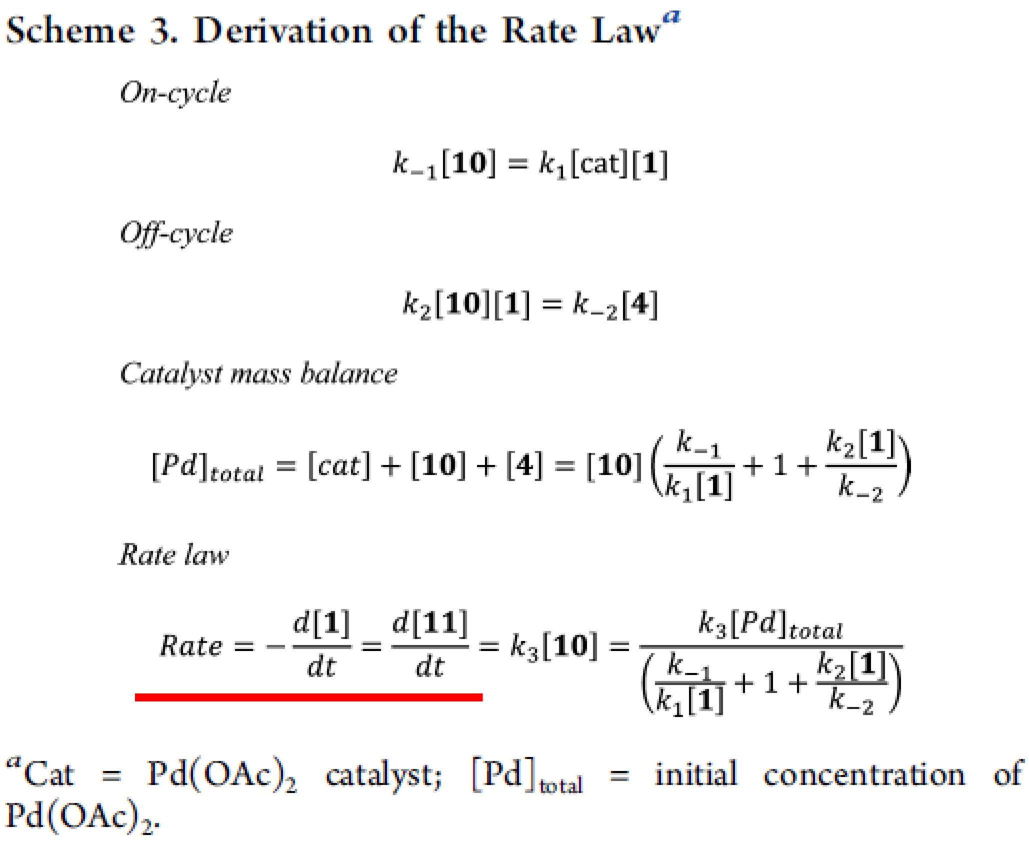
$$Rate = -\frac{d[\mathbf{1}]}{dt} = \frac{d[\mathbf{11}]}{dt} = k_3[\mathbf{10}] = \frac{k_3[Pd]_{total}}{\left(\frac{k_{-1}}{k_1[\mathbf{1}]} + 1 + \frac{k_2[\mathbf{1}]}{k_{-2}}\right)}$$

[a] Cat = $Pd(OAc)_2$ catalyst; $[Pd]_{total}$ = initial concentration of $Pd(OAc)_2$.

$$\boxed{\text{Initial rate} \approx \frac{k_{-2}k_3}{k_2}\frac{[\text{Pd}]_{\text{total}}}{[\mathbf{1}]}}$$

Initial rate can be considered a constant.

Change of the reaction rate



Scheme 3. Derivation of the Rate Law[a]

On-cycle

$$k_{-1}[\mathbf{10}] = k_1[\text{cat}][\mathbf{1}]$$

Off-cycle

$$k_2[\mathbf{10}][\mathbf{1}] = k_{-2}[\mathbf{4}]$$

Catalyst mass balance

$$[Pd]_{total} = [cat] + [\mathbf{10}] + [\mathbf{4}] = [\mathbf{10}]\left(\frac{k_{-1}}{k_1[\mathbf{1}]} + 1 + \frac{k_2[\mathbf{1}]}{k_{-2}}\right)$$

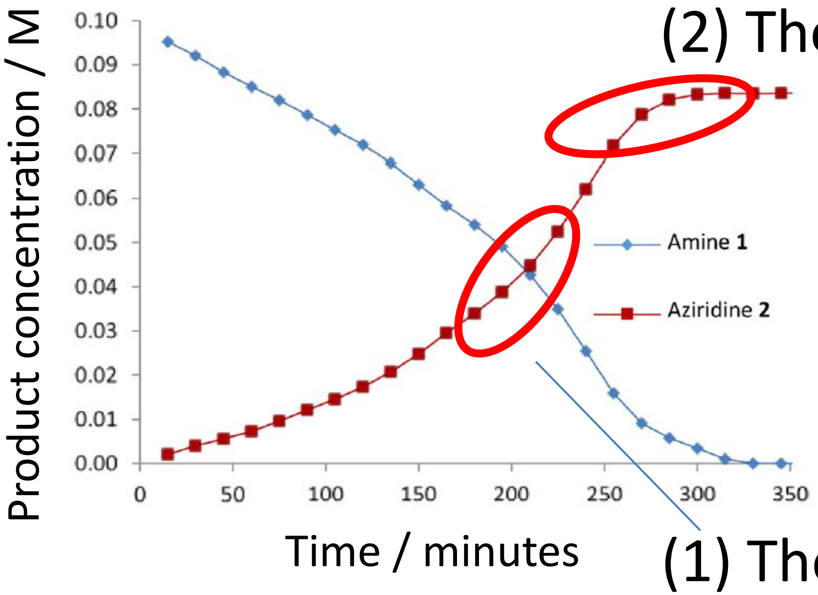
Rate law

$$\underline{Rate = -\frac{d[\mathbf{1}]}{dt} = \frac{d[\mathbf{11}]}{dt}} = k_3[\mathbf{10}] = \frac{k_3[Pd]_{total}}{\left(\frac{k_{-1}}{k_1[\mathbf{1}]} + 1 + \frac{k_2[\mathbf{1}]}{k_{-2}}\right)}$$

[a] Cat = $Pd(OAc)_2$ catalyst; $[Pd]_{total}$ = initial concentration of $Pd(OAc)_2$.

Reaction rate changes to first-order with respect to substrate at the end.

Interpretation of Kinetic Studies



(2) The reaction rate decreases.

(1) The reaction rate increases.

(1) Why does the reaction rate increase?

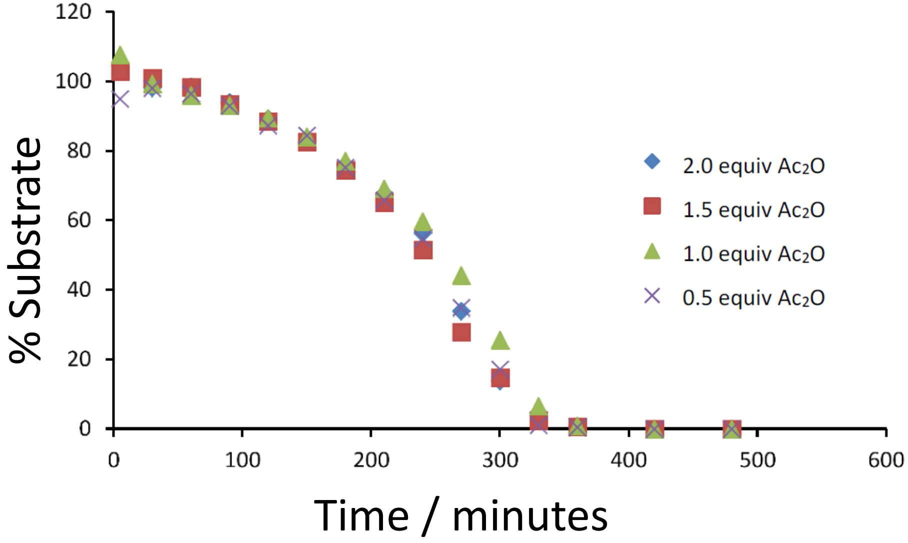
> Less palladium is sequestered in unproductive off-cycle bis-amine complex because of AcOH.

(2) Why does the reaction rate decrease?

>Reaction rate changes as the reaction proceeds.

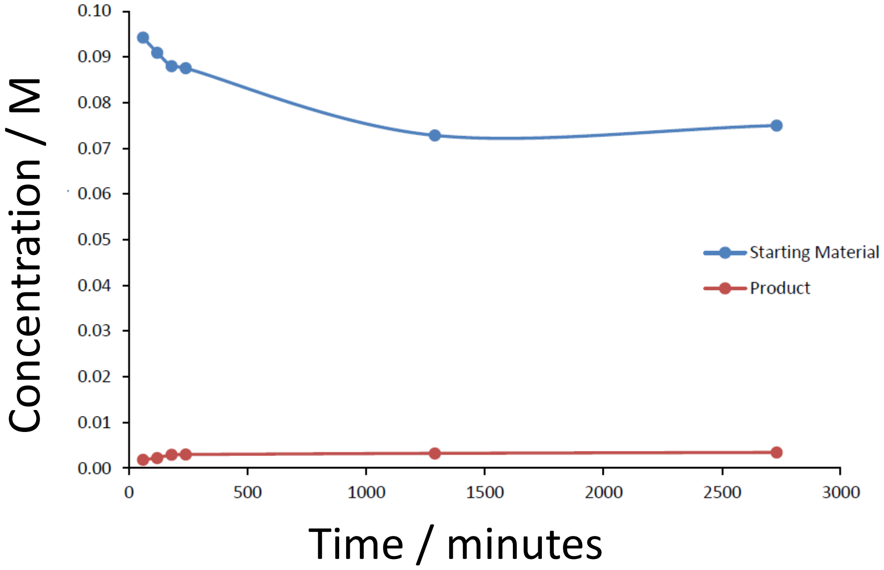
Role of Acetic Anhydride

Effect of Acetic Anhydride



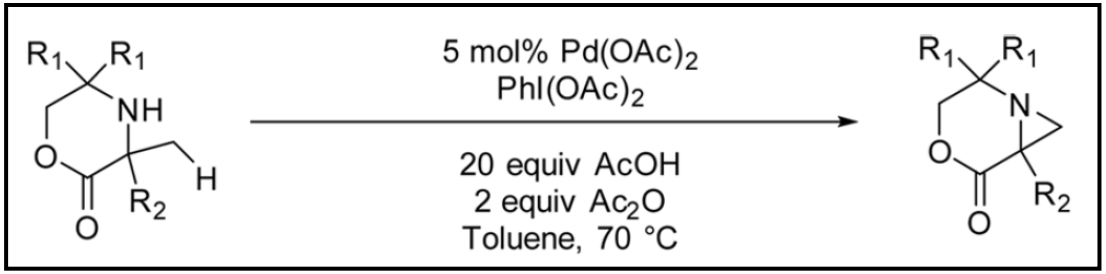
✔ Changing the concentration of acetic anhydride had little effect.

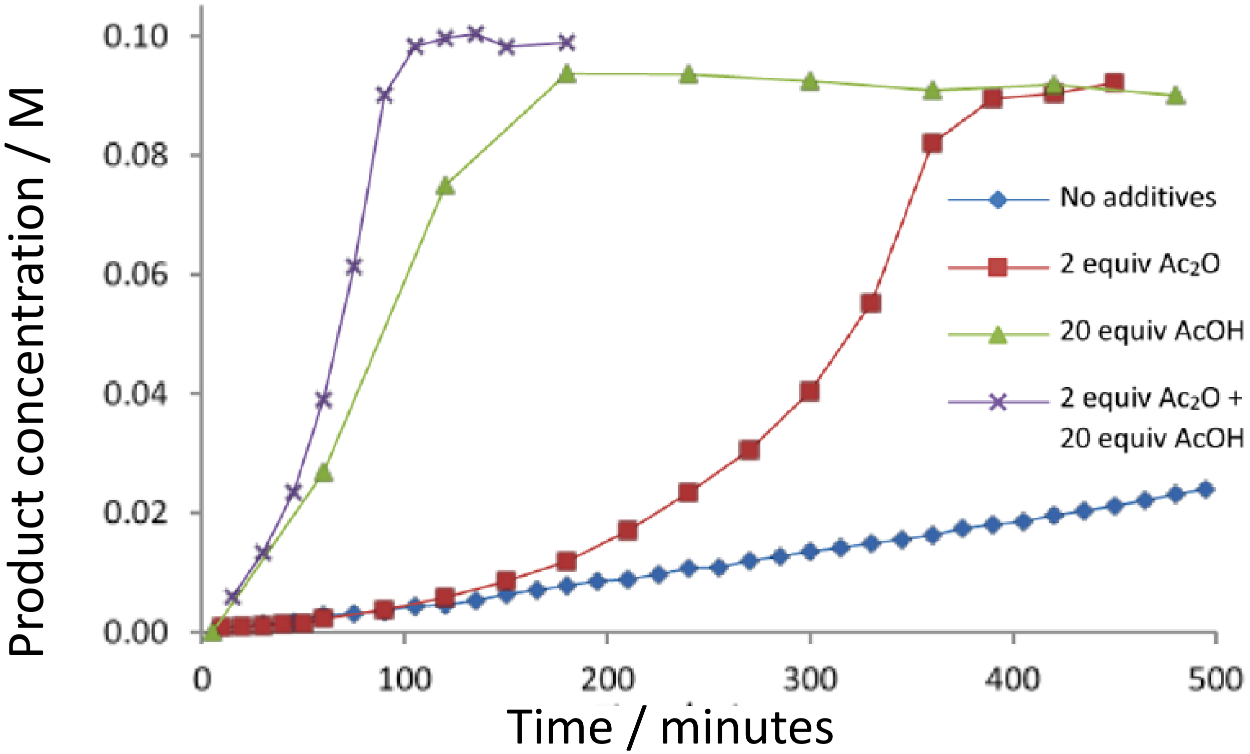
Effect of water



✔ Water was found to be detrimental to the reaction.

Optimized conditions





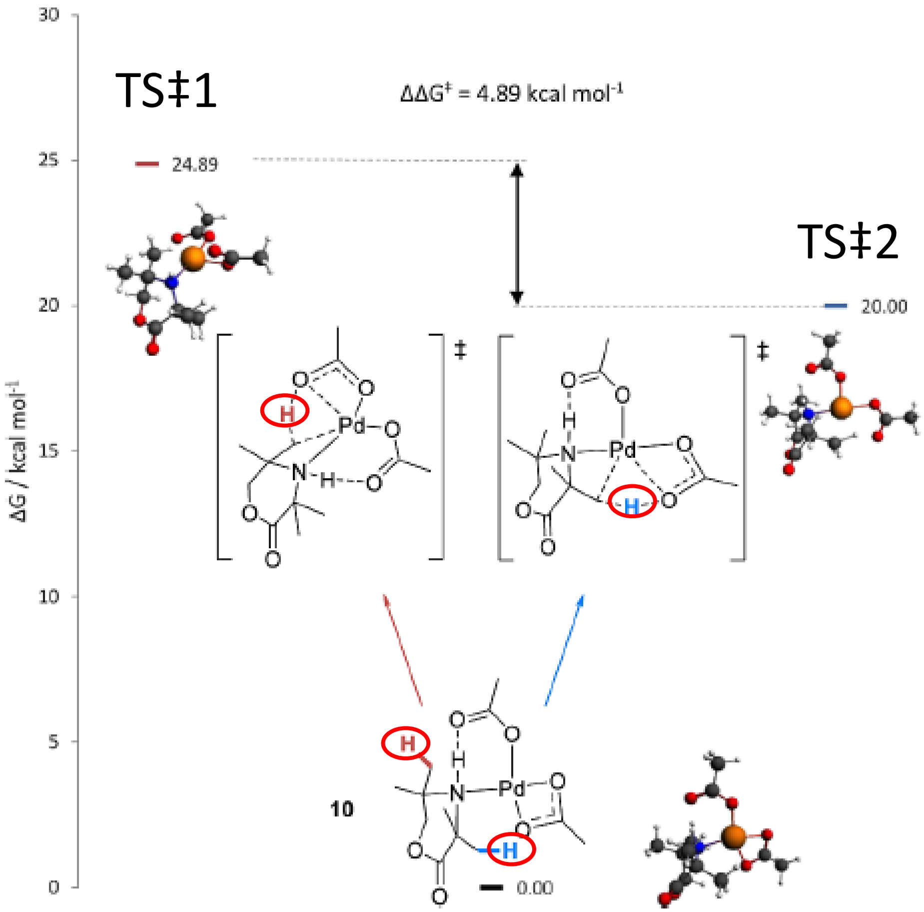
✔ Addition of 20 equiv of acetic acid and 2 equiv of acetic anhydride led to an improved reaction.

Explanation of the regioselectivity and chemoselectivity

DFT studies insights into

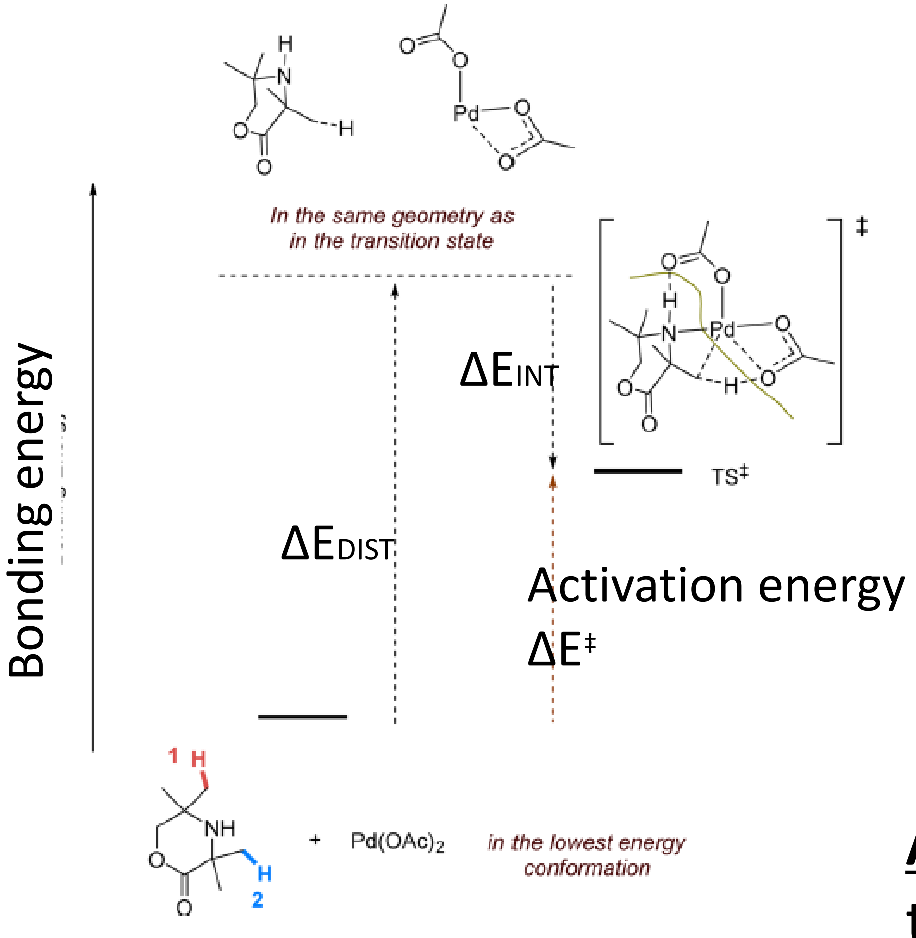
1. the regioselectivity of the C−H activation
2. the chemoselectivity of the C−N reductive elimination.

The regioselectivity of the C–H activation



TS‡2 is more stable than TS‡1.

Important factor for the regioselectivity



Bonding energy

ΔE$_{\text{INT}}$

ΔE$_{\text{DIST}}$

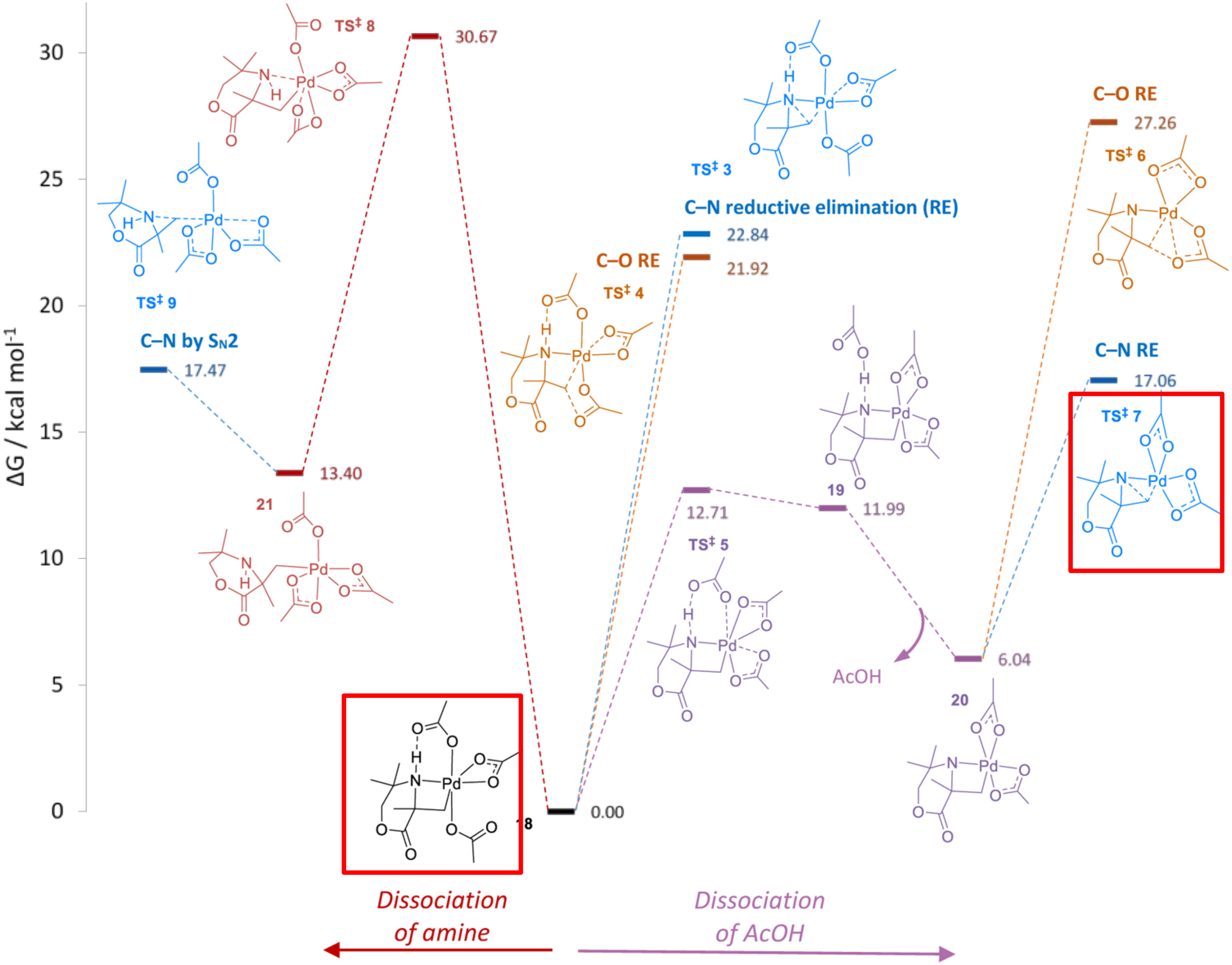
Activation energy
ΔE‡

Distortion−Interaction Analysis

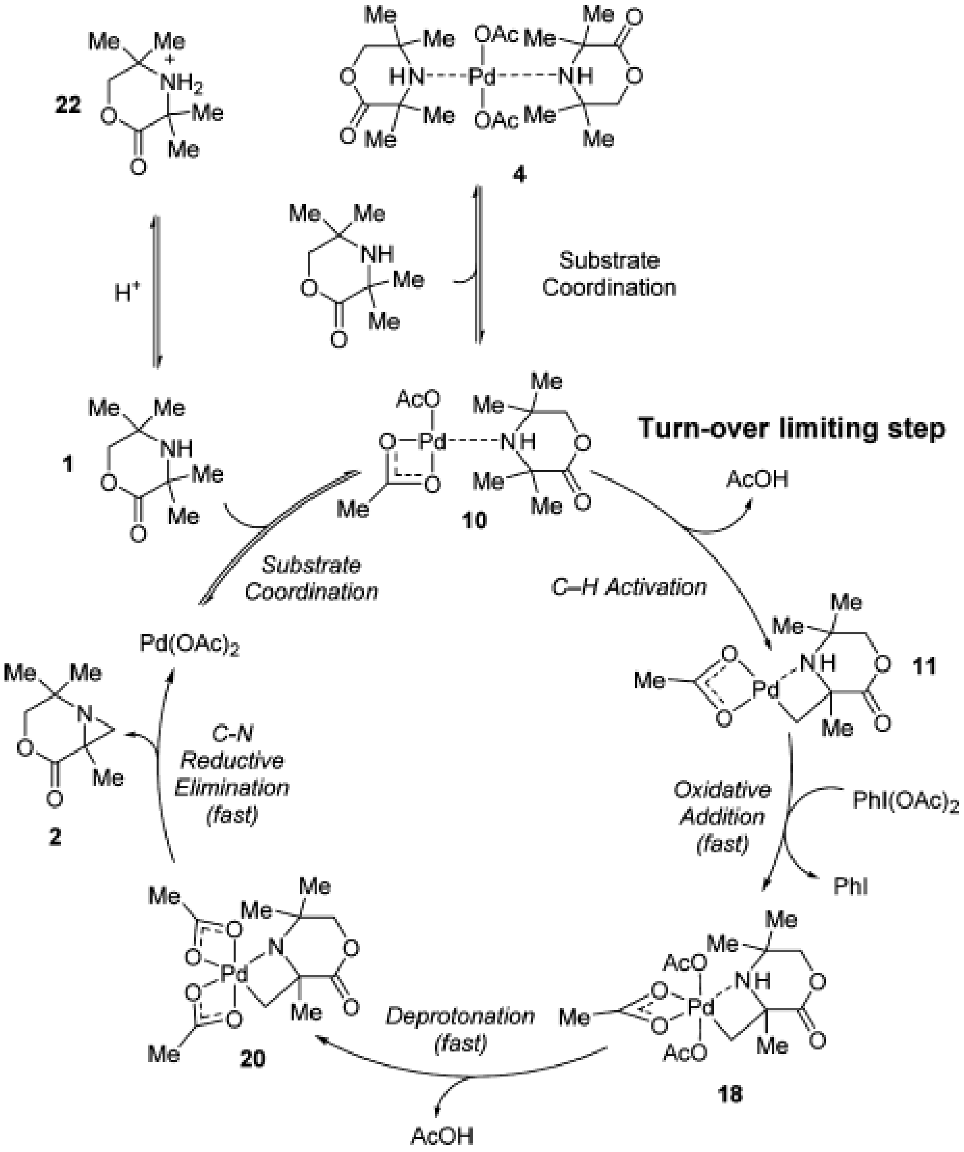
	$\Delta E^{\ddagger}$	ΔE_{DIST}	ΔE_{INT}
TS‡ 1	2.70	85.12	−82.42
TS‡ 2	0.08	87.97	−87.89

Acidity of the C−H bonds closest to the carbonyl lowers the energy required to cleave the C−H bond

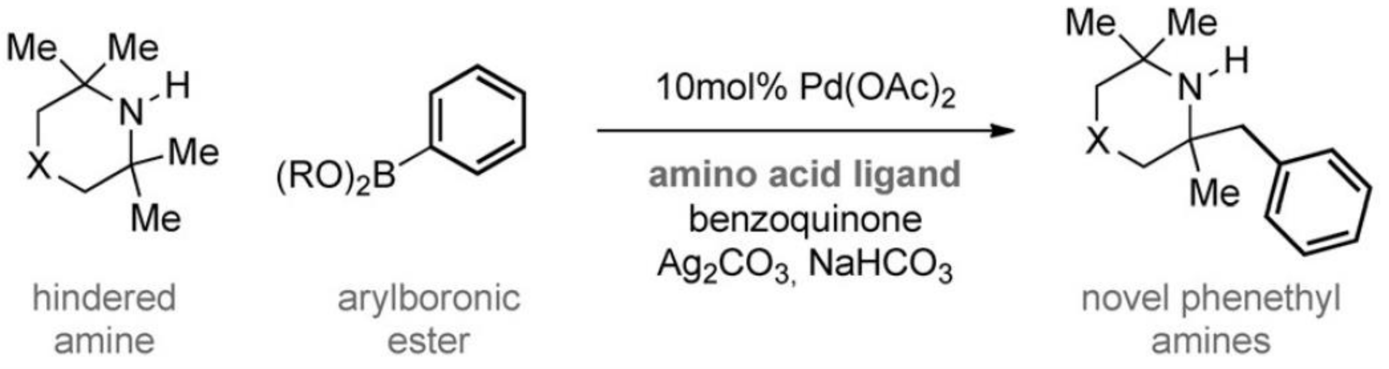
The chemoselectivity of the C–N reductive elimination



Final Catalytic Cycle



Application of the reaction mode

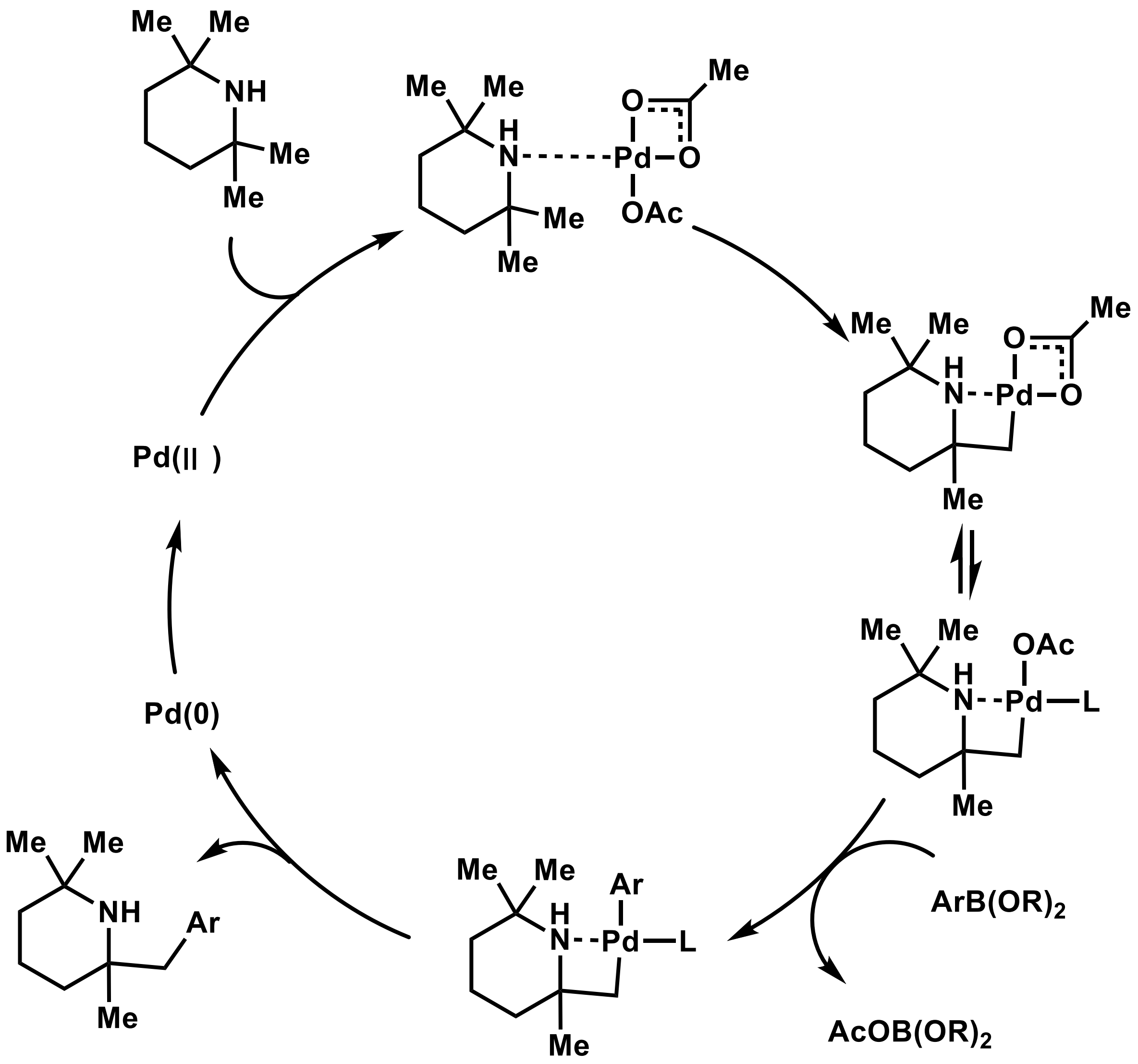


Content

✔ They expand the toolbox of direct functionalization reactions to an arylation process by the reaction mode.

Gaunt, M. - J. *et al. Angew. Chem. Int. Ed*. **2015**, *54*, 15840

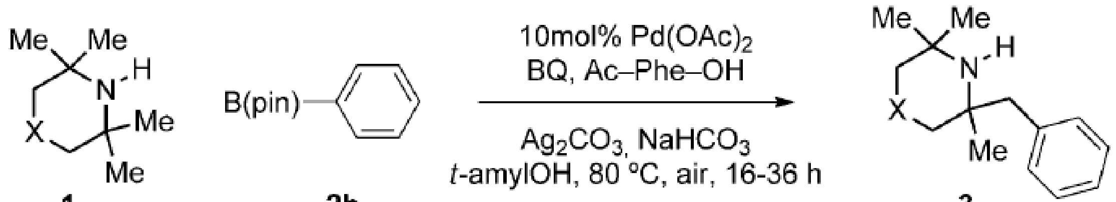
Proposed reaction mechanism



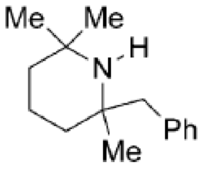
Yu, J. –Q. *et al. J. Am. Chem. Soc.* **2011**, *133*, 18183

Gaunt, M. - J. *et al. Angew. Chem. Int. Ed*. **2015**, *54*, 15840

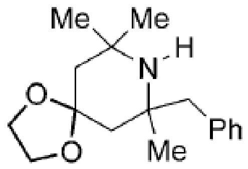
Scope of the reaction



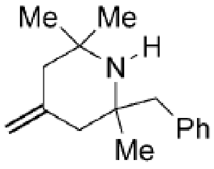
1 **2b** **3**



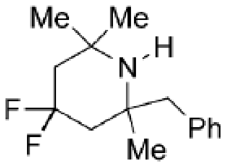
3a, 61% (11%)



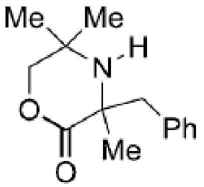
3b, 63% (8%)
gram scale



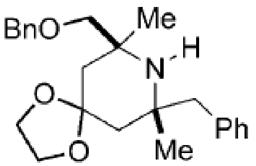
3c, 68%



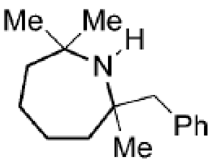
3d, 50%



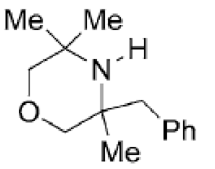
3e, trace



3f, 42%[b]

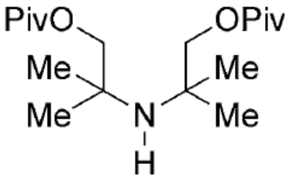


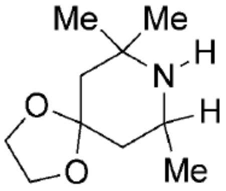
3g, 54%



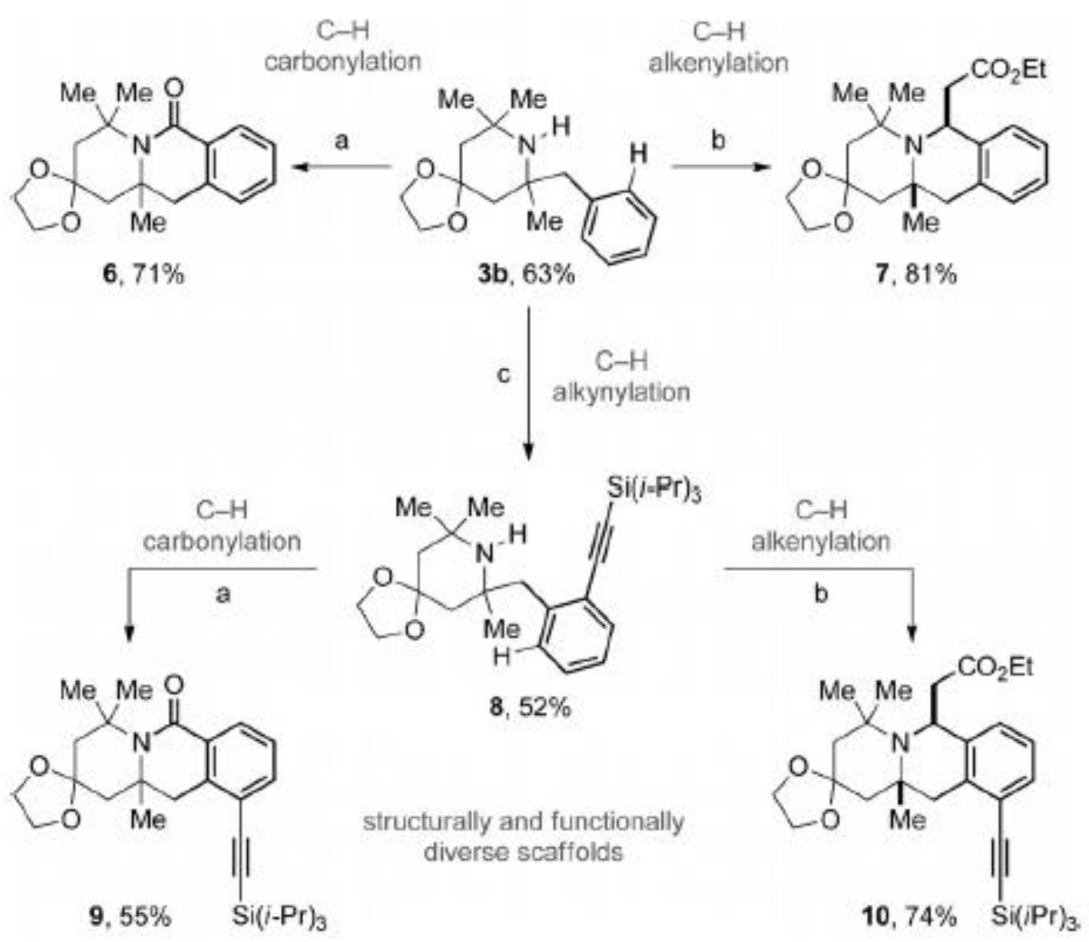
3h, 45% (8%)

unreactive under
these conditions





Further conversion of the products



Gaunt, M. -J. *et al. Chem. Sci*. **2011**, *2*, 312
Zhao, S. -Y. *et al. Chem. Sci*. **2014**, *5*, 4962
Chen, G. *et al. Org. Lett*. **2012**, *14*, 2948

Summary of 2nd part

Summary of the presentation

✔ They developed a new palladium-catalysed C-H bond activation mode.

✔ They reported the detailed mechanistic studies.

✔ The reaction mode can be used for further application.

Limitation

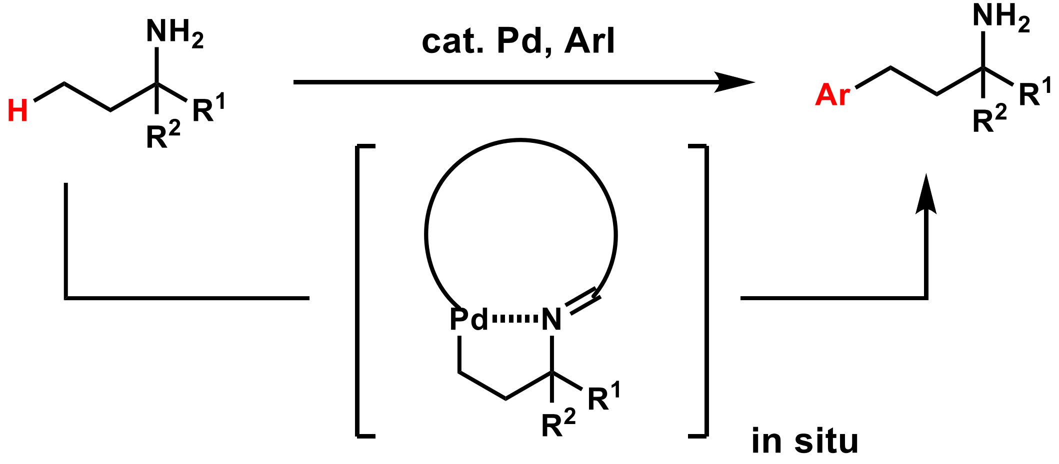
Substrate scope

Outlook

These insights lead to the rational design of related C–H functionalization reactions.

3. In situ installed and removed DG

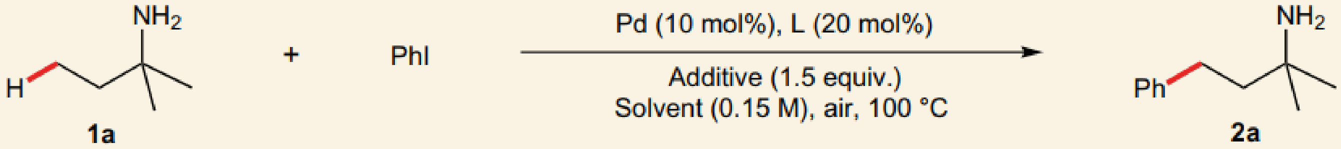
Concept

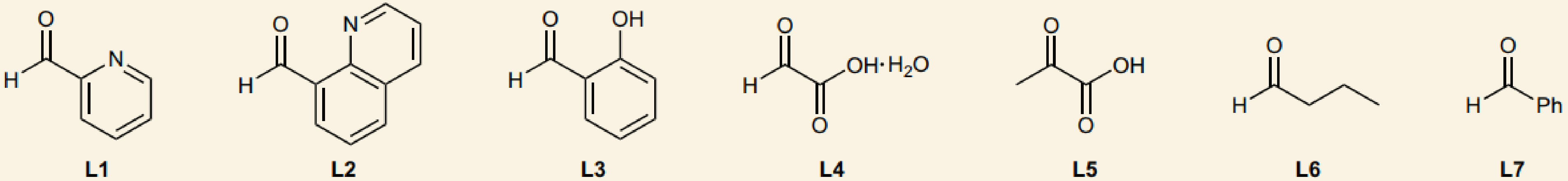


Recent report

1. Ge, H. –B. *et al. Nat. Chem.* **2017**, *9*, 26
2. Dong, G. *et al. Angew. Chem. Int. Ed*. **2016**, *55*, 9084
3. Murakami, M. *et al. Angew. Chem. Int. Ed*. **2017**, *56*, 1073

Additive screening



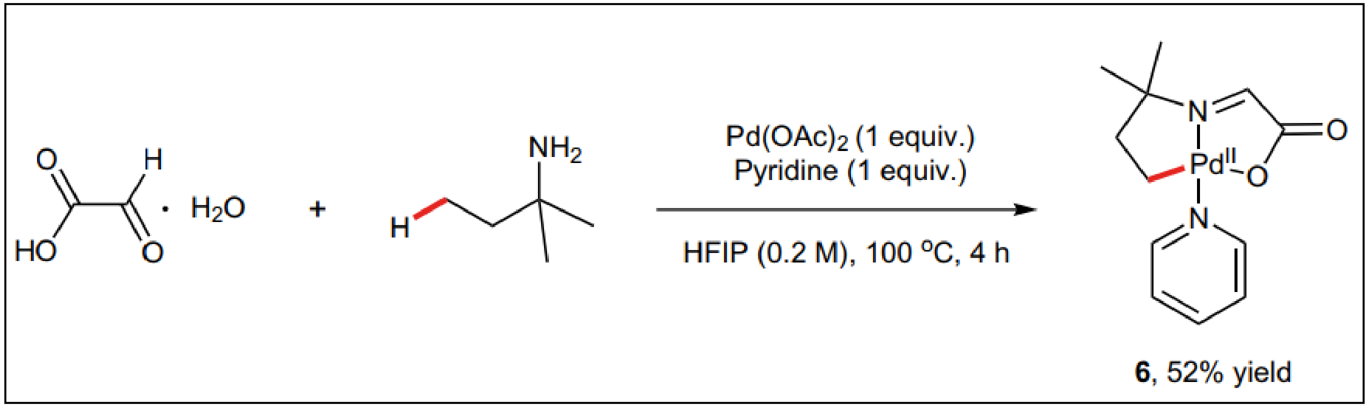


Entry	Pd source	Ligand	Additive	Solvent	Yield (%)
1	$Pd(OAc)_2$	L1	AgTFA	HOAc	Trace
2	$Pd(OAc)_2$	L2	AgTFA	HOAc	Trace
3	$Pd(OAc)_2$	L3	AgTFA	HOAc	5
4	$Pd(OAc)_2$	L4	AgTFA	HOAc	72
5	$Pd(OAc)_2$	L5	AgTFA	HOAc	12
6	$Pd(OAc)_2$	L6	AgTFA	HOAc	Trace
7	$Pd(OAc)_2$	L7	AgTFA	HOAc	Trace
8	$Pd(OAc)_2$	-	AgTFA	HOAc	10

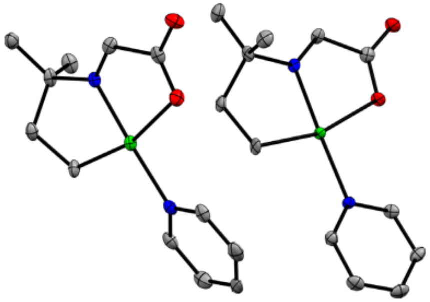
Aldehyde and carboxylic acid are important moiety.

Ge, H. –B. *et al. Nat. Chem*. **2017**, *9*, 26

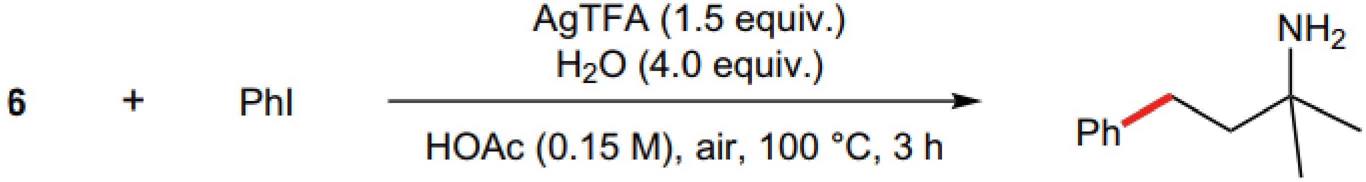
Proposed intermediate



6, 52% yield

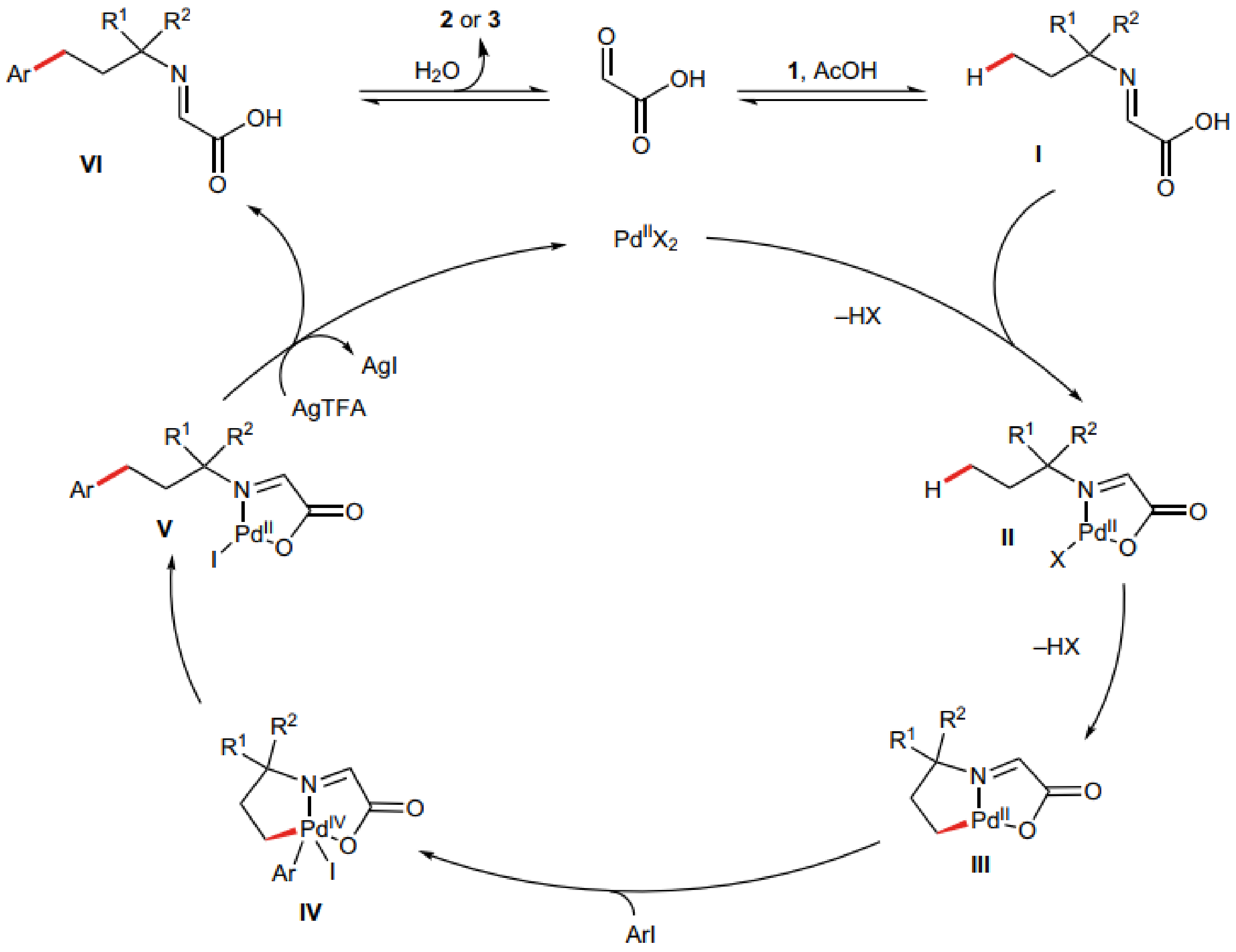


X-ray structure of **6**

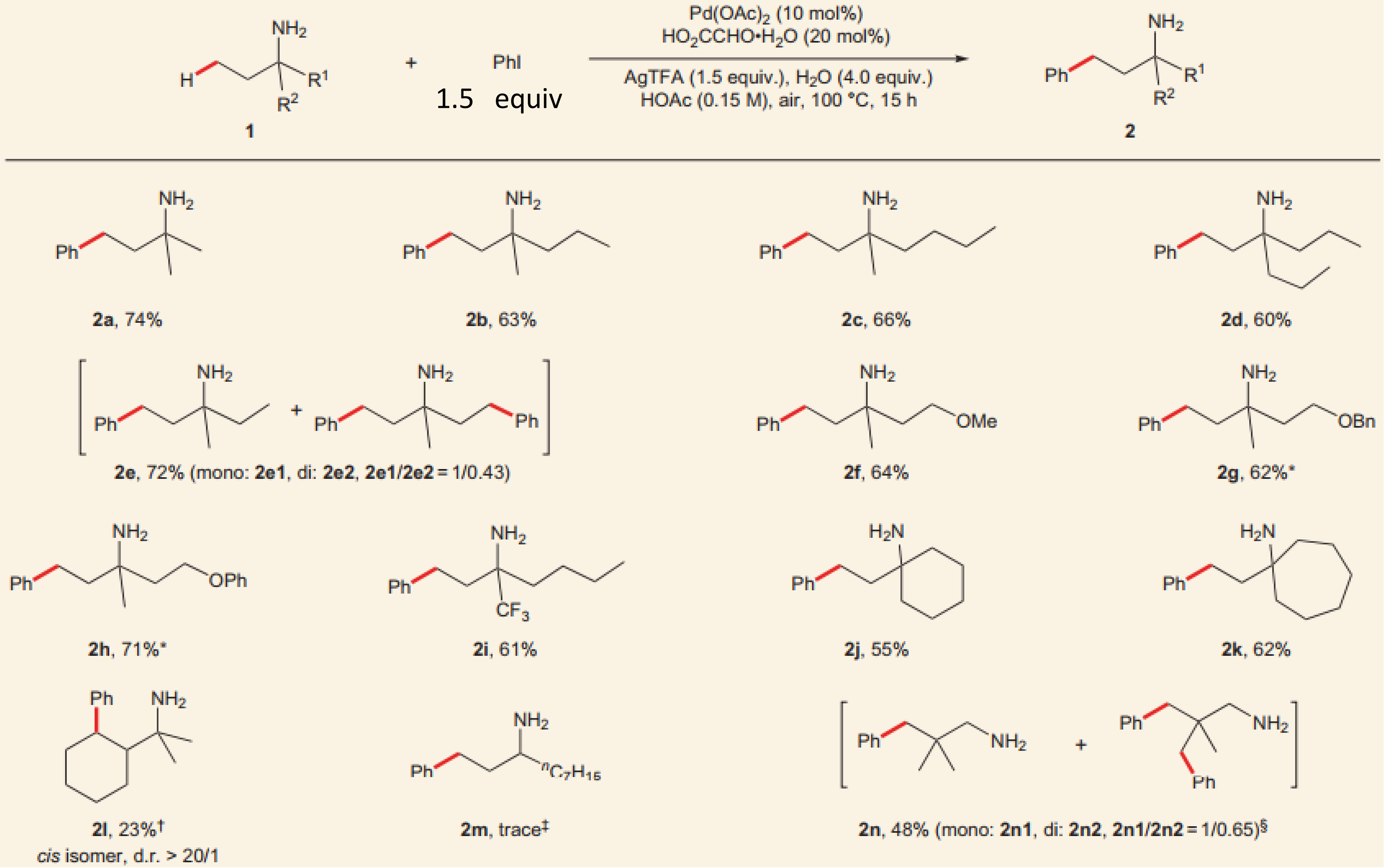


2a, 72% yield

Proposed mechanism



Substrate scope



Steric hindrance and Thorpe-Ingold effect are important.

Summary

Summary of 3rd part

✔ They developed aC-H activation of primary amine with additive as transient directing group.

Limitation

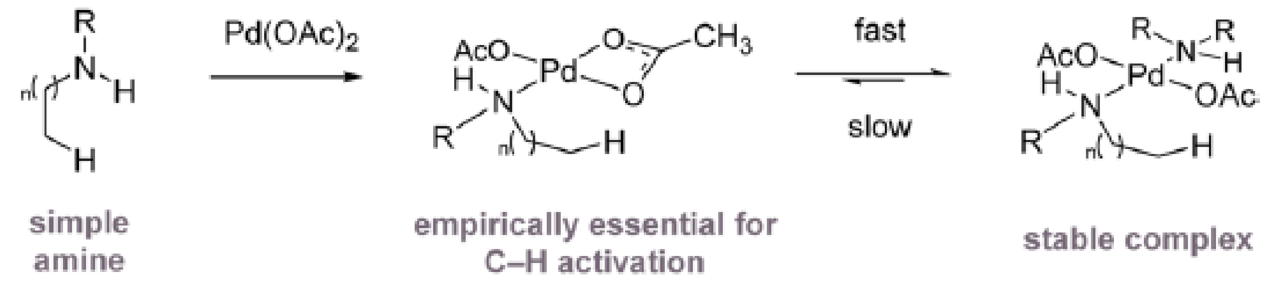
Substrate scope

Outlook

Expanding the scope

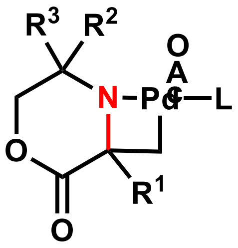
Summary

Problem

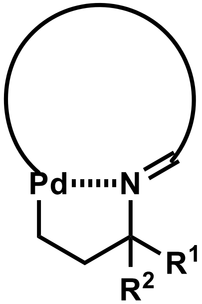


(a) Reaction of amines with palladium(II) acetate

Strategy1: Free amines as DG



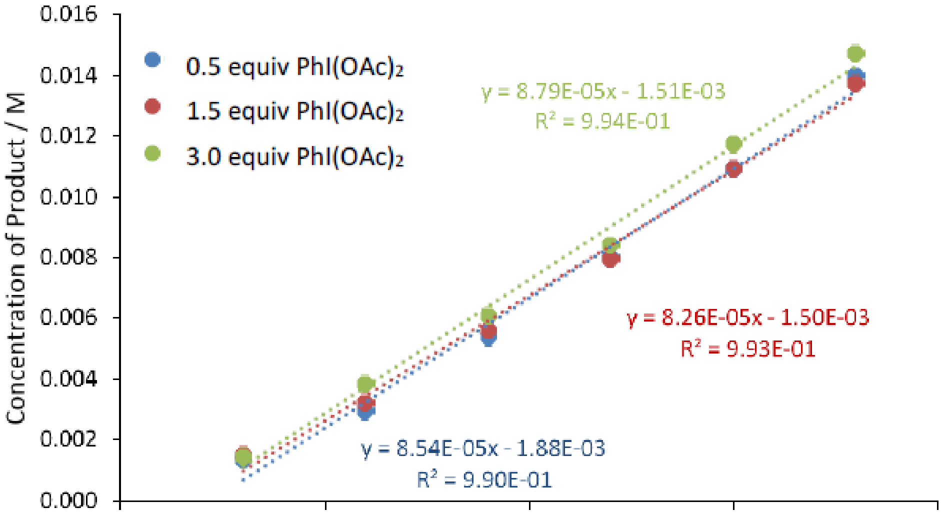
Strategy2: In situ installed and removed DG

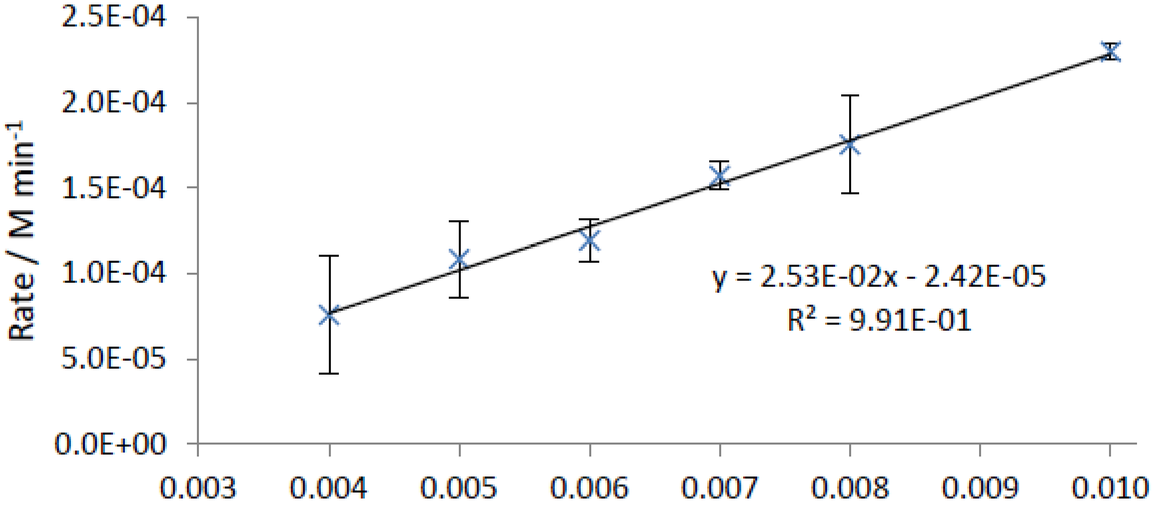


Appendix

Appendix1

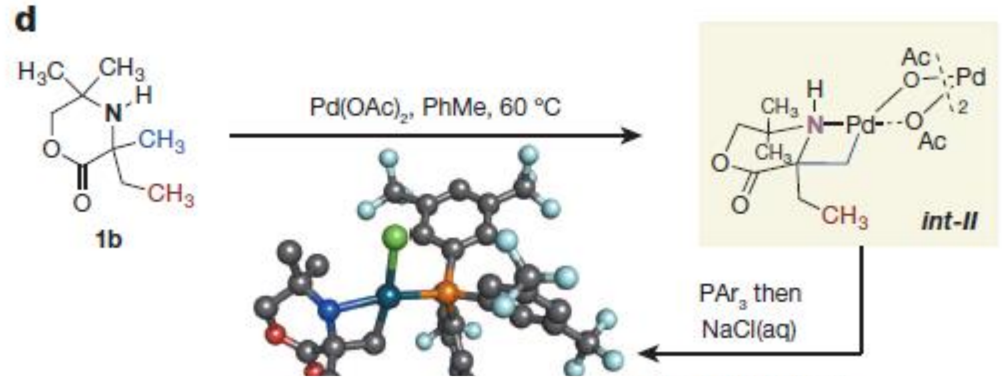
Zero Order in Oxidant (PhI(OAc)$_2$)

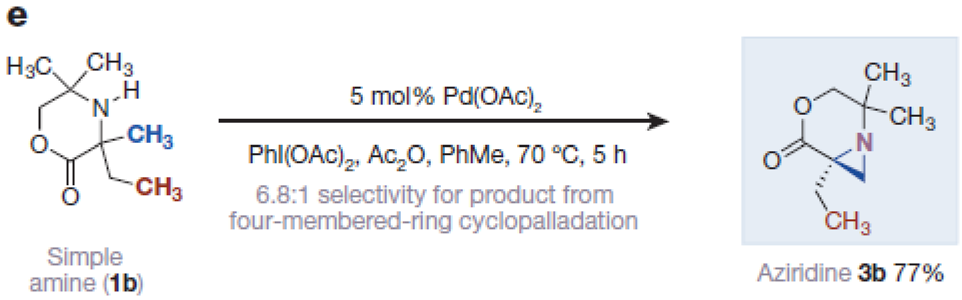


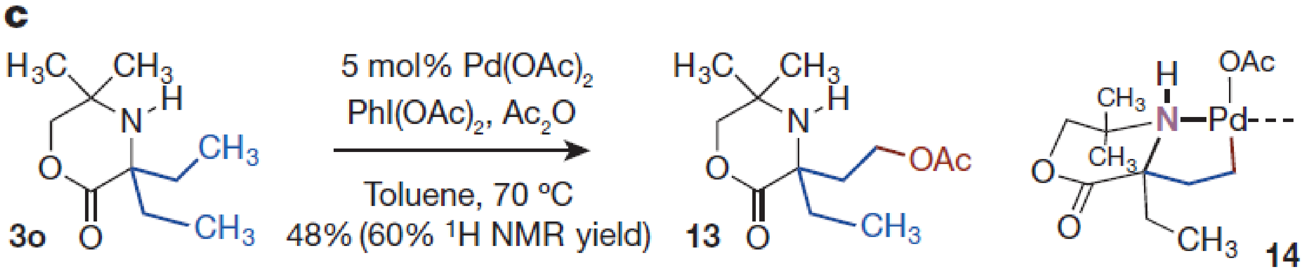


Gaunt, M. - J. *et al. J. Am. Chem. Soc.* **2015**, *137*, 10632

Appendix2



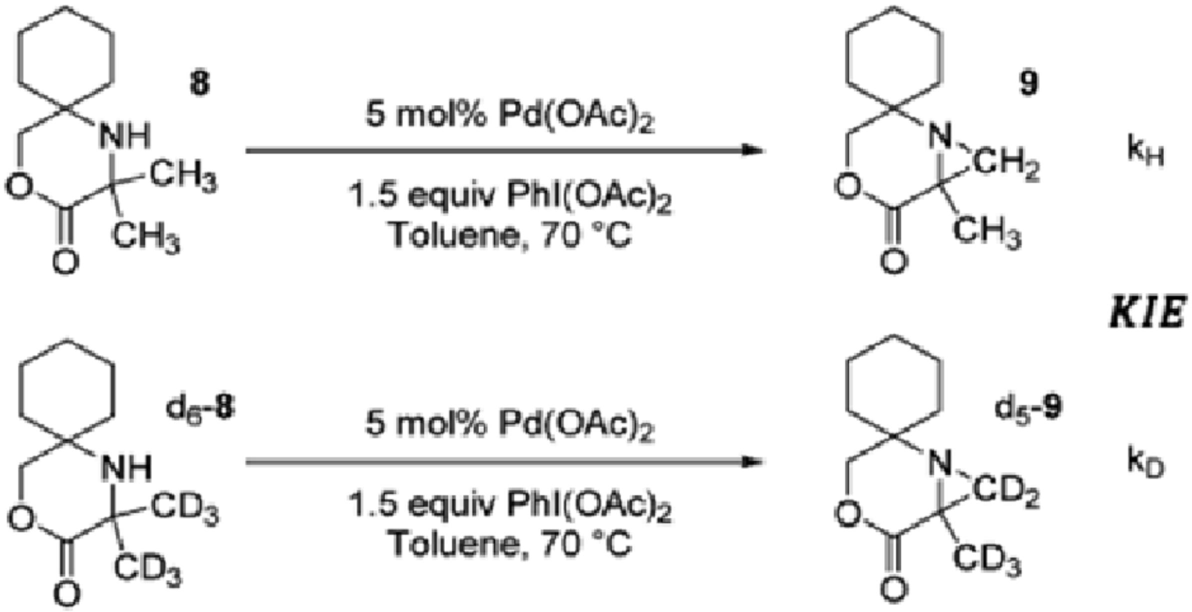




Gaunt, M. - J. *et al. Nature* **2014**, *510*, 129

Appendix3

AcOH present in the reaction

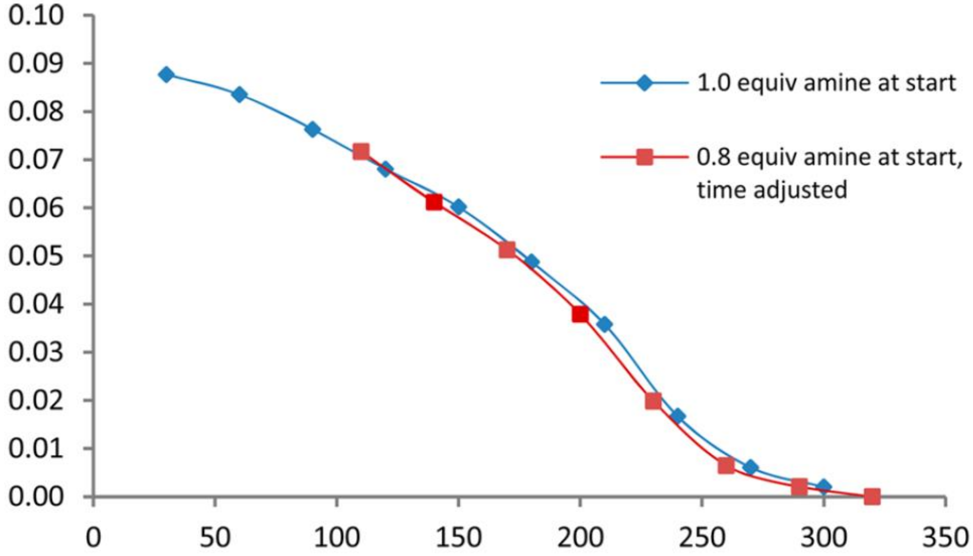


$$KIE = \frac{k_H}{k_D} = 3.9$$

(3.8 without AcOH)

Gaunt, M. - J. *et al. J. Am. Chem. Soc.* **2015**, *137*, 10632

Appendix4: autoinduction



Standard reaction

$$\mathbf{1} + \mathrm{PhI(OAc)_2} \xrightarrow[]{\text{0.1 equiv } \mathrm{Pd(OAc)_2}} \mathbf{2} + \mathrm{PhI(OAc)_2} + \mathrm{PhI} + \mathrm{AcOH}$$

1	PhI(OAc)$_2$	2	PhI(OAc)$_2$	PhI	AcOH
1.0 equiv	1.5 equiv	1.0 equiv	0.5 equiv	1.0 equiv	2.0 equiv

Same 'excess' reaction

$$\mathbf{1} + \mathrm{PhI(OAc)_2} \xrightarrow[]{\text{0.1 equiv } \mathrm{Pd(OAc)_2}} \mathbf{2} + \mathrm{PhI(OAc)_2} + \mathrm{PhI} + \mathrm{AcOH}$$

1	PhI(OAc)$_2$	2	PhI(OAc)$_2$	PhI	AcOH
0.8 equiv	1.3 equiv	0.8 equiv	0.5 equiv	0.8 equiv	1.6 equiv

Gaunt, M. - J. *et al. J. Am. Chem. Soc*. **2015**, *137*, 10632