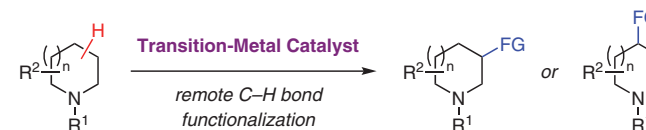


# Transition-Metal-Catalyzed Remote C–H Bond Functionalization of Cyclic Amines

Weijie Chen<sup>a,b</sup> Xiaoyu Yang<sup>a</sup>Xi Cao<sup>a</sup><sup>a</sup> School of Chemical Science and Engineering, Tongji University, 1239 Siping Rd, Shanghai 200092, P. R. of China<sup>b</sup> Institute for Advanced Studies, Tongji University, 1239 Siping Rd, Shanghai 200092, P. R. of China  
weijiechen@tongji.edu.cn

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**Abstract** C–H bond functionalization is one of the most effective strategies for the rapid synthesis of cyclic amines containing substituents on the ring, which are core structures of many bioactive molecules. However, it is much more challenging to perform this strategy on remote C–H bonds compared to the  $\alpha$ -C–H bonds of cyclic amines. This graphical review aims to provide a concise overview on transition-metal-catalyzed methods for the remote C–H bond functionalization of cyclic amines. Examples are categorized and demonstrated according to mechanistic pathways that initiate the reactions of cyclic amine substrates. Where relevant, selected substrate scope and detailed reaction mechanisms are given.

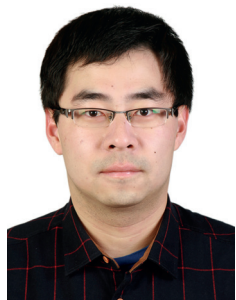
**Key words** C–H bond functionalization, remote, cyclic amines, transition metals, catalysis, synthesis

Cyclic amines are ubiquitous structures in natural products and pharmaceuticals, many of which contain one or multiple substituents on the ring at the  $\alpha$ -position as well as at positions remote from the nitrogen atom. The development of new synthetic methods to access these substituted cyclic amines is thus of great importance. For this purpose, C–H bond functionalization of parent aza-heterocycles arguably represents the most direct and facile strategy

among others, being particularly suitable for the late-stage modification of existing cyclic amine structures in complex molecules. Research in this field, however, has largely focused on the functionalization of  $\alpha$ -C–H bonds, while functionalization of more remote C–H bonds, such as  $\beta$ - and  $\gamma$ -C–H bonds, is much less studied. This is due to challenges associated with remote C–H bond functionalization of cyclic amines. Firstly, a handful of such reactions are initiated via the lone pair of electrons on the amine nitrogen atom, which is further away from remote C–H bonds compared to the  $\alpha$ -C–H bond. Secondly, reactions for the remote C–H bond functionalization of cyclic amines often involve labile endocyclic iminium ion and enamine intermediates, which are electrophiles and nucleophiles respectively in nature. This dramatically enhances the complexity of reaction pathways, and significantly increases the difficulty in controlling the selectivity of the target reaction. Thirdly, the conformations of cyclic compounds are not as flexible as those of acyclic compounds. As a result, strategies that are not uncommon for the remote C–H bond functionalization of acyclic amines are sometimes not feasible for cyclic amines. Despite the above challenges, significant progress has still been made in recent years toward the remote C–H bond functionalization of cyclic amines, with the majority of methods relying on transition-metal catalysis.

This graphical review summarizes the transition-metal-catalyzed methods developed to date for the purpose of C–H bond functionalization at remote positions of the rings of saturated cyclic amines, some of which involve concurrent  $\alpha$ -C–H bond functionalization as well. Reactions are grouped according to the mechanistic pathway that initiates the reaction of the cyclic amine substrate, and full references are grouped by Figure number. Transition-metal-catalyzed reactions using prefunctionalized substrates, such as cross-coupling with halogenated cyclic amines and hydrofunctionalization of partially unsaturated aza-heterocycles, are outside the scope of this review, and are thus not discussed.

## Biographical Sketches



**Weijie Chen** studied chemistry at the University of Science and Technology of China (USTC) (B.S. 2010), and conducted undergraduate research in the group of Prof. Liu-Zhu Gong. He then undertook his graduate studies in the lab of Prof. Daniel Seidel at Rutgers University (USA),

obtaining his Ph.D. in 2016. He subsequently worked as a postdoctoral fellow in the group of Prof. Michael Krische at the University of Texas at Austin (USA) from 2016 to 2017. He then moved to the University of Florida (USA) with the group of Prof. Daniel Seidel in the summer of 2017, and

continued his postdoctoral research until 2020. He started his independent career at Tongji University (China) in 2021.



**Xiaoyu Yang** studied chemistry at the University of Shanghai for Science and Technology (USST) (B.S. 2021).

He then moved to Tongji University for his M.Sc. degree, working with Dr. Weijie Chen. His research focuses on the

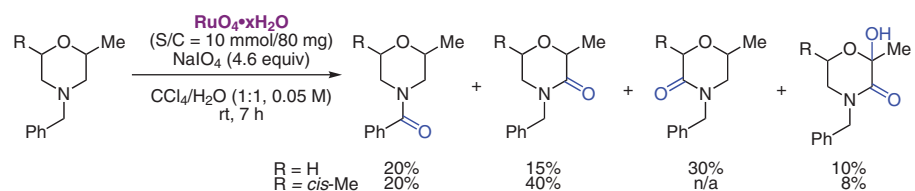
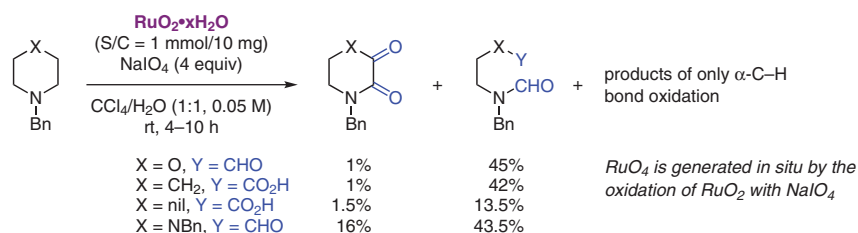
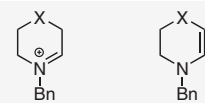
development of new synthetic methods toward nitrogen-containing compounds.



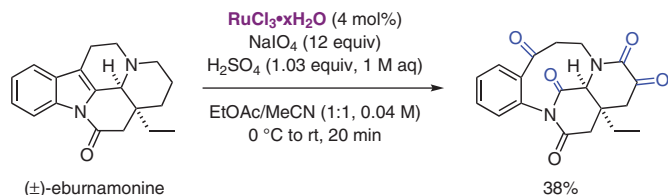
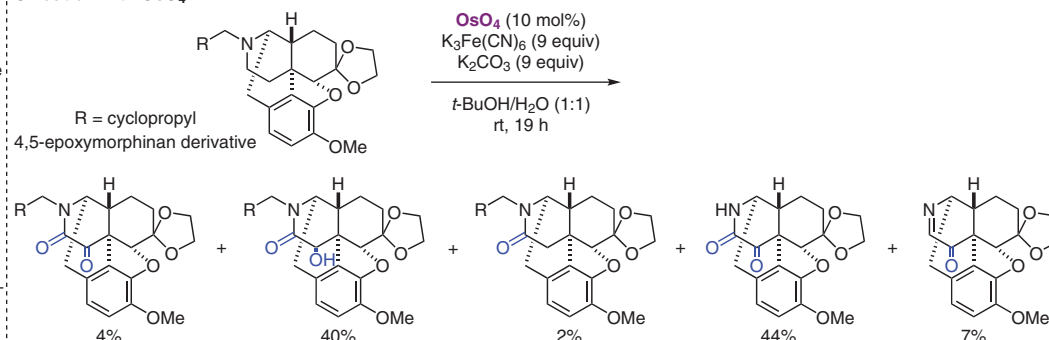
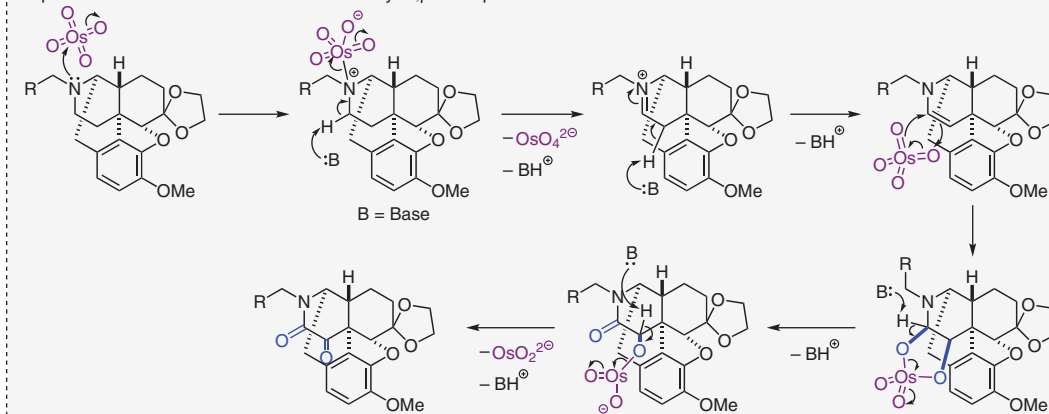
**Xi Cao** studied chemistry at Hunan Normal University (B.S. 2021). She then moved to Tongji University for her

Ph.D. studies, working with Dr. Weijie Chen. Her research focuses on the development of new synthetic methods to-

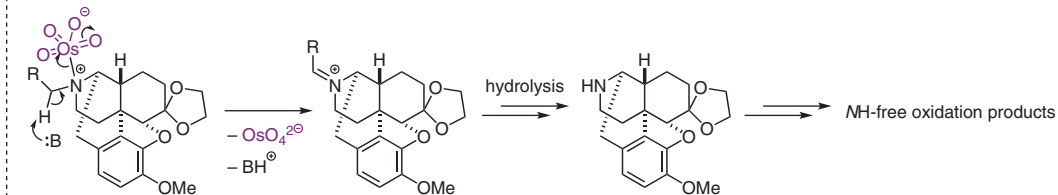
ward nitrogen-containing compounds.

Oxidation of *N*-benzyl morpholines with ruthenium tetroxide (RuO<sub>4</sub>)(1a) Tortorella, *Synthesis* **1976**, 598.Oxidation of other *N*-benzyl cyclic amines with RuO<sub>4</sub>Proposed key intermediates leading to  $\beta$ -C–H bond oxidation products(1b) Petride, *Cent. Eur. J. Chem.* **2004**, 2, 302.(1c) Petride, *Cent. Eur. J. Chem.* **2006**, 4, 674.

## Oxidation of natural products

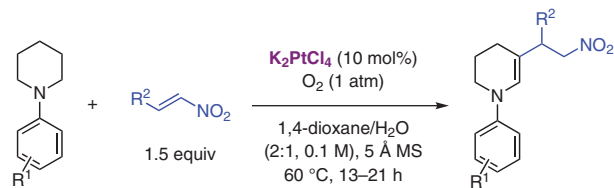
(1d) Westwood, *Org. Lett.* **2012**, 14, 6166.Oxidation with OsO<sub>4</sub>Proposed mechanism for formation of the *N*-alkyl- $\alpha,\beta$ -dioxo product

## Proposed intermediates for the formation of NH-free oxidation products

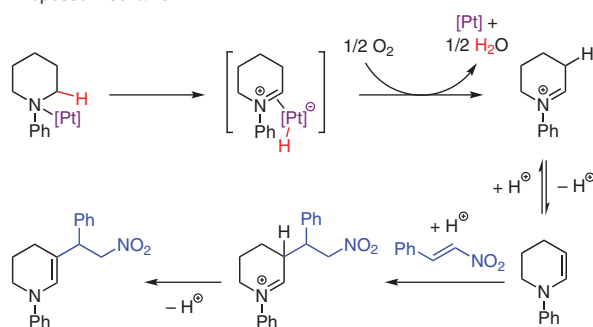
(1e) Nagase, *Synlett* **2009**, 2341.For a comprehensive graphical review on amine C–H bond functionalization, including part of the work covered in this graphical review, see: (1f) Seidel, *SynOpen* **2021**, 5, 173.For other selected reviews containing examples of transition-metal-catalyzed remote C–H bond functionalization of cyclic amines, see: (1g) Baudoin, *Chem. Eur. J.* **2010**, 16, 2654. (1h) Dai, *Beilstein J. Org. Chem.* **2016**, 12, 702. (1i) Bull, *Synthesis* **2019**, 51, 3171. (1j) Kapoor, *Adv. Synth. Catal.* **2020**, 362, 4513. (1k) Gaunt, *Chem. Rev.* **2020**, 120, 2613. (1l) Arisawa, *Synthesis* **2021**, 53, 2947. (1m) He & Fan, *Org. Chem. Front.* **2021**, 8, 4582. (1n) Foley, *Chem. Sci.* **2021**, 12, 4646.Figure 1 Oxidation with metal tetroxides<sup>1</sup>

## Platinum as catalyst

## Dehydrogenative Michael addition/cyclization with nitroolefins



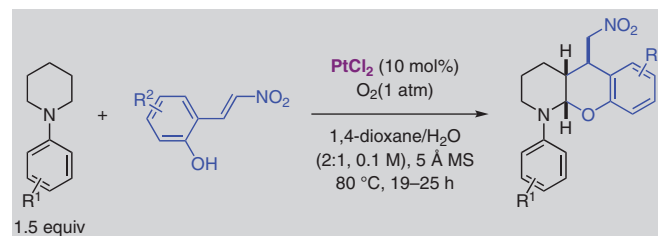
## Proposed mechanism



## Selected scope

R <sup>1</sup>	R <sup>2</sup>	% Yield
H	Ph	70
H	2-Me-C <sub>6</sub> H <sub>4</sub>	46
H	3-Cl-C <sub>6</sub> H <sub>4</sub>	54
H	4-MeO-C <sub>6</sub> H <sub>4</sub>	40
H	2-furyl	41
H	Cy	20*
4-MeO	Ph	71
4-Br	Ph	40
4-Me	2-Cl-C <sub>6</sub> H <sub>4</sub>	68

\* Reaction temperature is 80 °C.

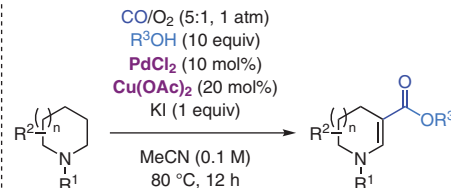


## Selected scope

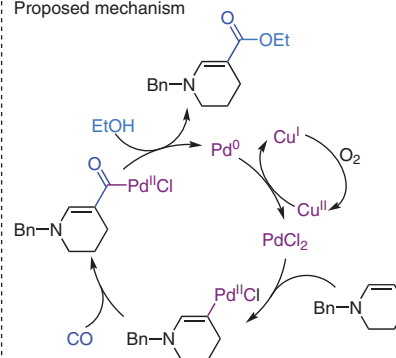
R <sup>1</sup>	R <sup>2</sup>	% Yield
H	H	65
4-MeO	H	57
4-Br	H	52
2-Bn	H	65
H	5-MeO	62

(2a) Liang, *J. Org. Chem.* **2010**, *75*, 2893.For the hydride abstraction mechanism in Pt(II)-catalyzed reactions involving acyclic secondary and tertiary amines, see: (2b) Brunet, *Organometallics* **2006**, *25*, 2943.

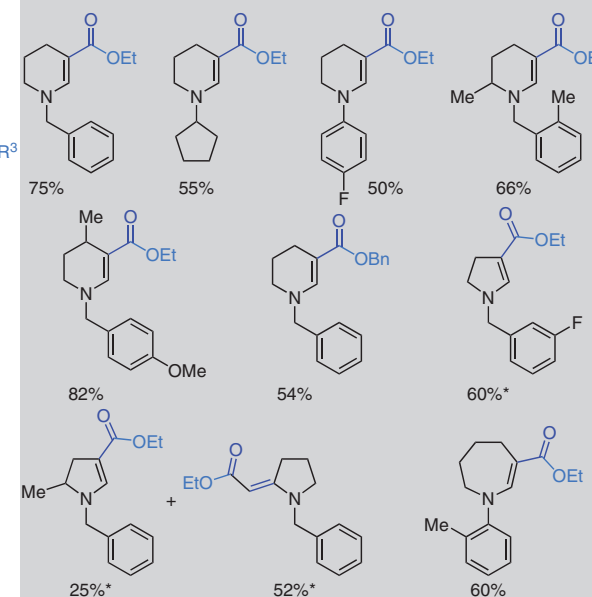
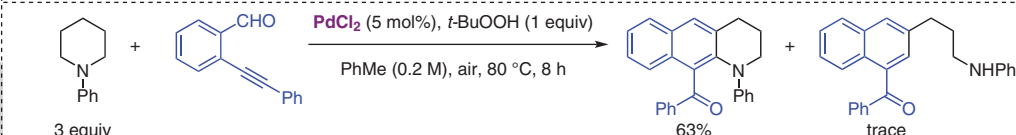
## Palladium as catalyst

Dehydrogenative  $\beta$ -alkoxy carbonylation

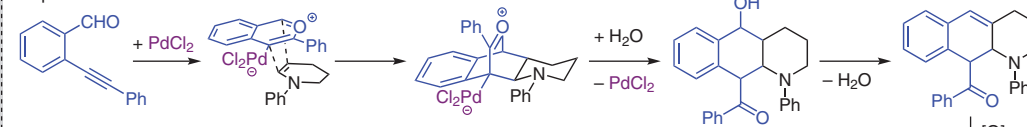
## Proposed mechanism

(2c) He & Fan, *Chem. Commun.* **2017**, *53*, 4002.

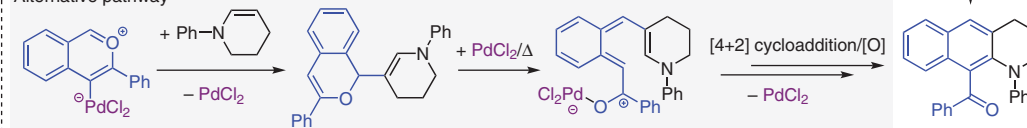
## Selected scope

\* Cu(OAc)<sub>2</sub> (1 equiv) is used under air to avoid over-oxidation forming pyrrole products.

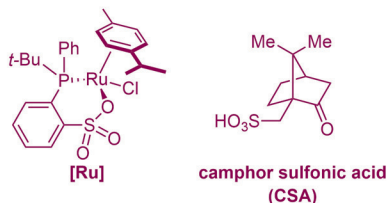
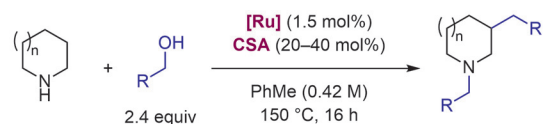
## Proposed mechanism



## Alternative pathway

(2d) He & Fan, *Org. Lett.* **2020**, *22*, 9053.Figure 2 Hydride abstraction from cyclic amines, part I<sup>2</sup>

## Ruthenium as catalyst

Redox-neutral *N*- and  $\beta$ -dialkylation of secondary cyclic amines with alcohols

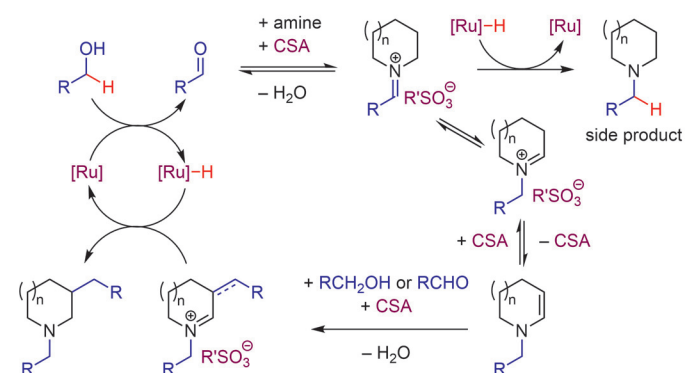
## Selected scope

n	R	% Yield
0	Ph	80
0	4-F-C <sub>6</sub> H <sub>4</sub>	61
0	2-Br-C <sub>6</sub> H <sub>4</sub>	70
0	<i>n</i> -pentyl	50*
1	4-Me-C <sub>6</sub> H <sub>4</sub>	68
1	2-Cl-C <sub>6</sub> H <sub>4</sub>	62
1	4-F <sub>3</sub> C-C <sub>6</sub> H <sub>4</sub>	52
2	Ph	68

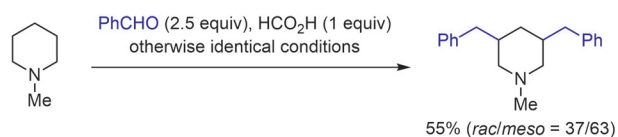
\* 170 °C, 24 h, *n*-hexanol (0.245 M) as solvent.

(3a) Bruneau, *Adv. Synth. Catal.* **2010**, 352, 3141.

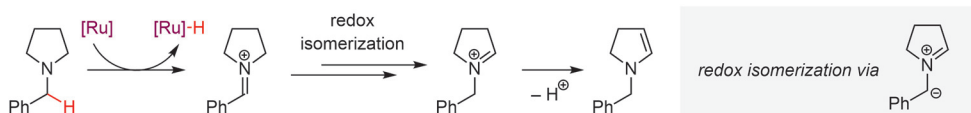
## Proposed mechanism



This reaction is an exception of this category – hydride abstraction occurs on primary alcohols.

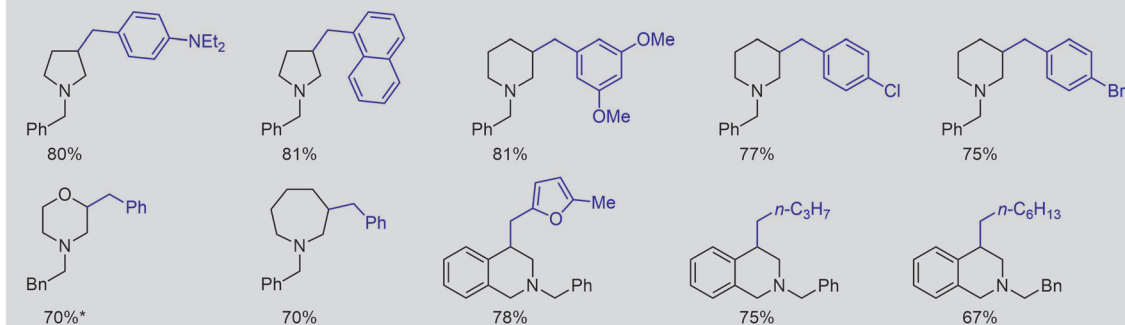
Reductive variant of Ru-catalyzed  $\beta$ -alkylation of tertiary cyclic amines with aldehydes $\beta,\beta'$ -Dialkylation of *N*-methylpiperidine

## Proposed mechanism for the formation of an enamine intermediate



(3b) Bruneau, *J. Am. Chem. Soc.* **2011**, 133, 10340.

## Selected scope



\* Amine is used in 1.1 equiv; HCO<sub>2</sub>H (2 equiv)

See also: (3c) Bruneau, *Green Chem.* **2013**, 15, 775.

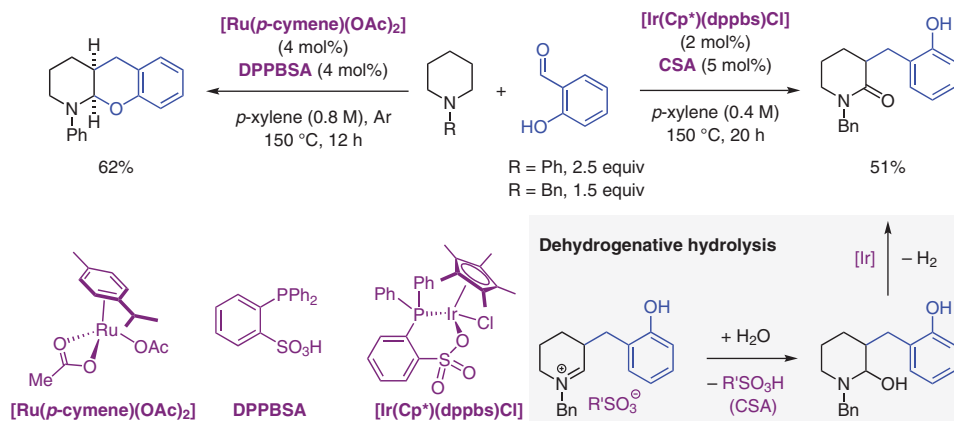
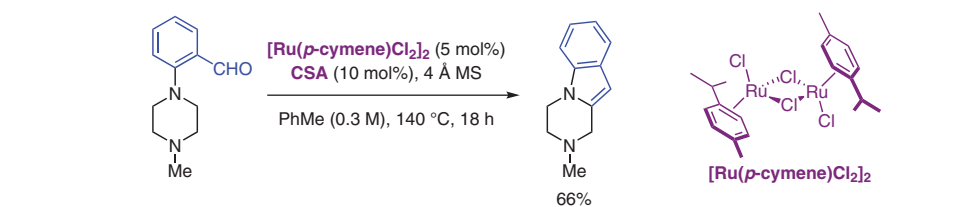
For  $\beta$ -alkylation of 1,2,3,4-tetrahydroisoquinolines (THIQ), see: (3d) Bruneau, *J. Org. Chem.* **2012**, 77, 3674.

For  $\beta$ -alkylation of *N*-alkyl-*N*'-*p*-nitrophenyl piperazines, see: (3e) Suresh, *Adv. Synth. Catal.* **2021**, 363, 453.

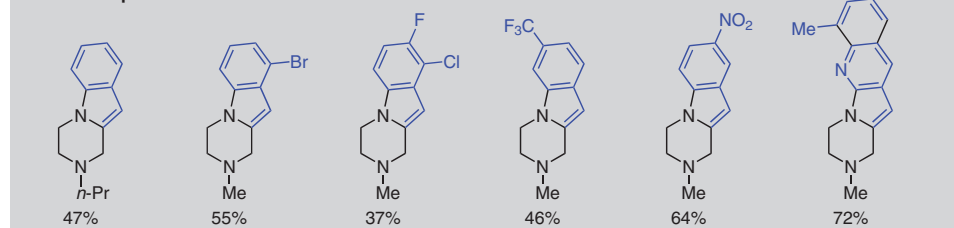
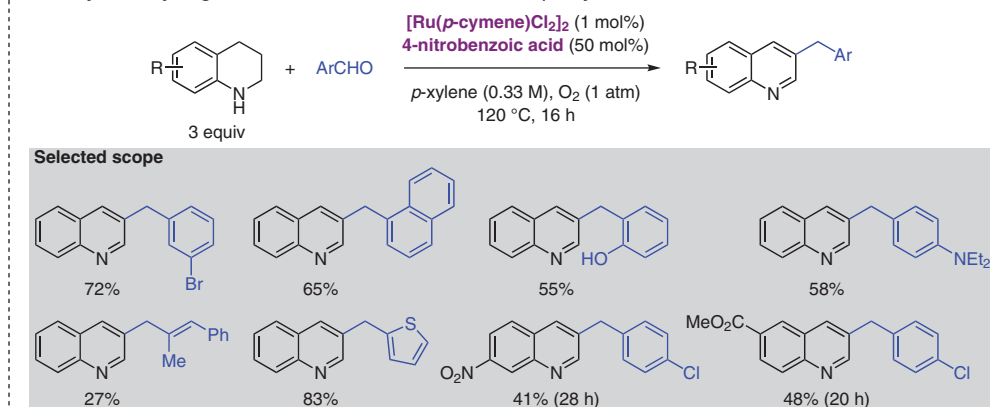
For  $\beta$ -alkylation of cyclic amines catalyzed by ruthenium *N*-heterocyclic carbene (NHC) complexes, see: (3f) Özdemiş, *J. Organomet. Chem.* **2015**, 799–800, 311. (3g) Özdemiş, *Organometallics* **2015**, 34, 2296.

(3h) Özdemiş, *Tetrahedron* **2018**, 74, 645. (3i) Kaloğlu, *Tetrahedron* **2019**, 75, 2265.

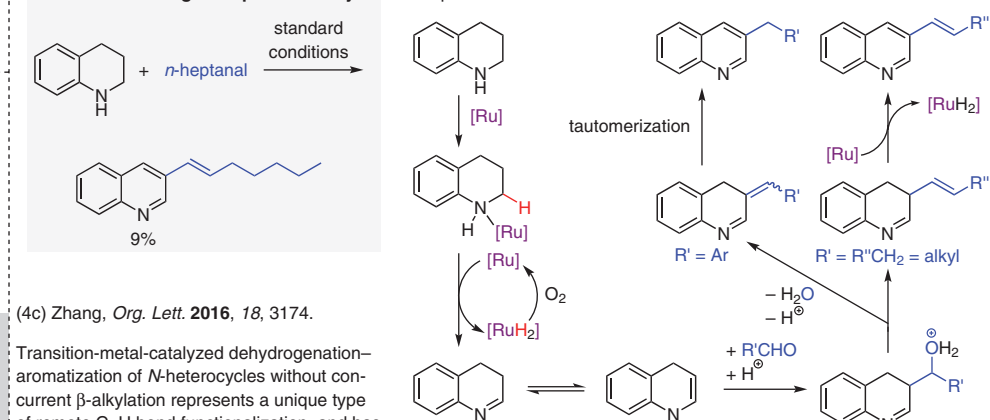
Figure 3 Hydride abstraction from cyclic amines, part II<sup>3</sup>

Ru-catalyzed cyclization involving  $\beta$ -C-H bond functionalization(4a) Achard, *Chem. Eur. J.* **2015**, *21*, 14319.

## Selected scope

(4b) Suresh, *Chem. Commun.* **2017**, *53*, 10448.Ru-catalyzed dehydrogenation-aromatization with concurrent  $\beta$ -alkylation

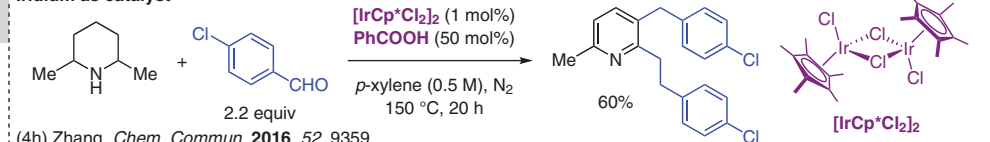
## Reaction involving an aliphatic aldehyde

(4c) Zhang, *Org. Lett.* **2016**, *18*, 3174.

Transition-metal-catalyzed dehydrogenation-aromatization of *N*-heterocycles without concurrent  $\beta$ -alkylation represents a unique type of remote C-H bond functionalization, and has been extensively reviewed. It is thus not discussed herein, see: (4d) Fujita, *Tetrahedron* **2020**, *76*, 130946.

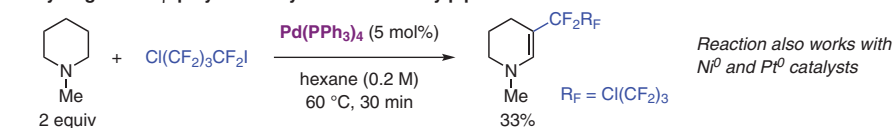
(4e) Zhang, *Catal. Sci. Technol.* **2021**, *11*, 3990. (4f) Banerjee, *Chem. Commun.* **2021**, *57*, 13042.(4g) He & Chen, *J. Phys. Chem. C* **2021**, *125*, 18553.

## Iridium as catalyst

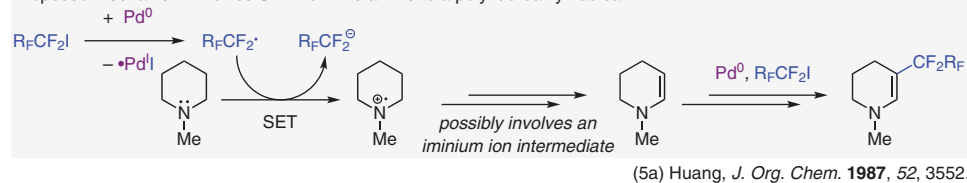
(4h) Zhang, *Chem. Commun.* **2016**, *52*, 9359.See also: (4a) and (4i) Kundu, *J. Org. Chem.* **2022**, *87*, 5603.Figure 4 Hydride abstraction from cyclic amines, part III<sup>4</sup>



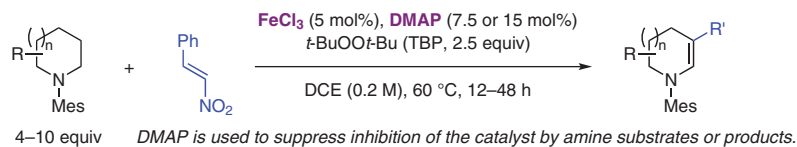
## Ground-state palladium as catalyst

Dehydrogenative  $\beta$ -polyfluoroalkylation of *N*-methylpiperidine

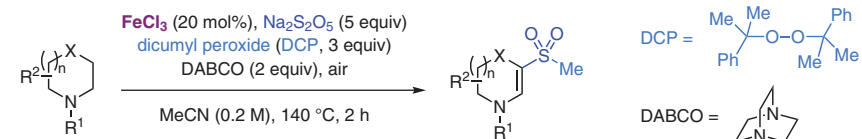
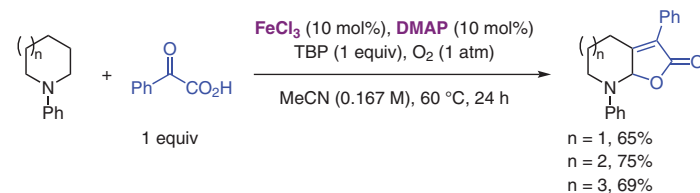
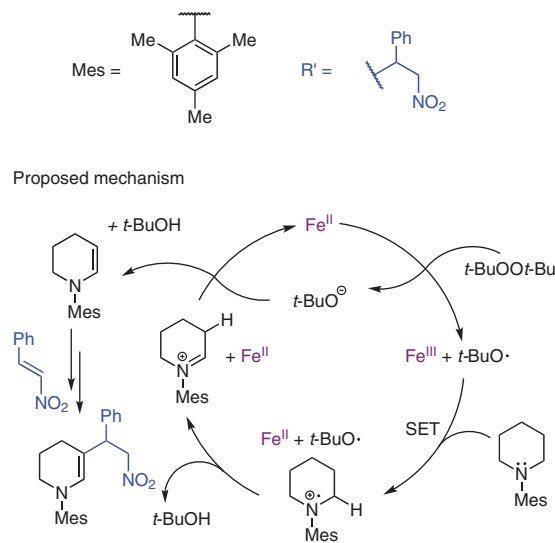
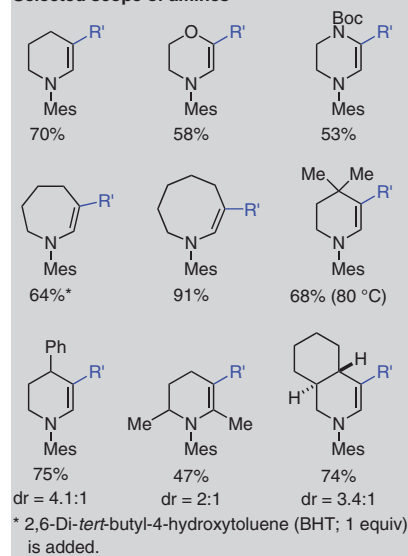
Proposed mechanism involves SET from the amine to a polyfluoroalkyl radical



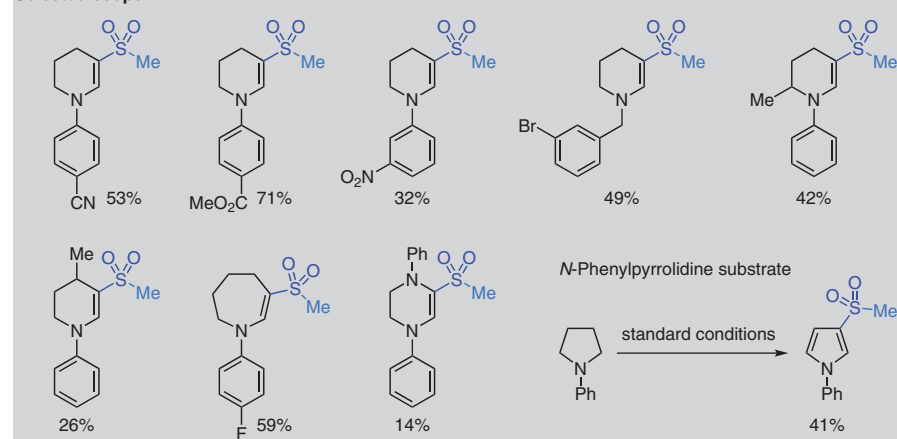
## Ground-state iron as catalyst



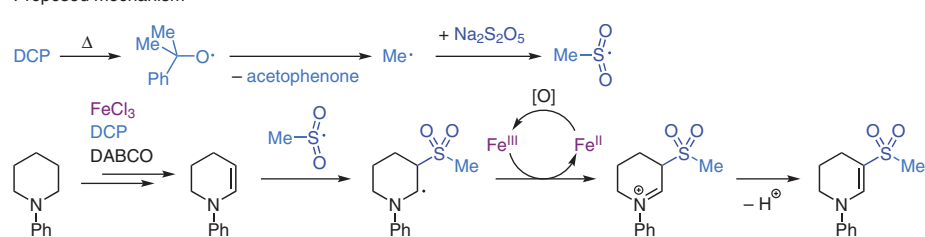
## Selected scope of amines



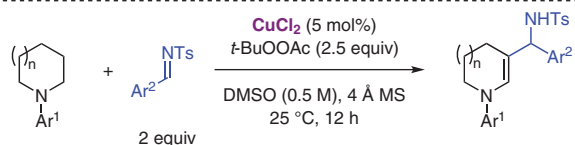
## Selected scope



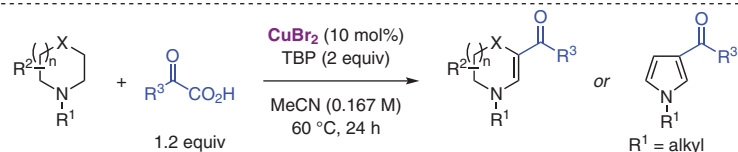
## Proposed mechanism

Figure 5 Single-electron transfer (SET) from cyclic amines, part I<sup>5</sup>

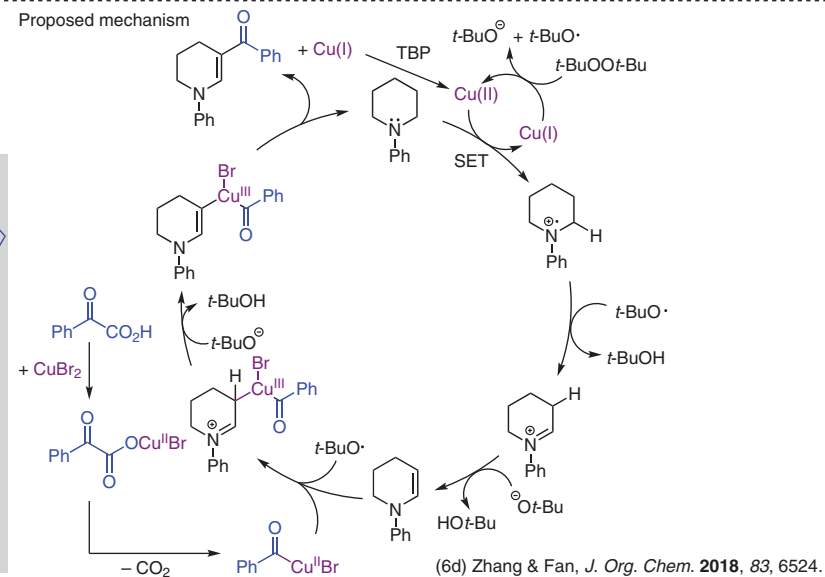
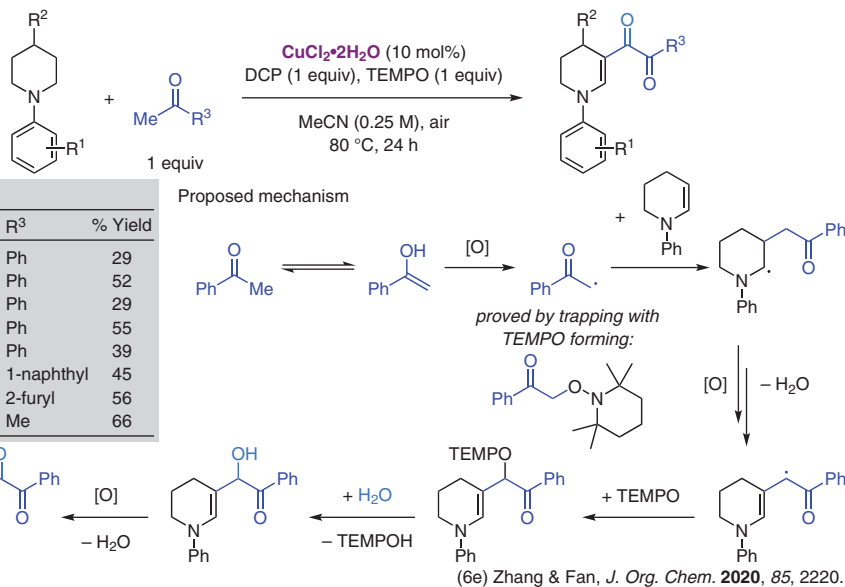
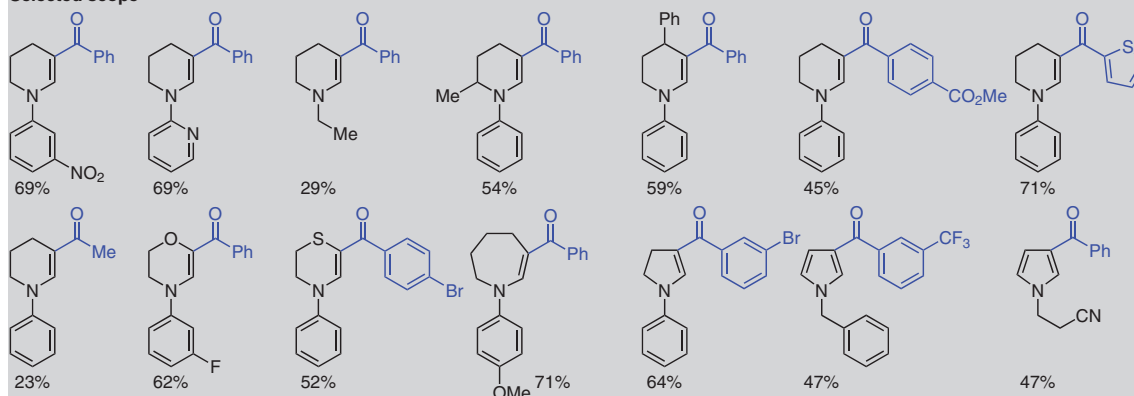
## Ground-state copper as catalyst

Cu-catalyzed  $\beta$ -C-H bond oxidation of tertiary cyclic amines in complex pharmaceuticals(6a) Touré, *J. Am. Chem. Soc.* **2013**, *135*, 12346.For related work involving Cu-catalyzed  $\beta$ -C-H bond oxidation of cyclic amines, see also: (6b) Fan, *Tetrahedron Lett.* **2019**, *60*, 151155.

Selected scope			
n	Ar <sup>1</sup>	Ar <sup>2</sup>	% Yield
1	Ph	4-F-C <sub>6</sub> H <sub>4</sub>	81
1	Ph	2-Me-C <sub>6</sub> H <sub>4</sub>	66
1	Ph	2-naphthyl	81
1	Ph	2-thienyl	51
1	4-Br-C <sub>6</sub> H <sub>4</sub>	Ph	93
2	Ph	Ph	70

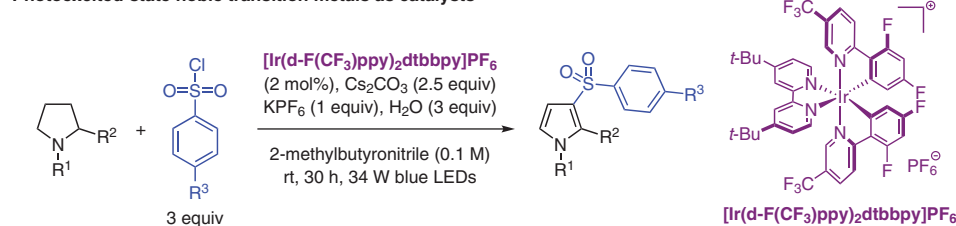
(6c) Zhou, *Chem. Commun.* **2017**, *53*, 8770.

## Selected scope

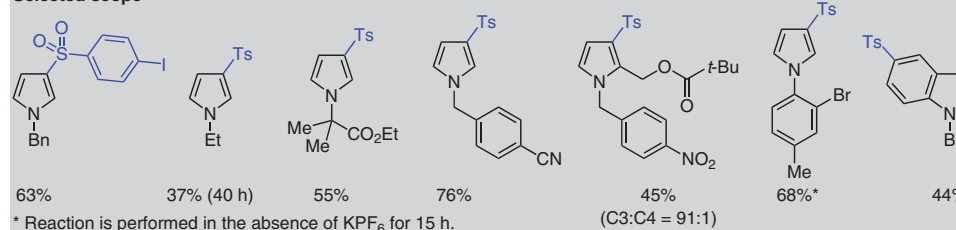
Figure 6 Single-electron transfer (SET) from cyclic amines, part II<sup>6</sup>



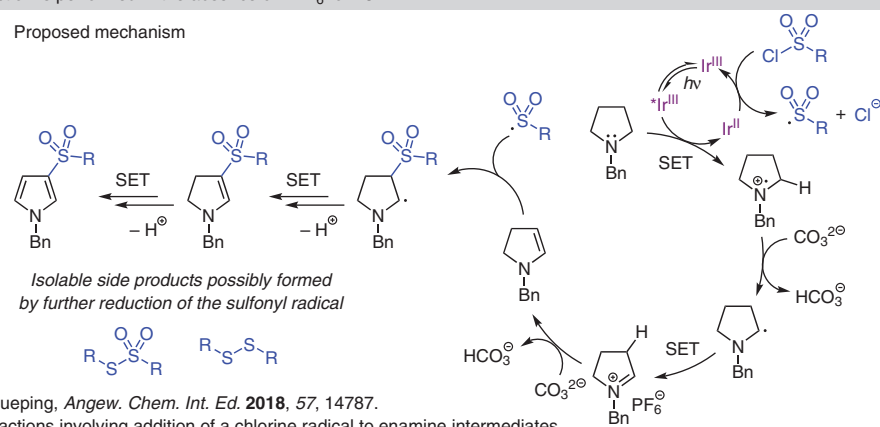
## Photoexcited-state noble transition metals as catalysts



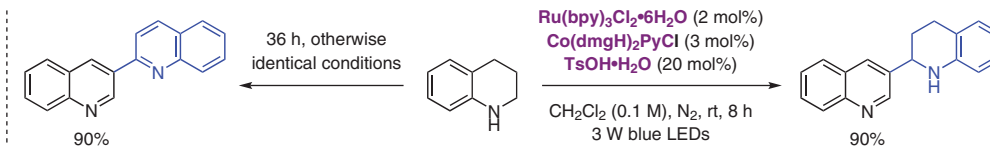
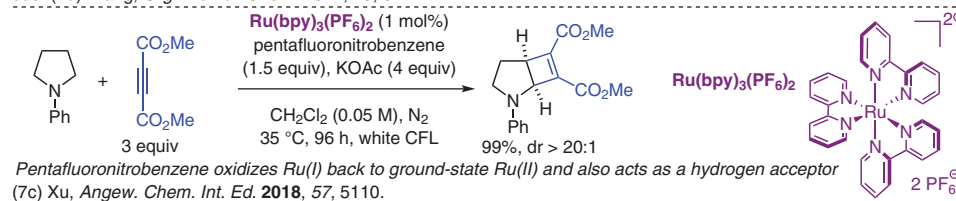
## Selected scope



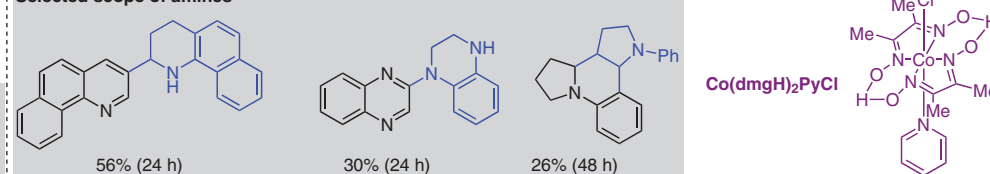
## Proposed mechanism

(7a) Rueping, *Angew. Chem. Int. Ed.* **2018**, *57*, 14787.

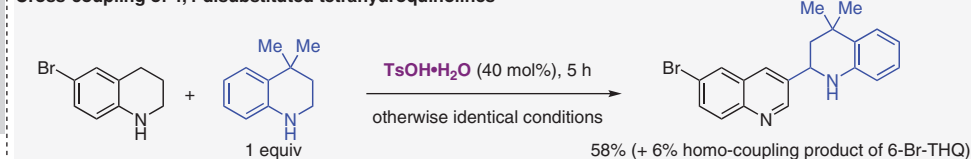
For reactions involving addition of a chlorine radical to enamine intermediates,

see: (7b) Wang, *Org. Biomol. Chem.* **2021**, *19*, 6141.

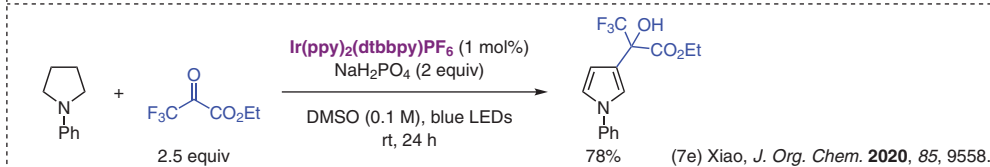
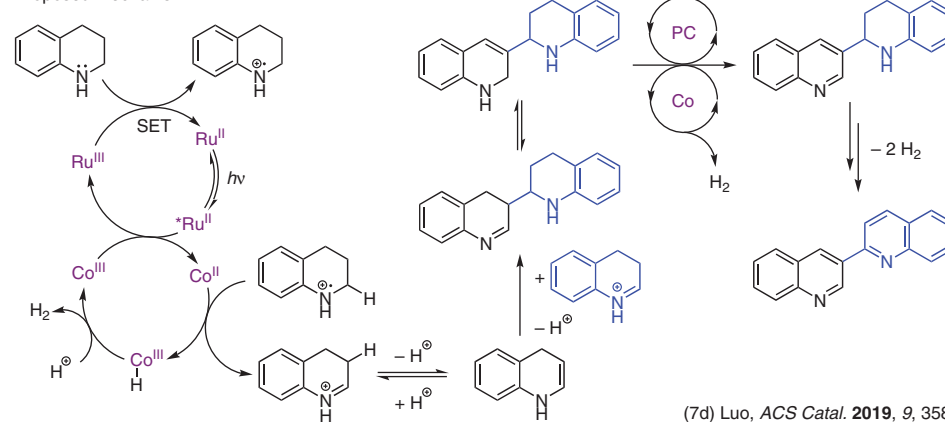
## Selected scope of amines

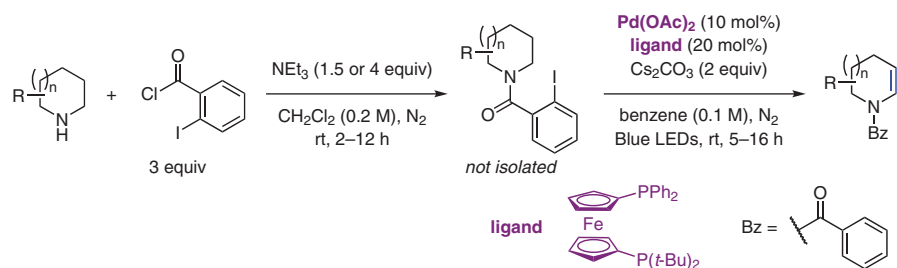


## Cross-coupling of 4,4-disubstituted tetrahydroquinolines

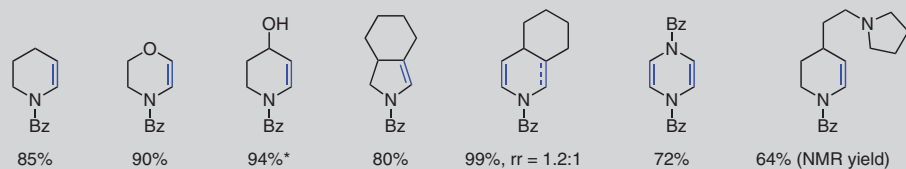


## Proposed mechanism

Figure 7 Single-electron transfer (SET) from cyclic amines, part III<sup>7</sup>

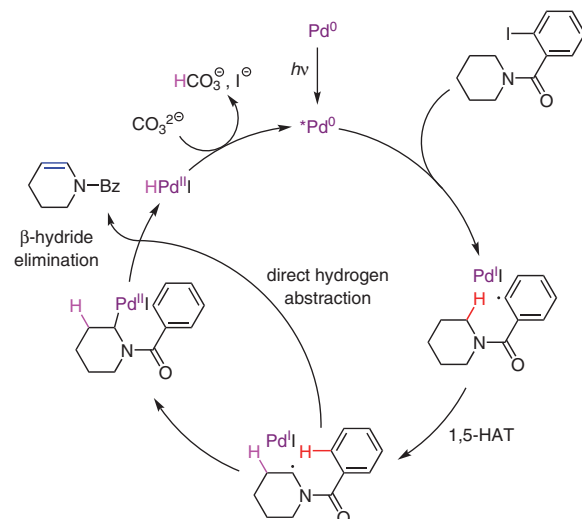


## Selected scope



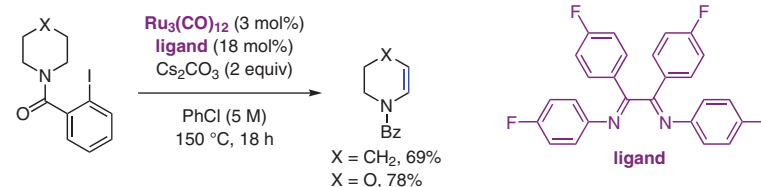
\* Yield of the one-step reaction from *N*-(*o*-iodobenzoyl)amine.

## Proposed mechanism

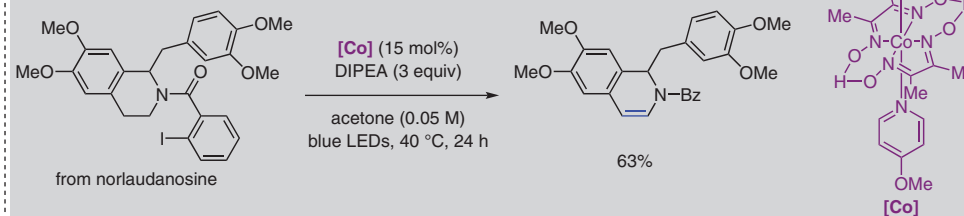


(8a) Gevorgyan, *J. Am. Chem. Soc.* **2018**, *140*, 2465.

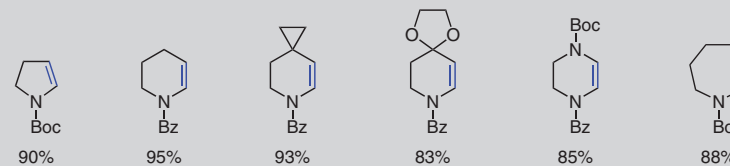
## Reactions with a similar mechanism catalyzed by other metals



(8b) Morandi, *Angew. Chem. Int. Ed.* **2021**, *60*, 7290.



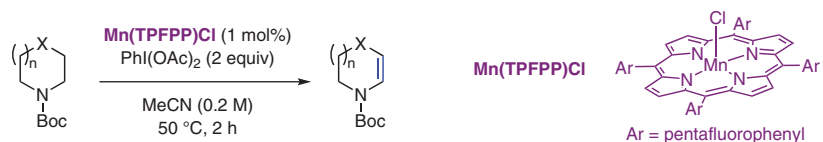
## Selected scope of other cyclic amines



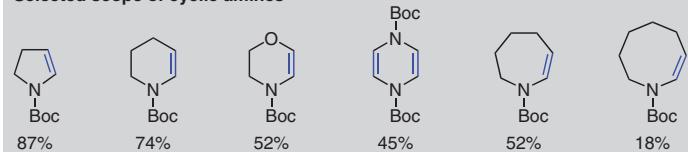
(8c) Zheng & Xu, *Chem. Sci.* **2022**, *13*, 7947.

For a similar reaction with computational studies, see: (8d) El-Sepelgy, *ACS Catal.* **2022**, *12*, 8868.

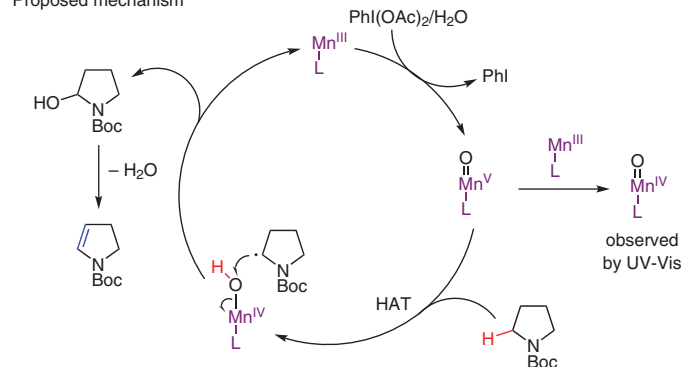
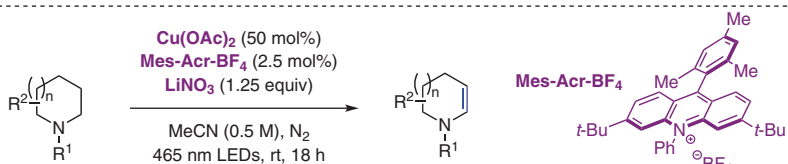
Figure 8 Hydrogen atom transfer (HAT) from cyclic amines, part I<sup>8</sup>



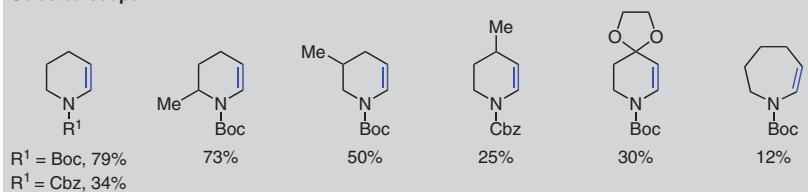
## Selected scope of cyclic amines



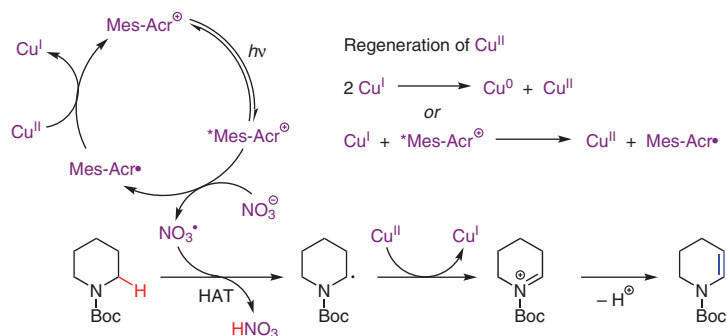
## Proposed mechanism

(9a) Groves, *ACS Catal.* 2019, 9, 9513.

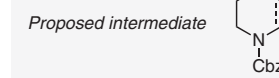
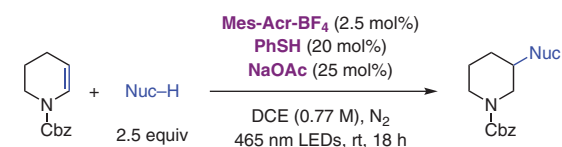
## Selected scope



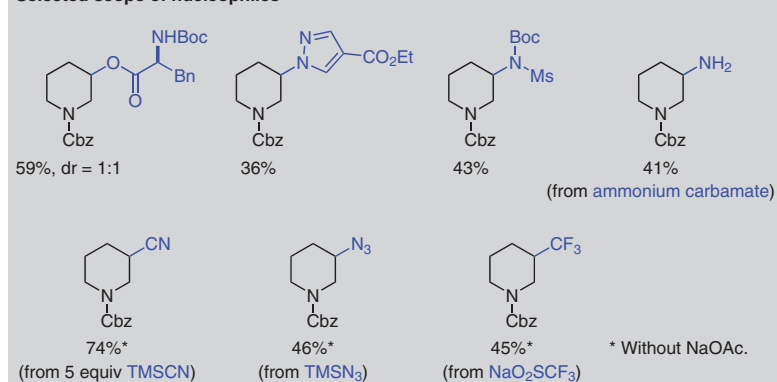
## Proposed mechanism



## Elaboration of ene-carbamates via hydrofunctionalization

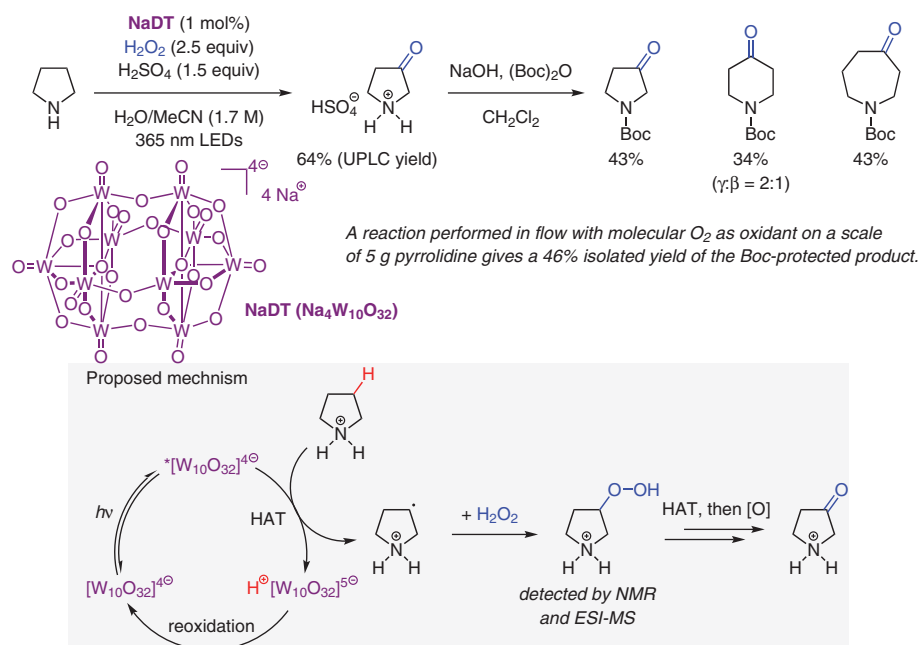
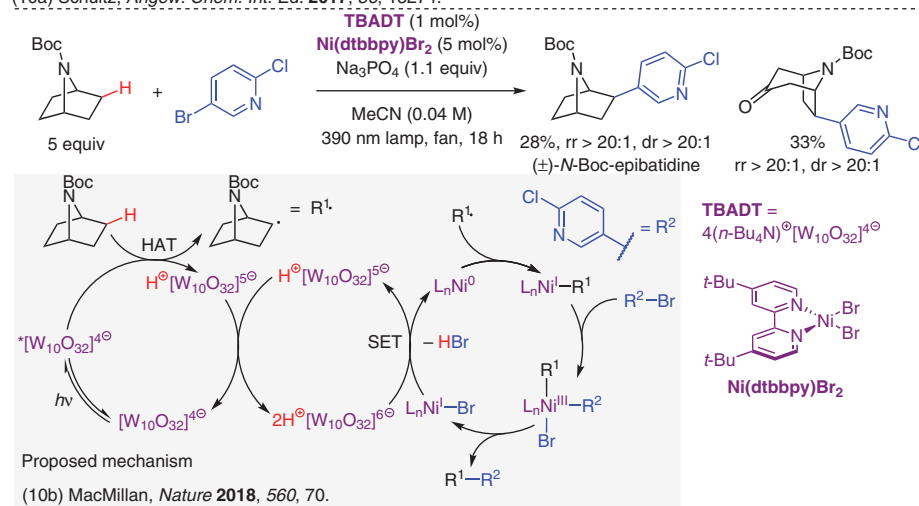
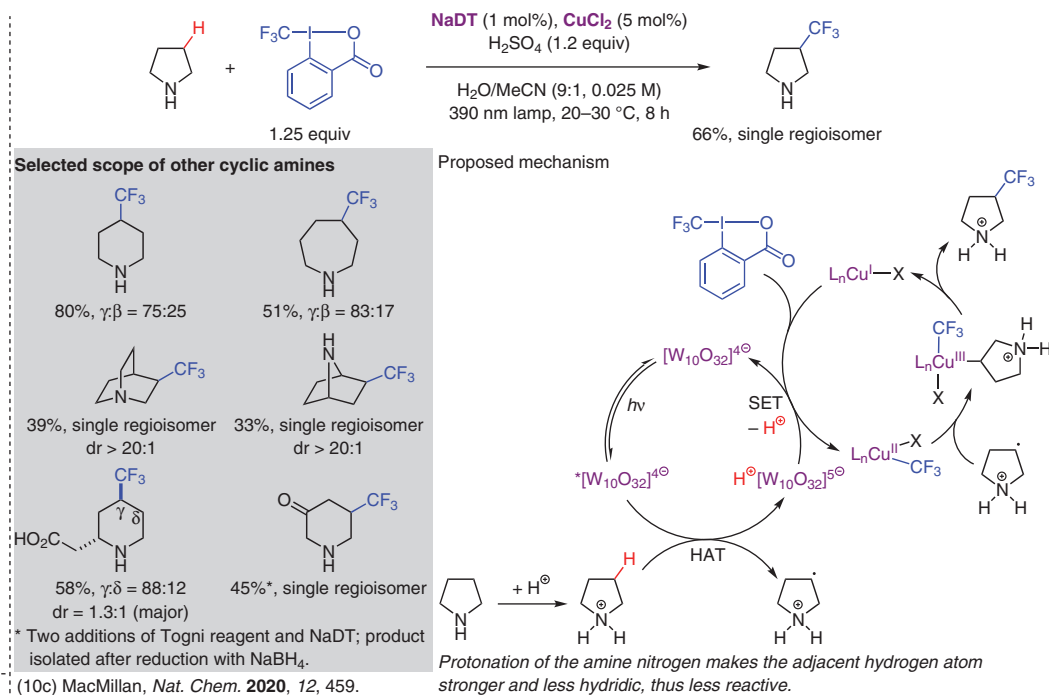
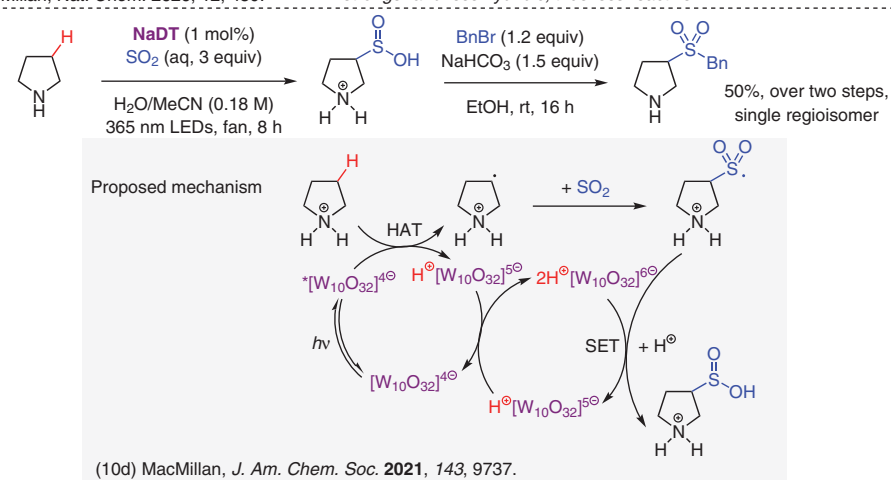


## Selected scope of nucleophiles

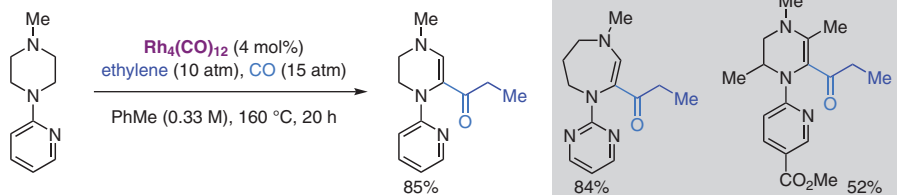
(9b) Niciewicz, *ACS Catal.* 2021, 11, 3153.For a study on visible-light photooxidation of nitrates, see: (9c) König, *Chem. Commun.* 2015, 51, 6568.

For mechanistic studies on a similar anti-Markovnikov hydrofunctionalization of alkenes, see:

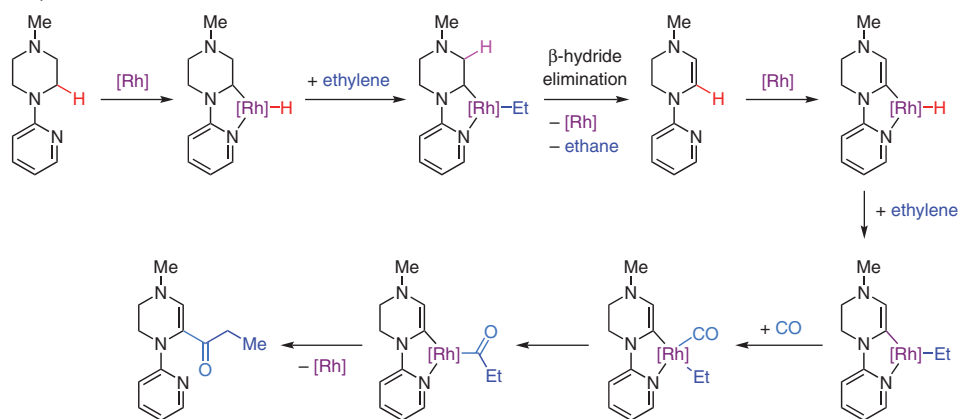
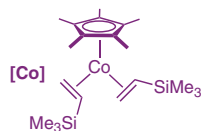
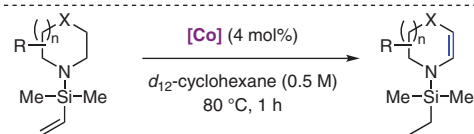
(9d) Niciewicz, *J. Am. Chem. Soc.* 2014, 136, 17024.Figure 9 Hydrogen atom transfer (HAT) from cyclic amines, part II<sup>9</sup>

(10a) Schultz, *Angew. Chem. Int. Ed.* **2017**, *56*, 15274.(10b) MacMillan, *Nature* **2018**, *560*, 70.(10c) MacMillan, *Nat. Chem.* **2020**, *12*, 459.(10d) MacMillan, *J. Am. Chem. Soc.* **2021**, *143*, 9737.Figure 10 Hydrogen atom transfer (HAT) from cyclic amines, part III<sup>10</sup>

## Seminal work



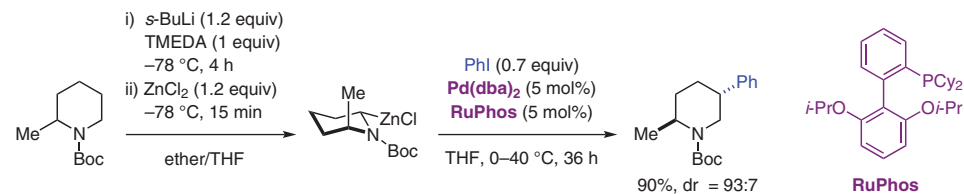
## Proposed mechanism

(11a) Murai, *Organometallics* **1997**, *16*, 3615.For reactions directed by an amido group, see: (11b) Murai, *Tetrahedron Lett.* **1997**, *38*, 7565.

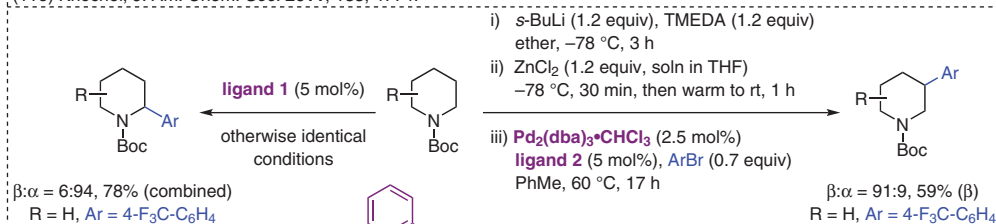
## Selected scope

n	R	X	% Yield (NMR)
1	H	CH <sub>2</sub>	>99
1	3-Me	CH <sub>2</sub>	>95 (2 h)
1	H	NMe	>95
1	H	O	>99
1	H	S	>90*
2	H	CH <sub>2</sub>	>90 (6 d)
3	H	CH <sub>2</sub>	>95

\* A Rh catalyst with the same structure is used.

(11c) Brookhart, *J. Am. Chem. Soc.* **2007**, *129*, 14544.See also: (11d) Bradley, *Chem. Commun.* **2012**, *48*, 368.

**Substrate-controlled.** Substrates without a 6-methyl group give  $\alpha$ -functionalization products.  
(11e) Knochel, *J. Am. Chem. Soc.* **2011**, *133*, 4774.



**Catalyst-controlled**

ligand 1 (5 mol%)  
otherwise identical conditions

ligand 2 (5 mol%), ArBr (0.7 equiv)  
PhMe, 60 °C, 17 h

$\beta$ : $\alpha$  = 6:94, 78% (combined)  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 85:15, 51%

$\beta$ : $\alpha$  = 91:9, 62% (coupling at 80 °C)

$\beta$ : $\alpha$  = 82:18, 57%

$\beta$ : $\alpha$  = 98:2, 61% (coupling at 80 °C)

$\beta$ : $\alpha$  = 95:5, 43% (coupling at 80 °C)

\* Yields correspond to isolated yields of  $\beta$ -arylation products.

ligand 1 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

ligand 2 (SPhos)

i) *s*-BuLi (1.2 equiv), TMEDA (1.2 equiv)  
ether, -78 °C, 3 h

ii) ZnCl<sub>2</sub> (1.2 equiv, soln in THF)  
-78 °C, 30 min, then warm to rt, 1 h

iii) Pd<sub>2</sub>(dba)<sub>3</sub>•CHCl<sub>3</sub> (2.5 mol%)  
ligand 2 (5 mol%), ArBr (0.7 equiv)  
PhMe, 60 °C, 17 h

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
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$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
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$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
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$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
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$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

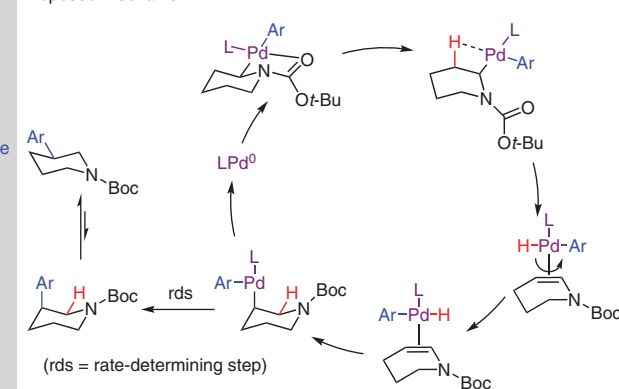
$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

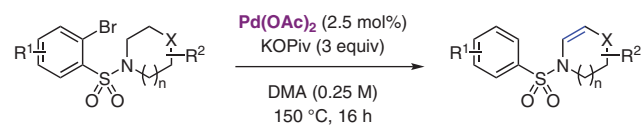
$\beta$ : $\alpha$  = 91:9, 59% ( $\beta$ )  
R = H, Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>

## Proposed mechanism

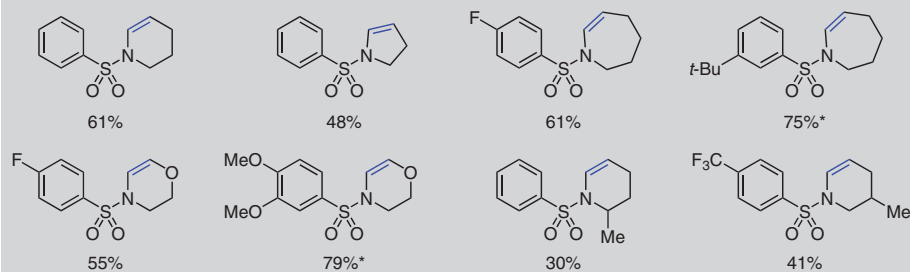
(11f) Baudoin, *Chem. Sci.* **2013**, *4*, 2241.

For a palladium-catalyzed ligand-controlled  $\beta$ -functionalization of Boc-1,3-oxazinanes and its application in the synthesis of  $\beta^2$ -amino acids, see: (11g) Baudoin, *Nat. Catal.* **2019**, *2*, 882.

**Figure 11** Directed  $\alpha$ -C-H bond activation of cyclic amines, followed by  $\beta$ -hydride elimination, part I<sup>11</sup>

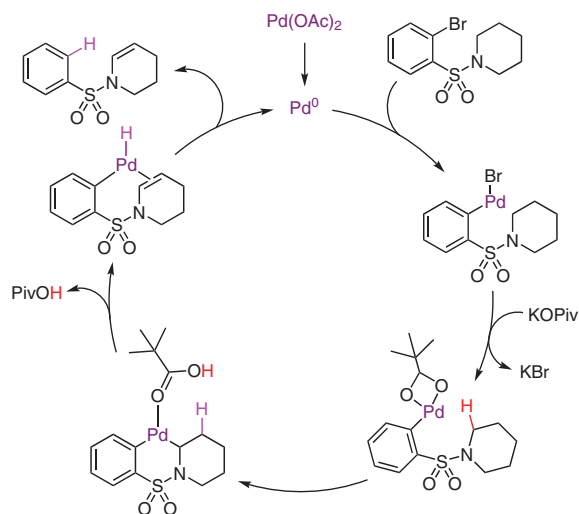


## Selected scope

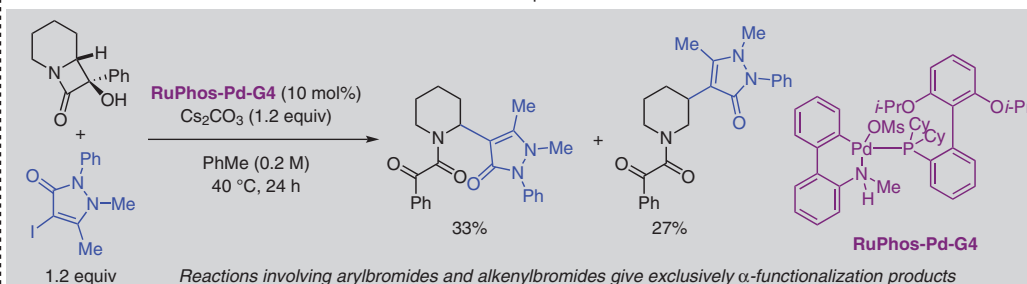
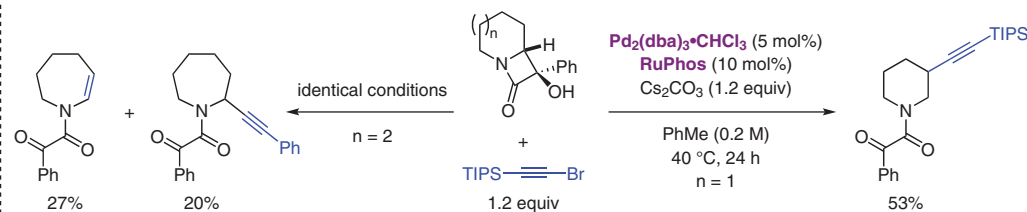


\*  $\text{PdCl}(\text{C}_6\text{H}_5)_2(\text{dppb})$  (5 mol%) is used as the catalyst. **dppb** = 1,4-bis(diphenylphosphino)butane.

## Proposed mechanism

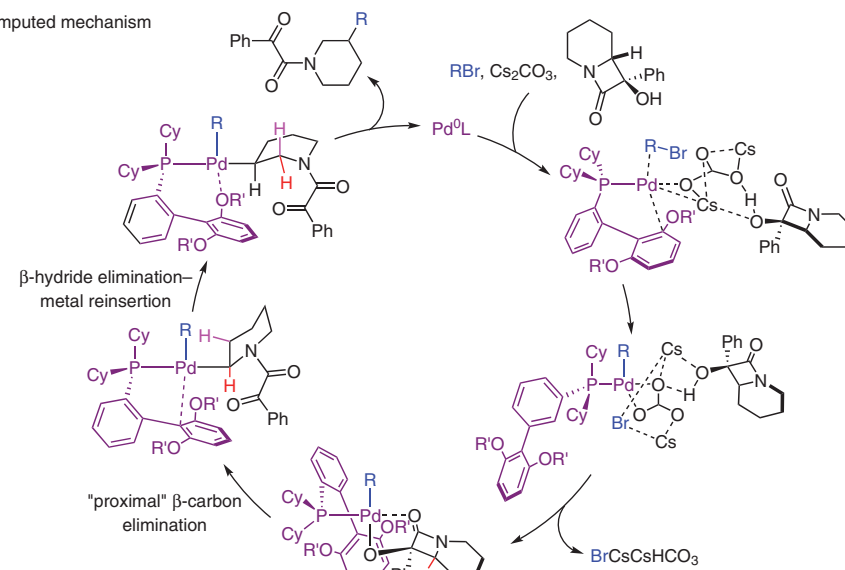


(12a) Doucet, *Adv. Synth. Catal.* **2014**, 356, 119.



Reactions involving arylbromides and alkenylbromides give exclusively  $\alpha$ -functionalization products

## Computed mechanism

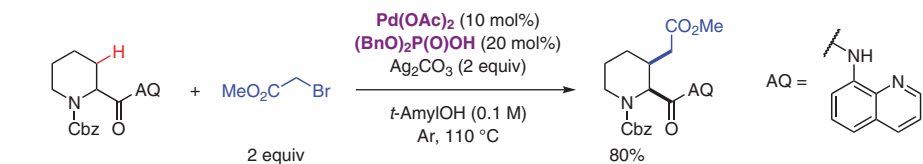


(12b) Musaev, Yeung & Sarpong, *ACS Catal.* **2020**, 10, 2929.

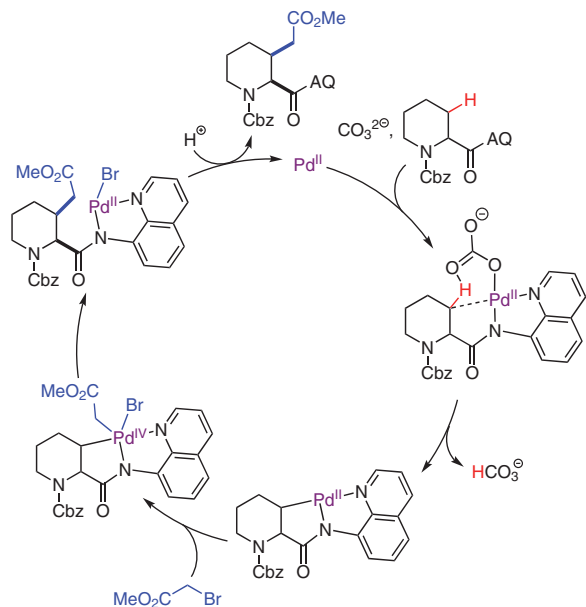
For computational studies on the reactivity and selectivity of this reaction, see: (12c) Sarpong & Musaev, *J. Am. Chem. Soc.* **2020**, 142, 21140.

**Figure 12** Directed  $\alpha$ -C-H bond activation of cyclic amines, followed by  $\beta$ -hydride elimination, part II<sup>12</sup>





Proposed mechanism



The silver cation is speculated to 1) promote the oxidative addition via a  $\text{S}_{\text{N}}2$  pathway; 2) act as a halide scavenger promoting the reductive elimination; and 3) remove the halide from  $\text{Pd}^{\text{II}}$  to regenerate a more active  $\text{Pd}^{\text{II}}$  catalyst.

(13a) Chen, *J. Am. Chem. Soc.* **2013**, *135*, 12135.For a review on the topic of this Figure, see: (1i) Bull, *Synthesis* **2019**, *51*, 3171.

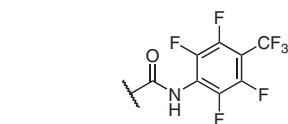
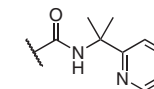
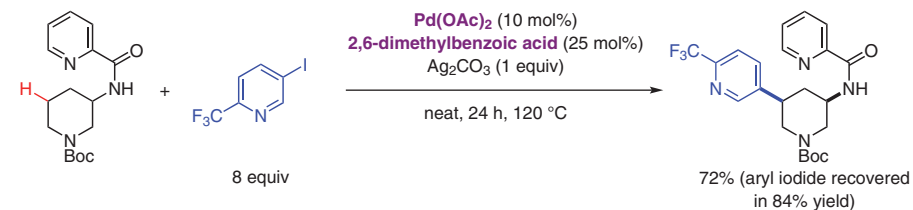
For other reactions using C2-8-aminoquinolinamide as a directing group, see:

(13b) Bull, *Org. Lett.* **2014**, *16*, 4956. (13c) Liu & Zhang, *Eur. J. Org. Chem.* **2015**, 142.(13d) Xu, *Org. Lett.* **2015**, *17*, 3798. (13e) Bull, *Eur. J. Org. Chem.* **2016**, 139.(13f) Cao & Wu, *Asian J. Org. Chem.* **2016**, *5*, 608.(13g) Schreiber, *J. Am. Chem. Soc.* **2017**, *139*, 11300.(13h) Mykhailiuk, *Org. Biomol. Chem.* **2019**, *17*, 4342.

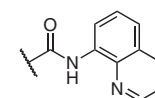
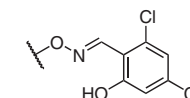
For the application of this method to the synthesis and modification of bioactive compounds, see:

(13i) Wu, *Org. Lett.* **2014**, *16*, 480. (13j) Cao, Dong & Wu, *J. Org. Chem.* **2016**, *81*, 956.(13k) Kazmaier, *J. Org. Chem.* **2016**, *81*, 11646.(13l) Wu, *Tetrahedron Lett.* **2017**, *58*, 606. See also: (13f) and (13g).

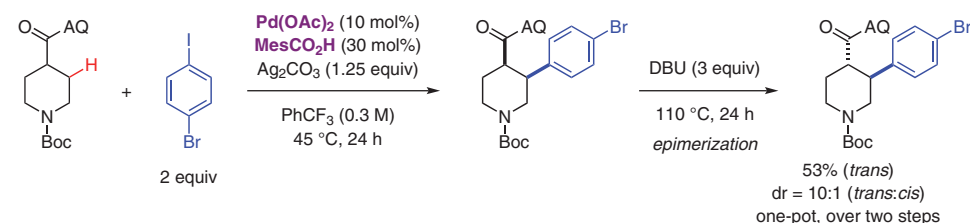
## Other C2-directing groups

(13m) Stamos & Yu, *Chem. Eur. J.* **2016**, *22*, 4748.(13n) Ge, *Org. Lett.* **2015**, *17*, 3738.(13o) Maes, *ACS Catal.* **2016**, *6*, 4486.See also: (13p) Maulide, *Angew. Chem. Int. Ed.* **2018**, *57*, 10737. (13q) Maes, *Angew. Chem. Int. Ed.* **2021**, *60*, 21988.

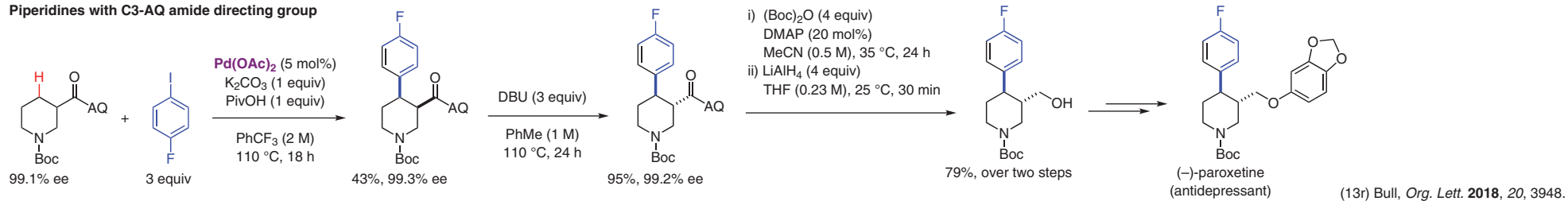
## Other C3-directing groups

(13r) Bull, *Org. Lett.* **2018**, *20*, 3948.(13s) Melillo & Yu, *Angew. Chem. Int. Ed.* **2020**, *59*, 7783.

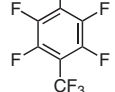
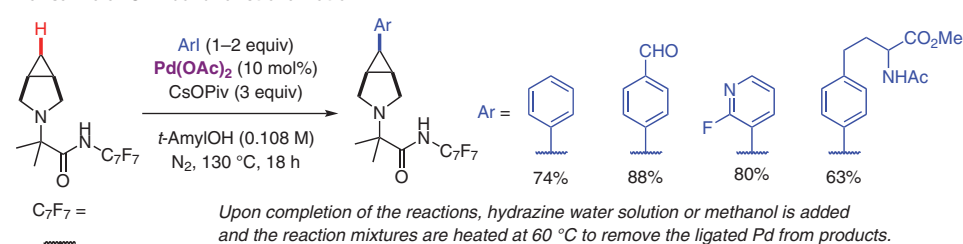
## C4-directing groups

(13t) Bull, *Adv. Synth. Catal.* **2022**, *364*, 1488. See also: (13s)Figure 13 Directed  $\beta$ -C-H bond activation of cyclic amines<sup>13</sup>

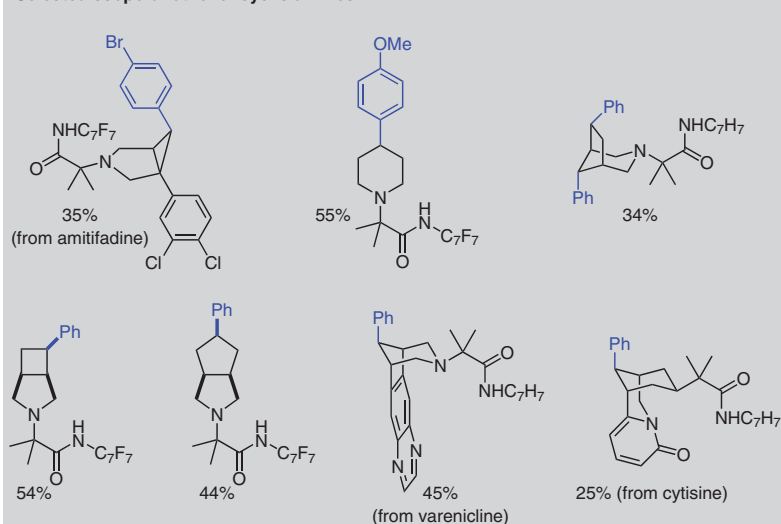
## Piperidines with C3-AQ amide directing group



## Transannular C–H bond functionalization

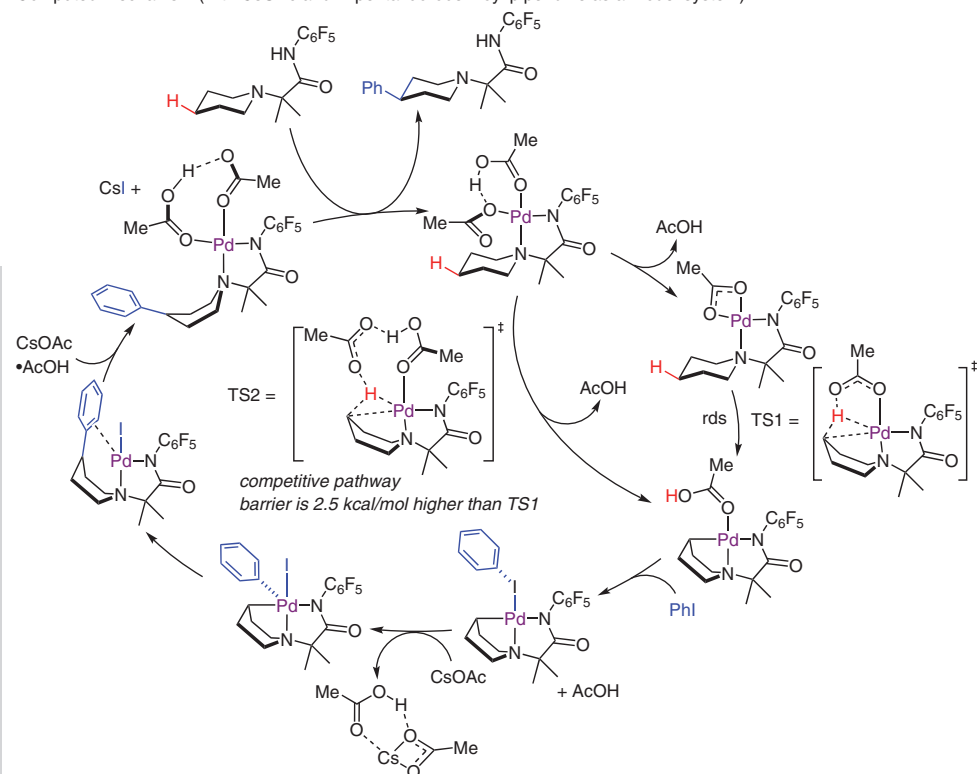


## Selected scope of other alicyclic amines\*



\* 120–150 °C, 20–30 equiv ArI, neat or in *t*-AmylOH under air; work-up with  $\text{NaBH}_4$  if amination product forms.

(14a) Sanford, *Nature* 2016, 531, 220. See also: (14b) Sanford, *Synlett* 2019, 30, 417.

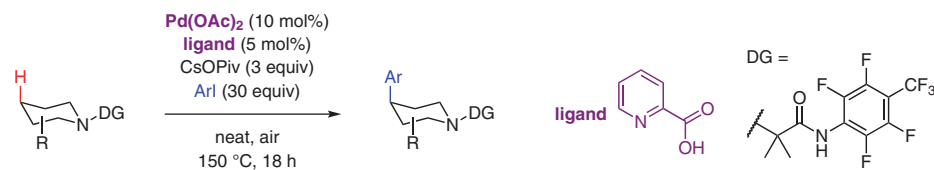
Computed mechanism (with CsOAc and *N*-pentafluorobenzoyl piperidine as a model system)

- Cs salt facilitates the oxidative addition and iodine abstraction steps to regenerate the active catalyst.
- The regeneration of  $\text{Pd}(\text{OAc})_2$  is not expected to occur; the product is directly displaced by another substrate's directing group.

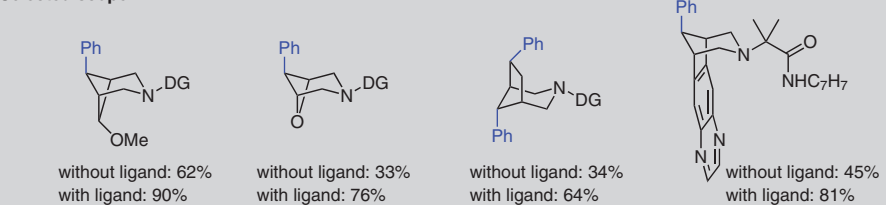
(14c) Zimmerman, *ACS Catal.* 2017, 7, 5466.

For a study on the synthesis of a model complex for this reaction, see: (14d) Sanford, *Organometallics* 2019, 38, 138.

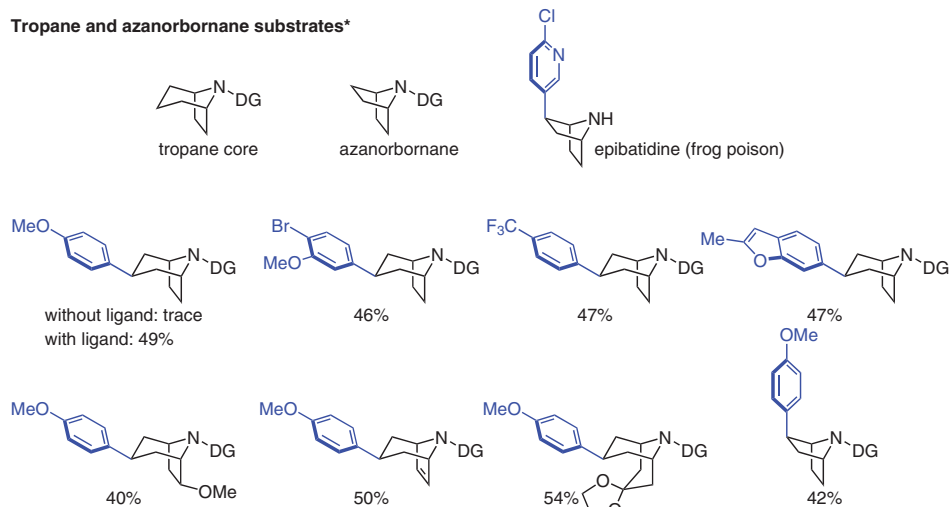
Figure 14 Directed  $\gamma$ - and more remote C–H bond activation of cyclic amines, part I<sup>14</sup>

Transannular C–H functionalization with a 2<sup>nd</sup>-generation Pd catalyst system

## Selected scope



## Tropane and azanorbornane substrates\*



\* 140 °C, 45 equiv ArI; reaction of the azanorbornane substrate is performed with quinoline-2-carboxylic acid as the ligand.

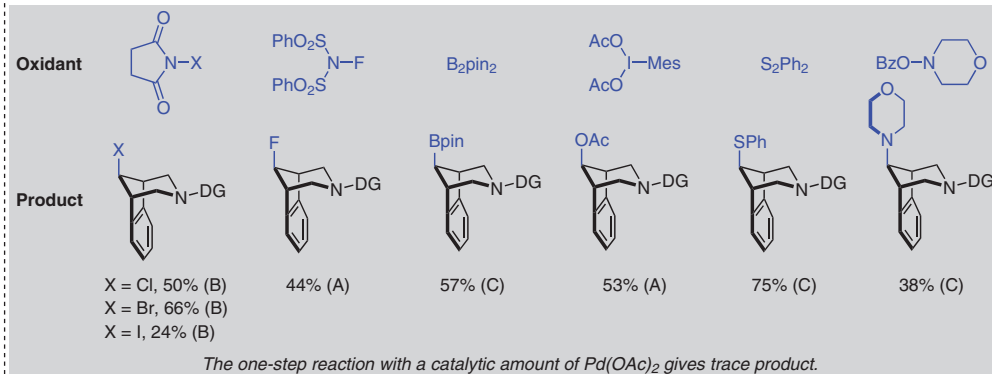
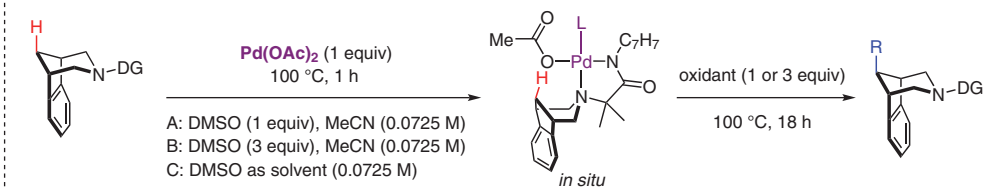
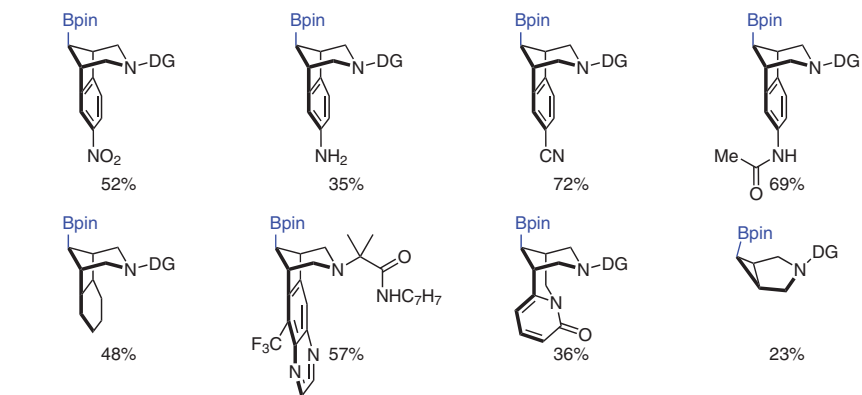
The effect of the ligand is thought to rescue off-cycle Pd species based on experimental studies.

(15a) Sanford, *J. Am. Chem. Soc.* **2018**, *140*, 5599.

For studies on this reaction with an increased substrate scope and its application in medicinal chemistry, see:

(15b) Li, Dechantsreiter & Dandapani, *J. Org. Chem.* **2020**, *85*, 6747.

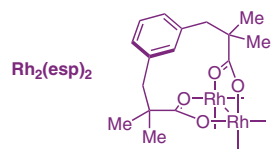
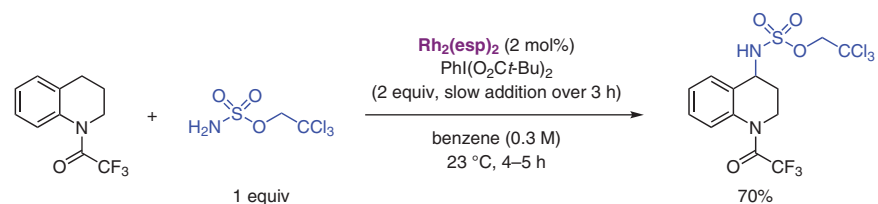
## Introduction of other functional groups

Selected scope of  $\gamma$ -borylation\*

\* Reaction time is 3 h for the borylation step.

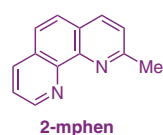
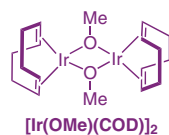
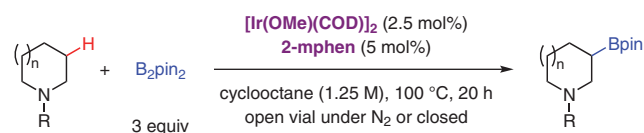
(15c) Sanford, *Angew. Chem. Int. Ed.* **2021**, *60*, 11227.

Figure 15 Directed  $\gamma$ - and more remote C–H bond activation of cyclic amines, part II<sup>15</sup>

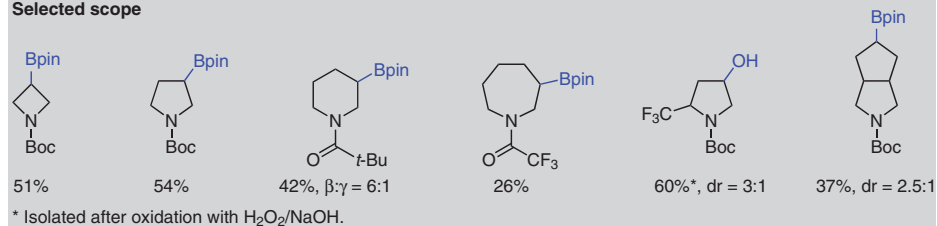


The reaction involves Rh-nitrenoid insertion into the C–H bond.

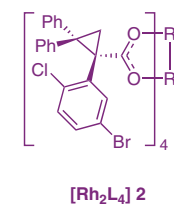
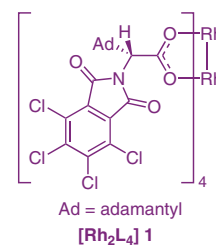
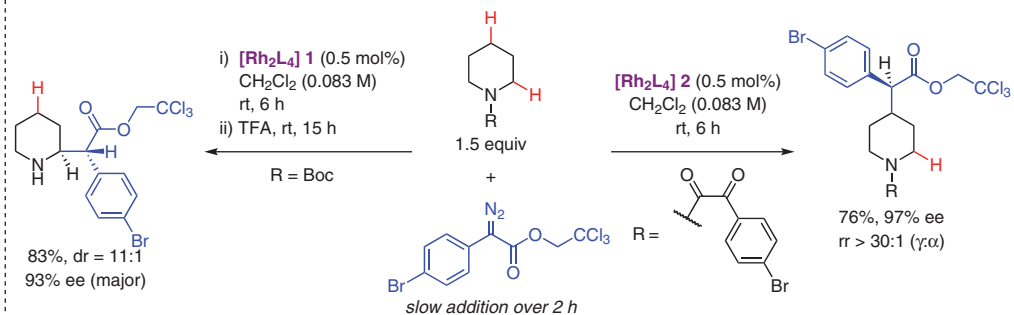
(16a) Du Bois, *J. Am. Chem. Soc.* **2007**, 129, 562.



#### Selected scope

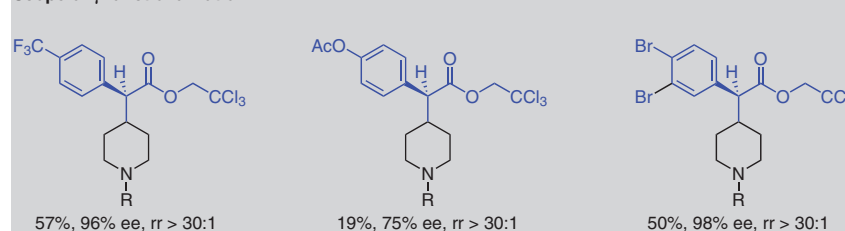


(16b) Hartwig, *Science* **2020**, 368, 736.



A stronger electron-withdrawing protecting group and a sterically more demanding catalyst improves  $\gamma$ - over  $\alpha$ -selectivity.

#### Scope of $\gamma$ -functionalization



(16c) Reiser & Davies, *Chem. Eur. J.* **2020**, 26, 4236.

Figure 16 Undirected remote C–H bond activation of cyclic amines<sup>16</sup>

## Conflict of Interest

The authors declare no conflict of interest.

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