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

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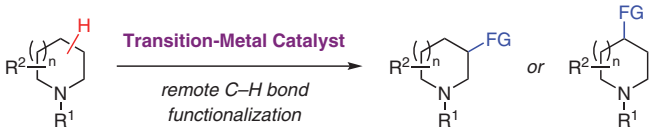

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Crowd-Reviewed

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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 α-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 α-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 α-C–H bonds, while functionalization of more remote C–H bonds, such as β- and γ-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 α-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 α-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.

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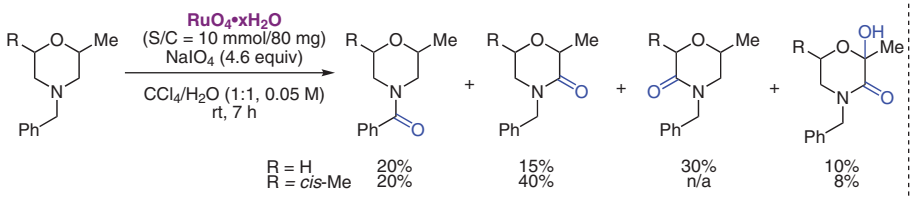
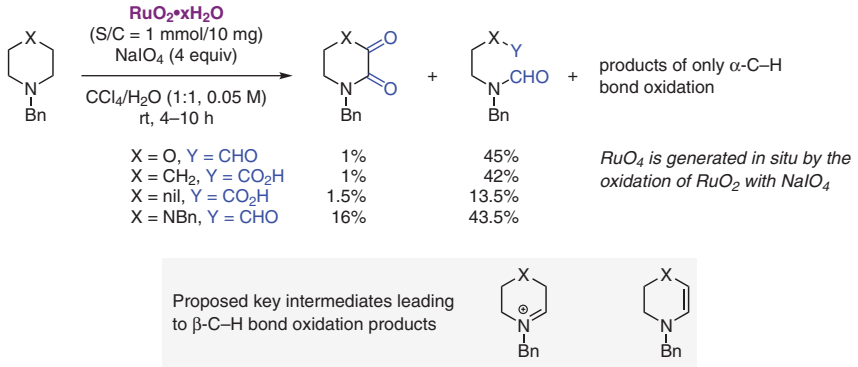
Oxidation of *N*-benzyl morpholines with ruthenium tetroxide (RuO_4)



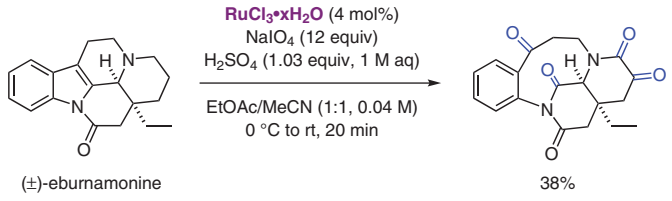
(1a) Tortorella, *Synthesis* **1976**, 598.

Oxidation of other *N*-benzyl cyclic amines with RuO_4



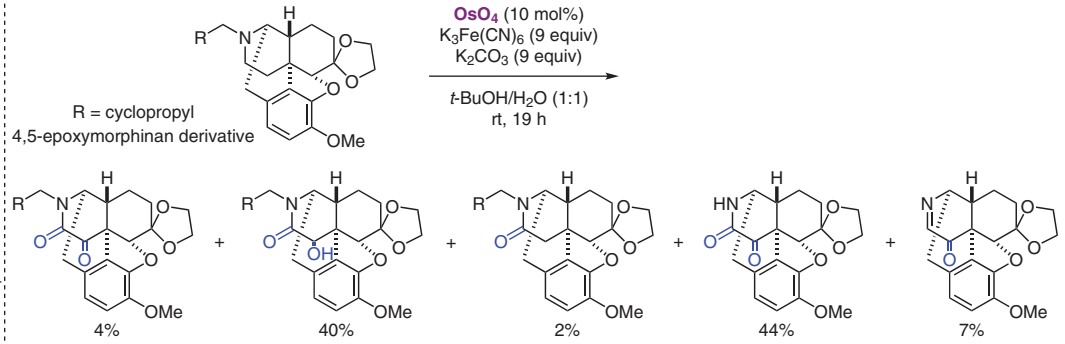
(1b) Petride, *Cent. Eur. J. Chem.* **2004**, *2*, 302.
(1c) Petride, *Cent. Eur. J. Chem.* **2006**, *4*, 674.

Oxidation of natural products

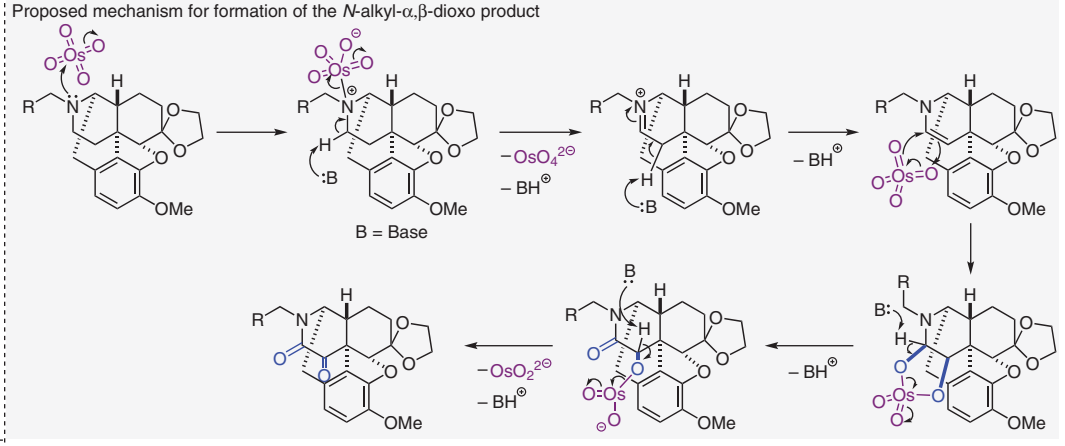


(1d) Westwood, *Org. Lett.* **2012**, *14*, 6166.

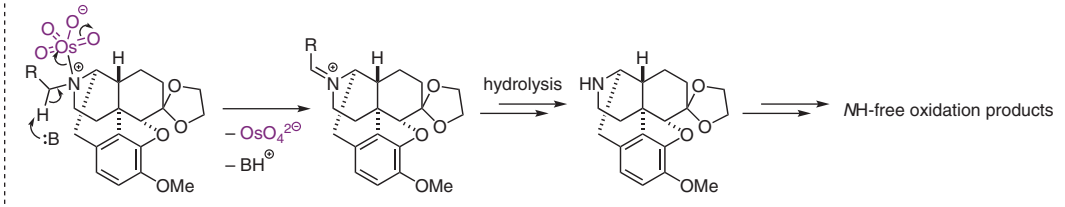
Oxidation with OsO_4



Proposed mechanism for formation of the *N*-alkyl-α,β-dioxo product



Proposed intermediates for the formation of *N*H-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[1]

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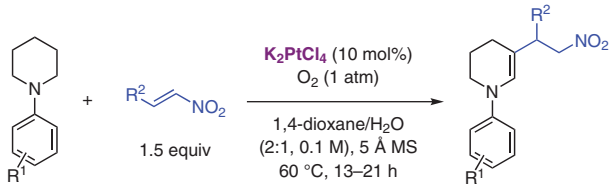
Platinum as catalyst

Dehydrogenative Michael addition/cyclization with nitroolefins

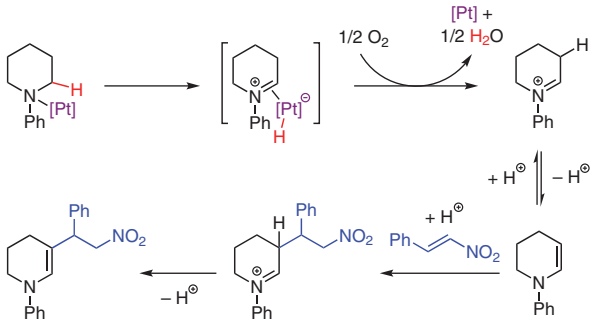


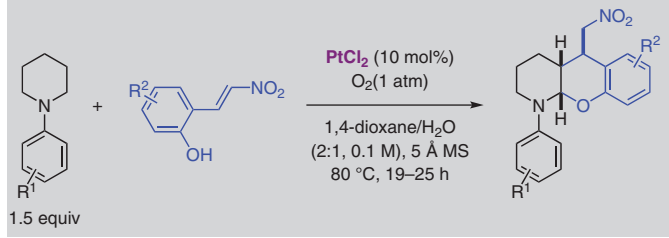
Selected scope

R^1	R^2	% Yield
H	Ph	70
H	2-Me-C_6H_4	46
H	3-Cl-C_6H_4	54
H	4-MeO-C_6H_4	40
H	2-furyl	41
H	Cy	20*
4-MeO	Ph	71
4-Br	Ph	40
4-Me	2-Cl-C_6H_4	68

* Reaction temperature is 80 °C.

Proposed mechanism





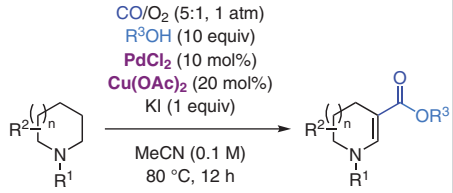
Selected scope

R^1	R^2	% Yield
H	H	65
4-MeO	H	57
4-Br	H	52
2-Bn	H	65
H	5-MeO	62

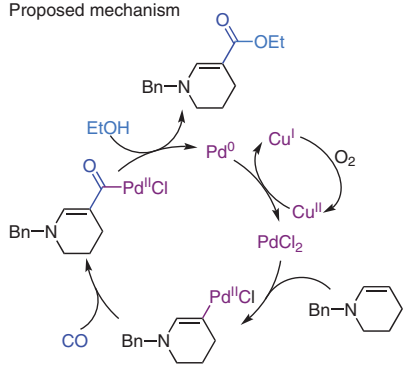
(2a) Liang, *J. Org. Chem.* **2010**, *75*, 2893.
For the hydride abstraction mechanism in Pt(II)-catalyzed reactions involving acyclic secondary and tertiary amines, see: (2b) Brunet, *Organometallics* **2006**, *25*, 2943.

Palladium as catalyst

Dehydrogenative β-alkoxy carbonylation

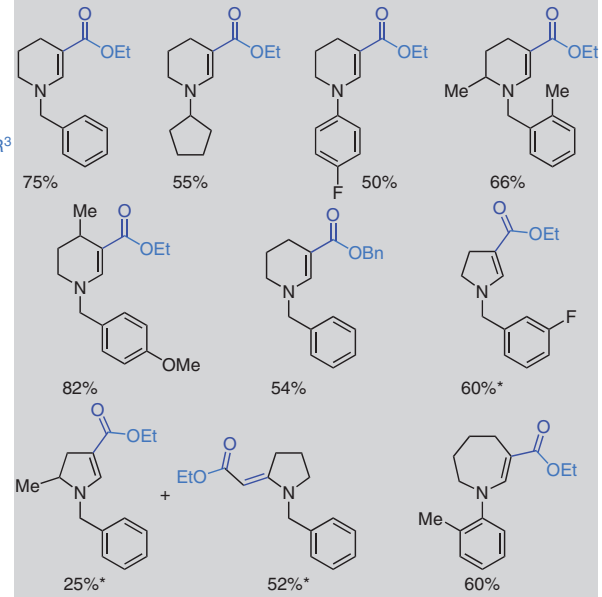


Proposed mechanism

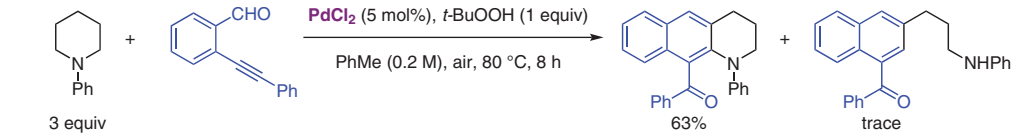


(2c) He & Fan, *Chem. Commun.* **2017**, *53*, 4002.

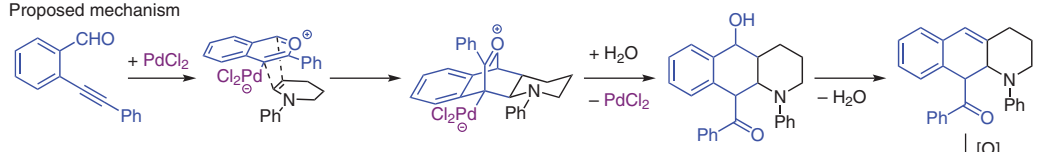
Selected scope



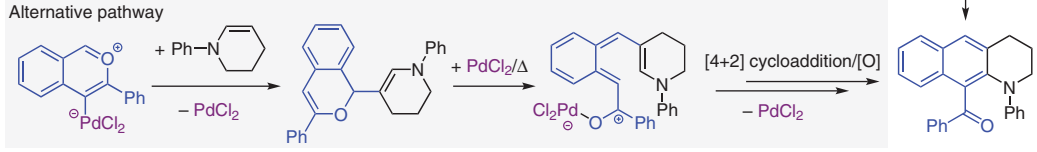
* $Cu(OAc)_2$ (1 equiv) is used under air to avoid over-oxidation forming pyrrole products.



Proposed mechanism



Alternative pathway



(2d) He & Fan, *Org. Lett.* **2020**, *22*, 9053.

Figure 2 Hydride abstraction from cyclic amines, part I[2]

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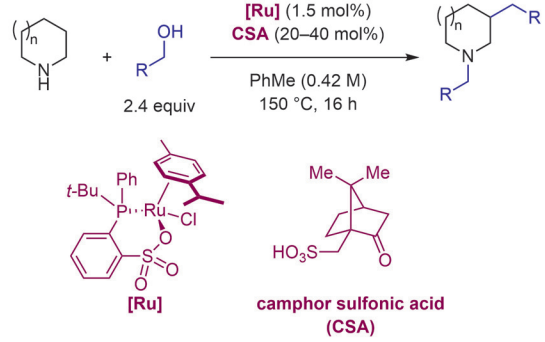
Ruthenium as catalyst

Redox-neutral *N*- and β-dialkylation of secondary cyclic amines with alcohols

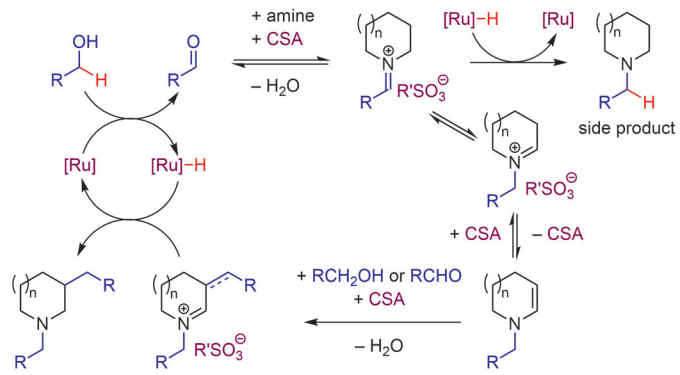


Selected scope

n	R	% Yield
0	Ph	80
0	4-F-C_6H_4	61
0	2-Br-C_6H_4	70
0	*n*-pentyl	50*
1	4-Me-C_6H_4	68
1	2-Cl-C_6H_4	62
1	4-F_3C-C_6H_4	52
2	Ph	68

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

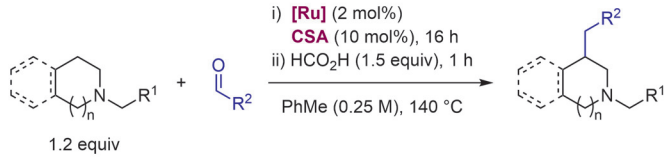
Proposed mechanism



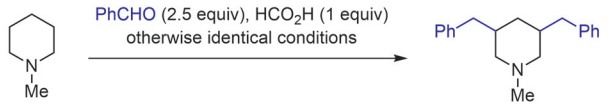
This reaction is an exception of this category – hydride abstraction occurs on primary alcohols.

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

Reductive variant of Ru-catalyzed β-alkylation of tertiary cyclic amines with aldehydes

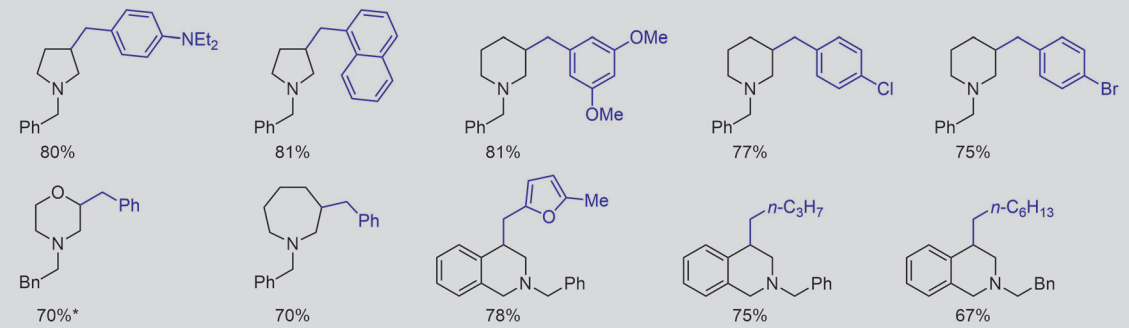


β,β'-Dialkylation of *N*-methylpiperidine



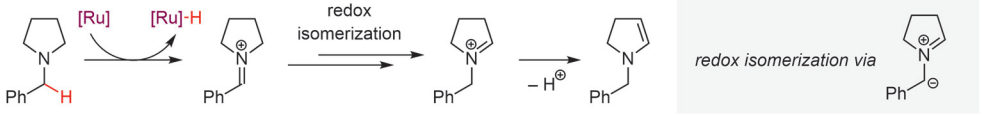
55% (*rac*/*meso* = 37/63)

Selected scope



* Amine is used in 1.1 equiv; HCO_2H (2 equiv)

Proposed mechanism for the formation of an enamine intermediate



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

See also: (3c) Bruneau, *Green Chem.* **2013**, *15*, 775.
For β-alkylation of 1,2,3,4-tetrahydroisoquinolines (THIQ), see: (3d) Bruneau, *J. Org. Chem.* **2012**, *77*, 3674.
For β-alkylation of *N*-alkyl-*N'*-*p*-nitrophenyl piperazines, see: (3e) Suresh, *Adv. Synth. Catal.* **2021**, *363*, 453.
For β-alkylation of cyclic amines catalyzed by ruthenium *N*-heterocyclic carbene (NHC) complexes, see: (3f) Özdemir, *J. Organomet. Chem.* **2015**, *799–800*, 311. (3g) Özdemir, *Organometallics* **2015**, *34*, 2296. (3h) Özdemir, *Tetrahedron* **2018**, *74*, 645. (3i) Kaloğlu, *Tetrahedron* **2019**, *75*, 2265.

Figure 3 Hydride abstraction from cyclic amines, part II[3]

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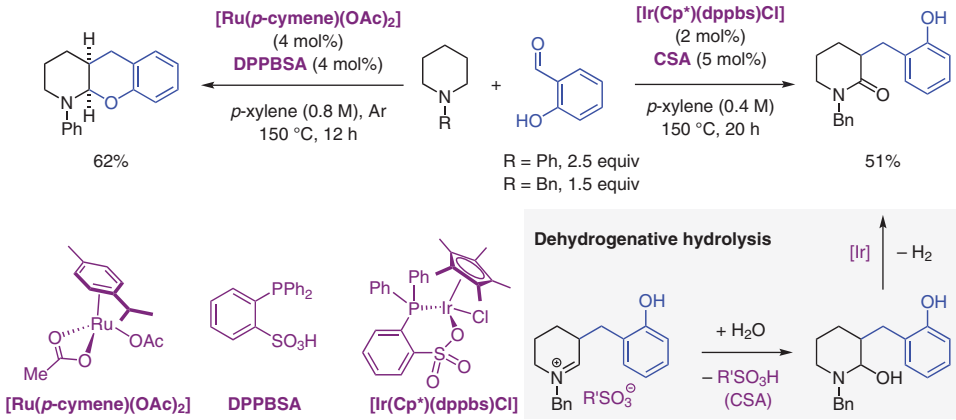
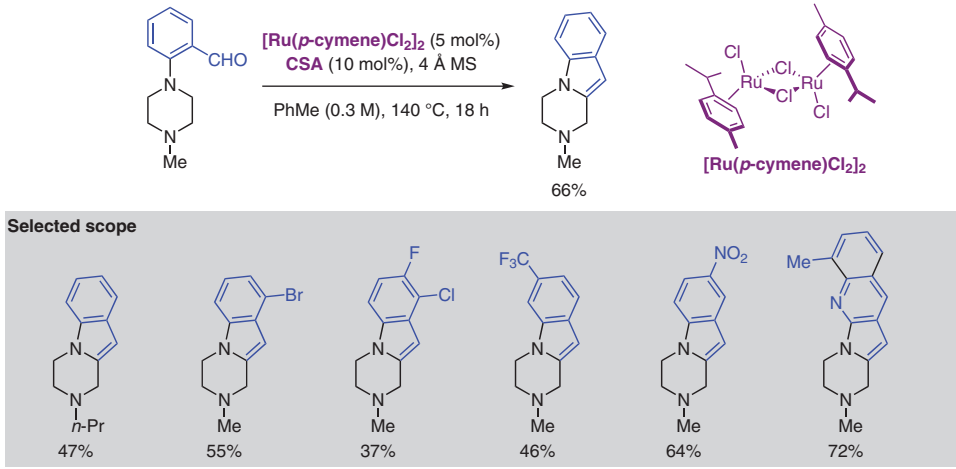
Ru-catalyzed cyclization involving β-C–H bond functionalization

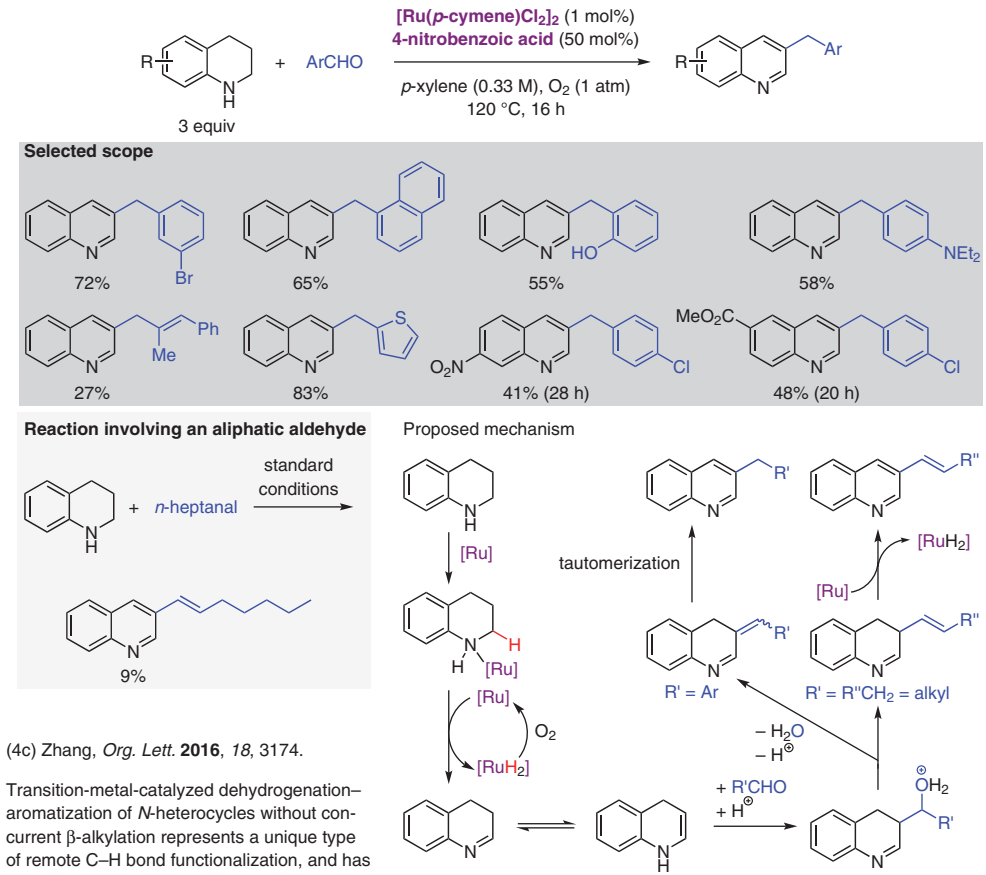


(4a) Achard, *Chem. Eur. J.* **2015**, *21*, 14319.



(4b) Suresh, *Chem. Commun.* **2017**, *53*, 10448.

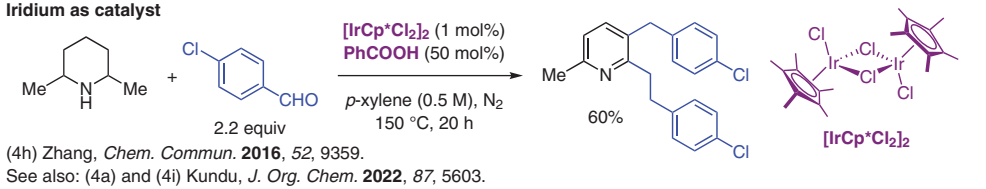
Ru-catalyzed dehydrogenation–aromatization with concurrent β-alkylation



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

Transition-metal-catalyzed dehydrogenation–aromatization of *N*-heterocycles without concurrent β-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[4]

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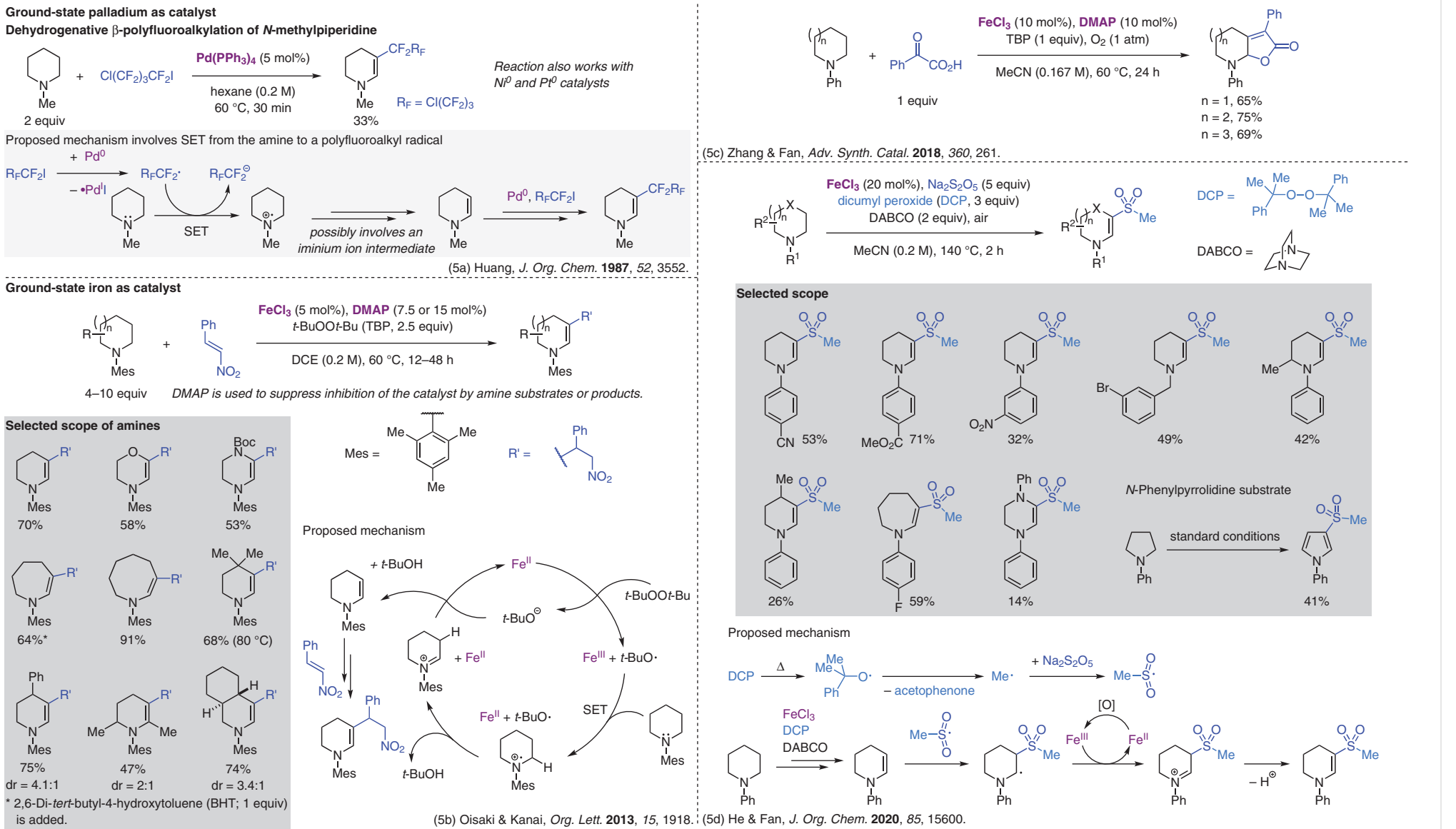

Figure 5 Single-electron transfer (SET) from cyclic amines, part I[5]

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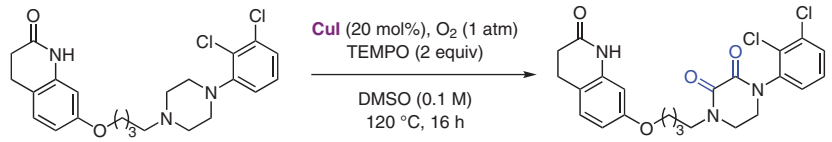
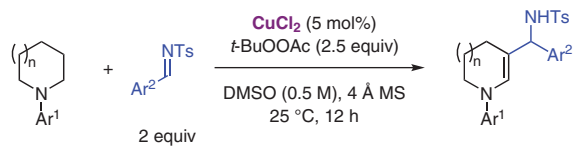
Ground-state copper as catalyst

Cu-catalyzed β-C–H bond oxidation of tertiary cyclic amines in complex pharmaceuticals



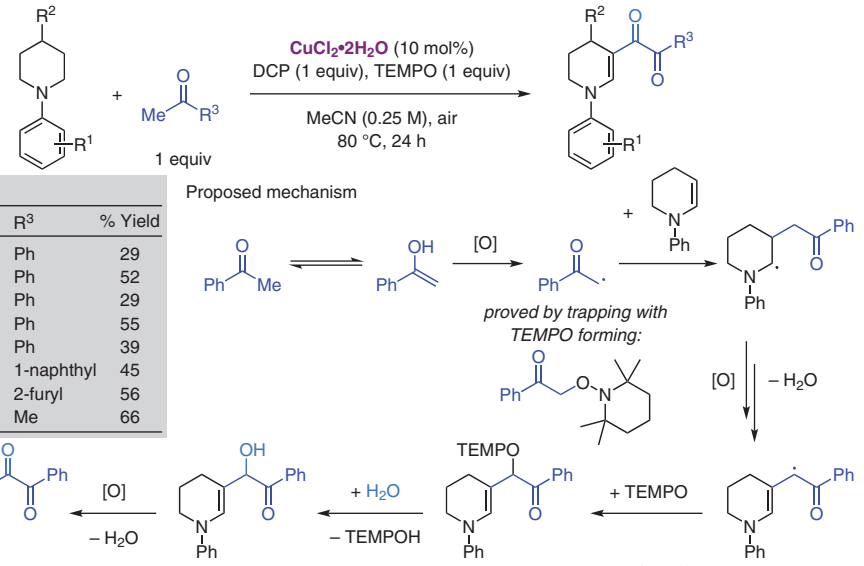
(6a) Touré, *J. Am. Chem. Soc.* **2013**, *135*, 12346.
For related work involving Cu-catalyzed β-C–H bond oxidation of cyclic amines, see also: (6b) Fan, *Tetrahedron Lett.* **2019**, *60*, 151155.



Selected scope

n	Ar¹	Ar²	% Yield
1	Ph	4-F-C_6H_4	81
1	Ph	2-Me-C_6H_4	66
1	Ph	2-naphthyl	81
1	Ph	2-thienyl	51
1	4-Br-C_6H_4	Ph	93
2	Ph	Ph	70

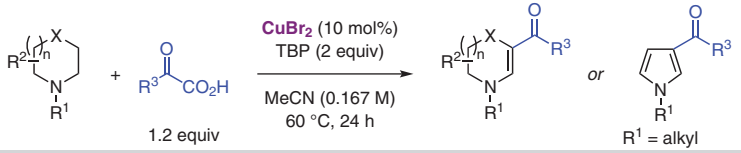
(6c) Zhou, *Chem. Commun.* **2017**, *53*, 8770.



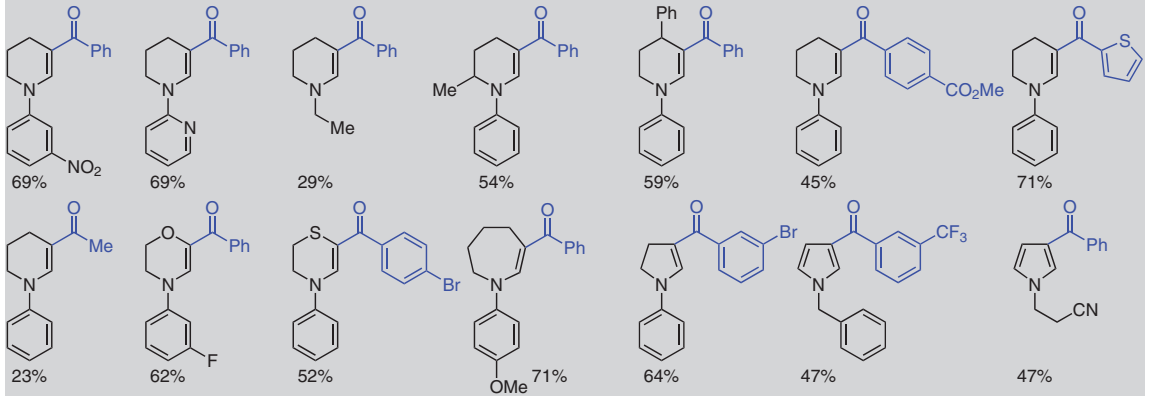
Selected scope

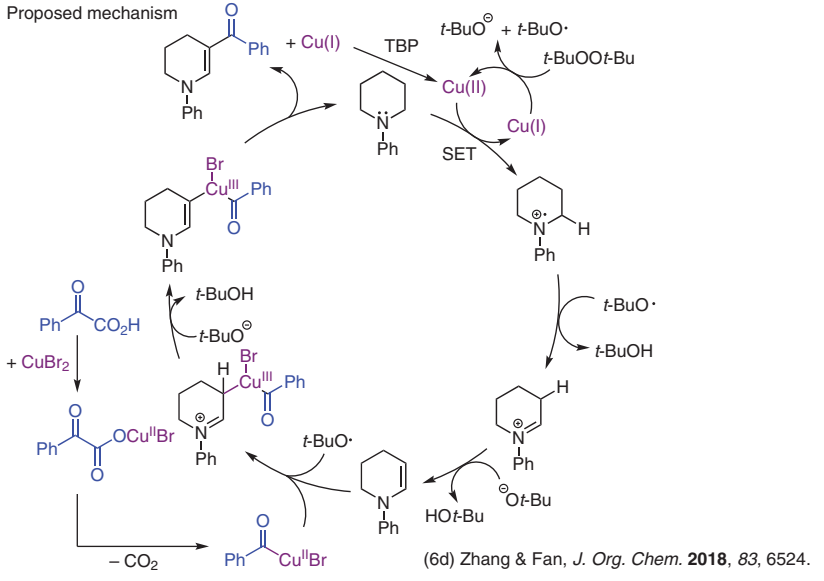
R¹	R²	R³	% Yield
4-F_3C	H	Ph	29
3-Br	H	Ph	52
2-MeO	H	Ph	29
H	Me	Ph	55
H	Ph	Ph	39
H	H	1-naphthyl	45
H	H	2-furyl	56
H	H	Me	66

(6e) Zhang & Fan, *J. Org. Chem.* **2020**, *85*, 2220.



Selected scope





(6d) Zhang & Fan, *J. Org. Chem.* **2018**, *83*, 6524.

Figure 6 Single-electron transfer (SET) from cyclic amines, part II[6]

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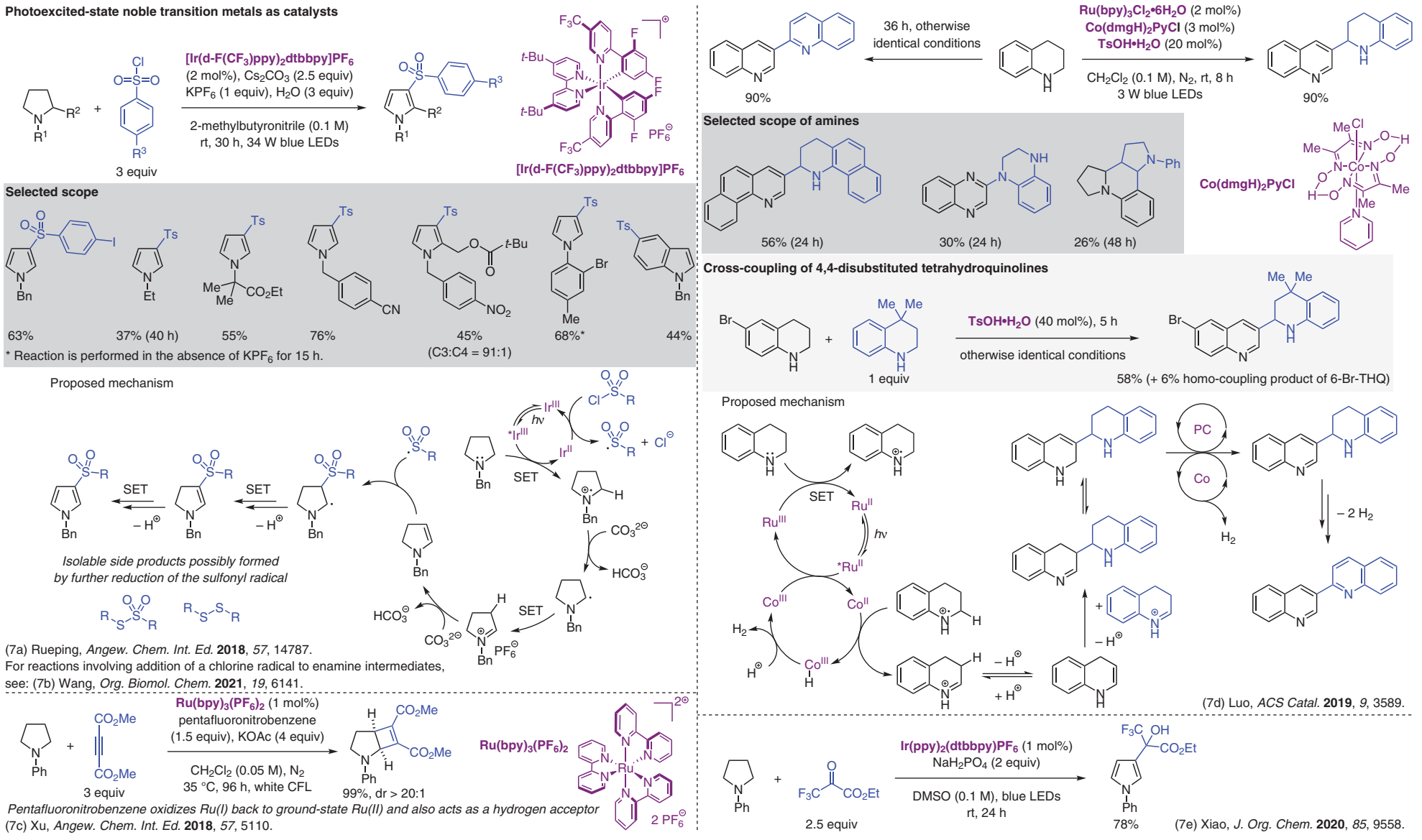

Figure 7 Single-electron transfer (SET) from cyclic amines, part III[7]

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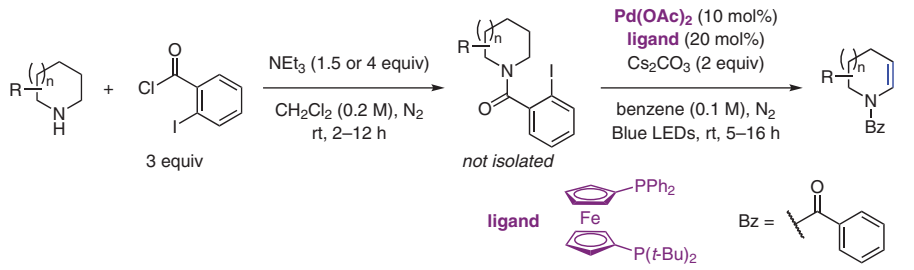
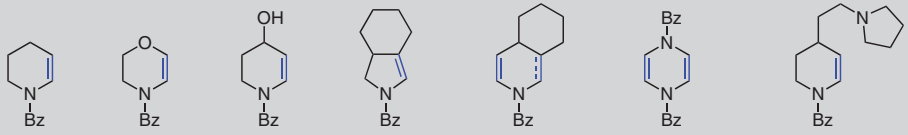


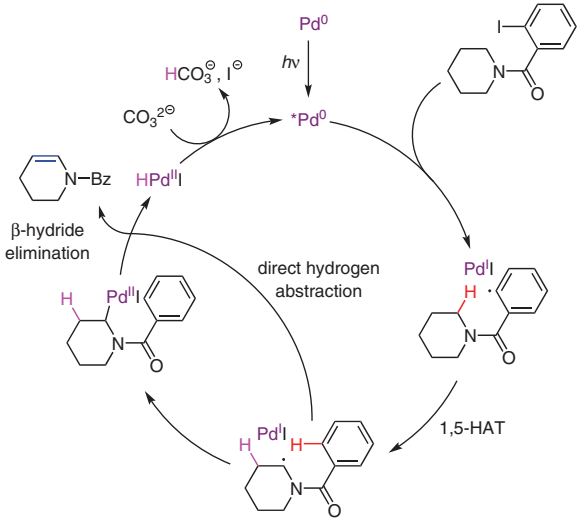
Selected scope



85% 90% 94%* 80% 99%, rr = 1.2:1 72% 64% (NMR yield)

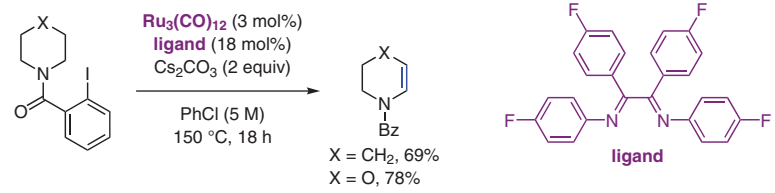
* Yield of the one-step reaction from *N*-(*o*-iodo)benzoyl amine.

Proposed mechanism

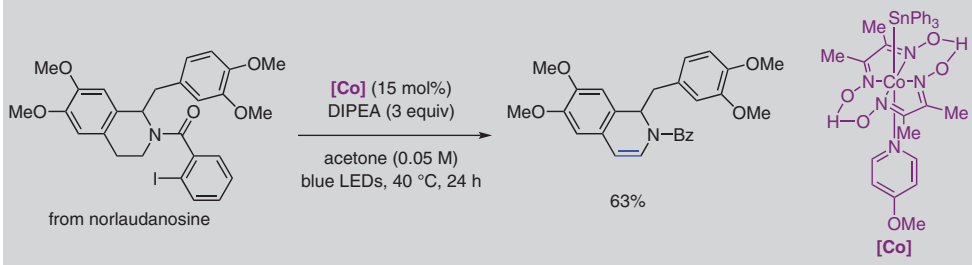


(8a) Gevorgyan, *J. Am. Chem. Soc.* **2018**, *140*, 2465.

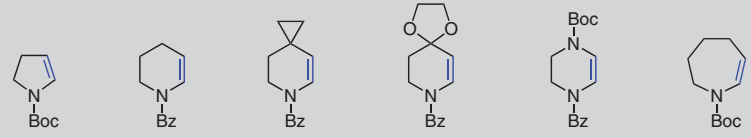
Reactions with a similar mechanism catalyzed by other metals



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



Selected scope of other cyclic amines



90% 95% 93% 83% 85% 88%

(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[8]

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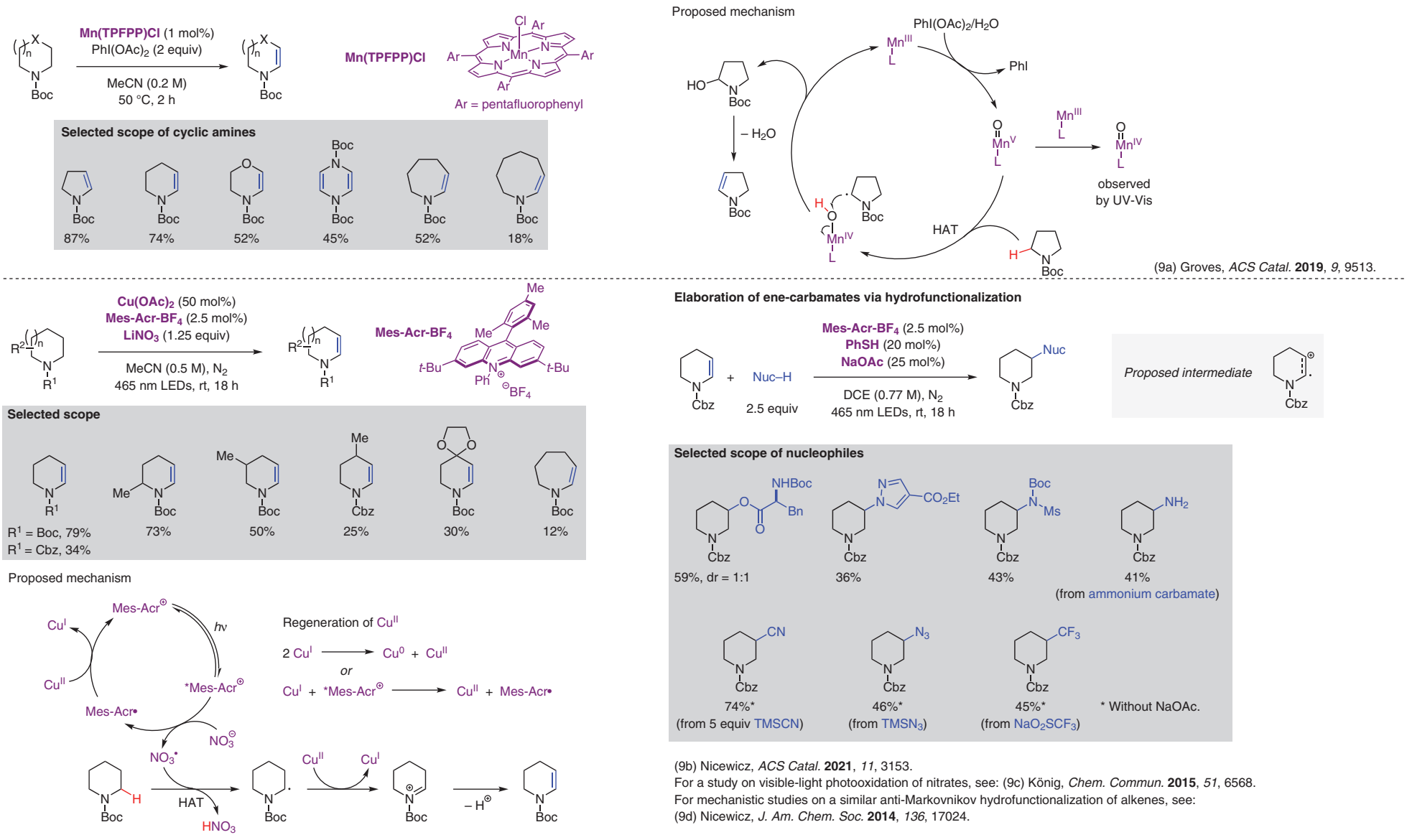

Figure 9 Hydrogen atom transfer (HAT) from cyclic amines, part II[9]

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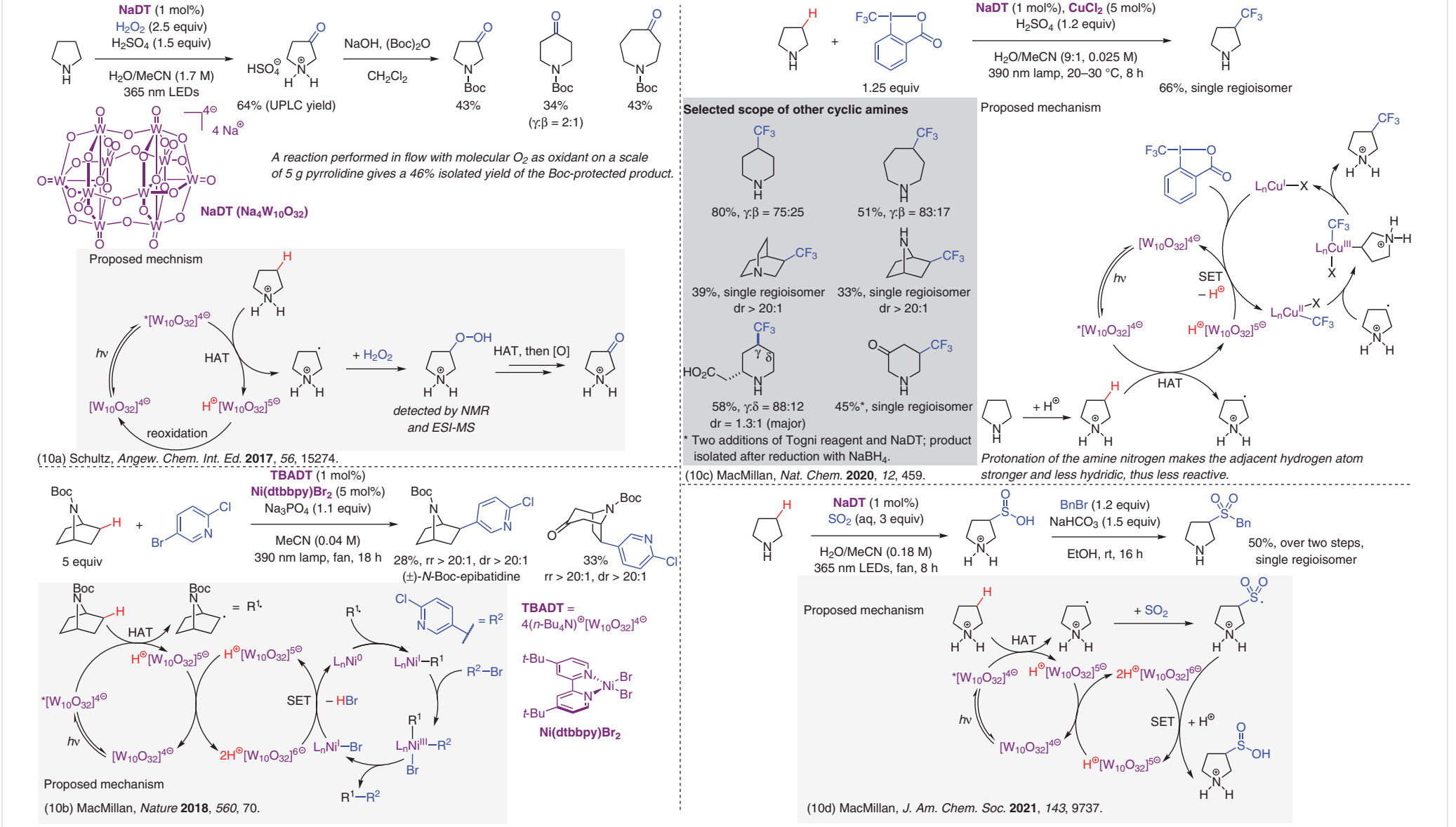

Figure 10 Hydrogen atom transfer (HAT) from cyclic amines, part III[10]

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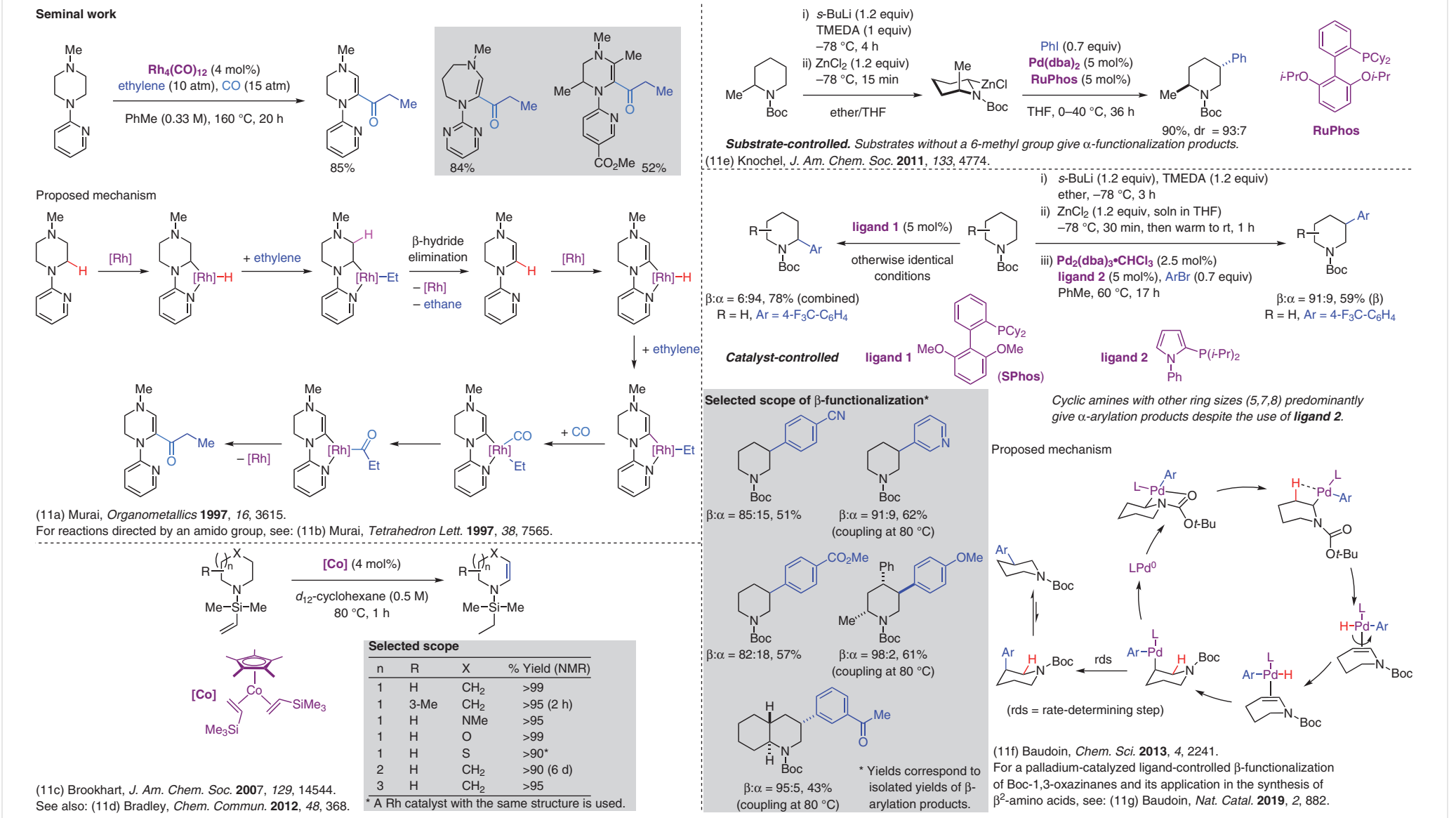

Figure 11 Directed α-C–H bond activation of cyclic amines, followed by β-hydride elimination, part I[11]

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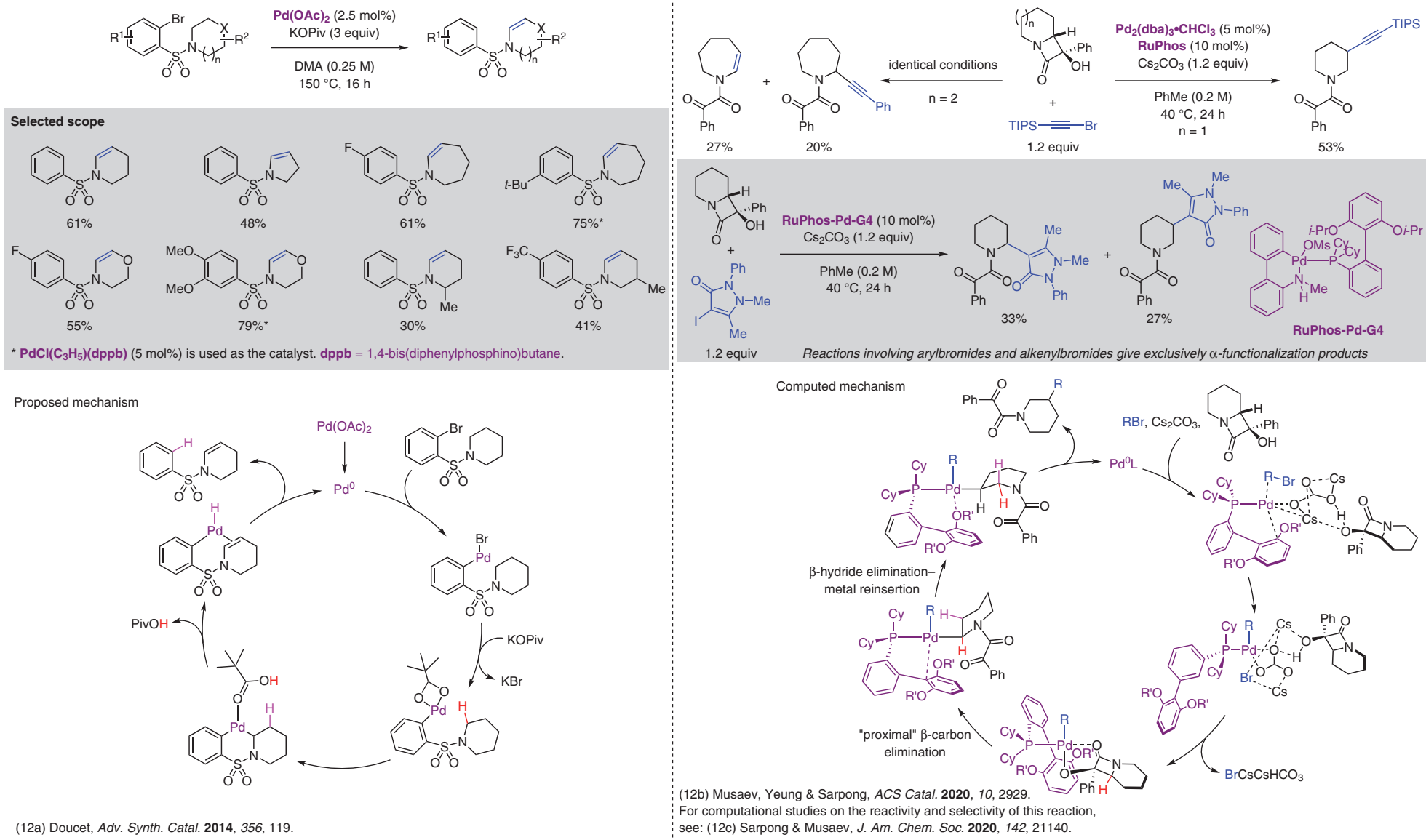
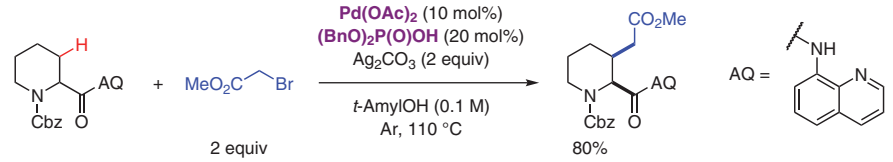
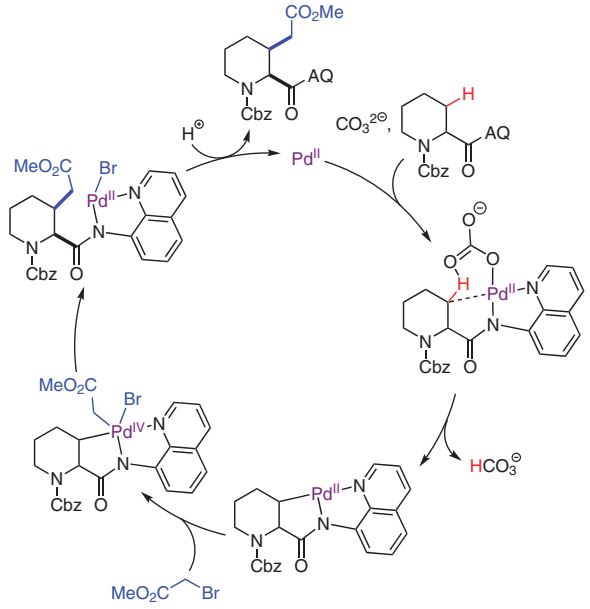


Figure 12 Directed α-C–H bond activation of cyclic amines, followed by β-hydride elimination, part II[12]



Proposed mechanism

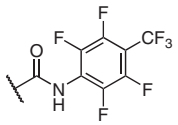


The silver cation is speculated to 1) promote the oxidative addition via a S_N2 pathway; 2) act as a halide scavenger promoting the reductive elimination; and 3) remove the halide from Pd^{II} to regenerate a more active Pd^{II} catalyst.

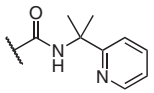
(13a) Chen, *J. Am. Chem. Soc.* **2013**, *135*, 12135.

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. Biomo. 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).

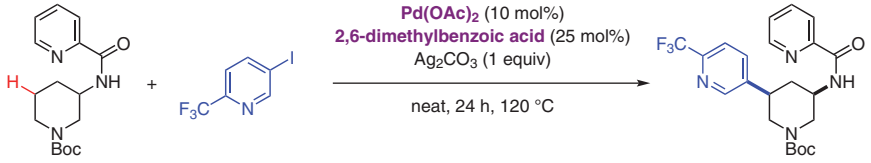
Other C2-directing groups



(13m) Stamos & Yu, *Chem. Eur. J.* **2016**, *22*, 4748.

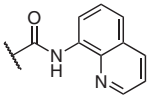


(13n) Ge, *Org. Lett.* **2015**, *17*, 3738.

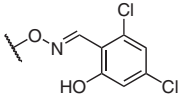


(13o) Maes, *ACS Catal.* **2016**, *6*, 4486.
See also: (13p) Maulide, *Angew. Chem. Int. Ed.* **2018**, *57*, 10737. (13q) Maes, *Angew. Chem. Int. Ed.* **2021**, *60*, 21988.

Other C3-directing groups

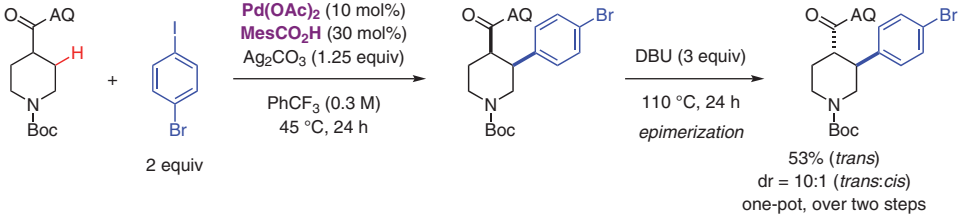


(13r) Bull, *Org. Lett.* **2018**, *20*, 3948.



(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 β-C–H bond activation of cyclic amines[13]

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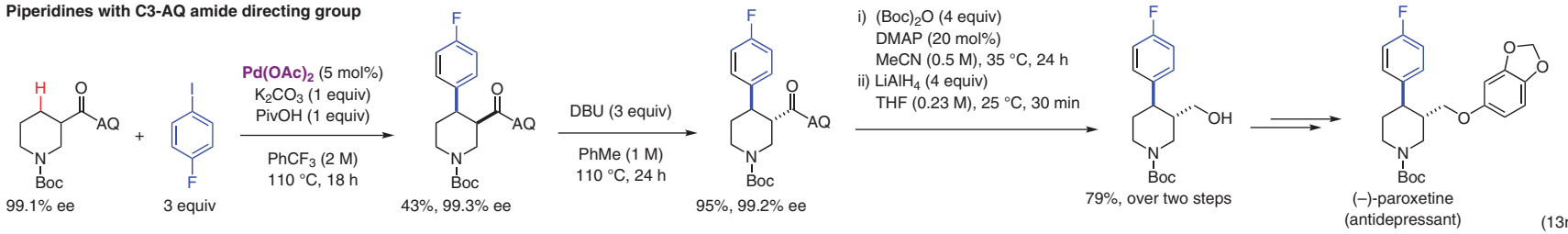
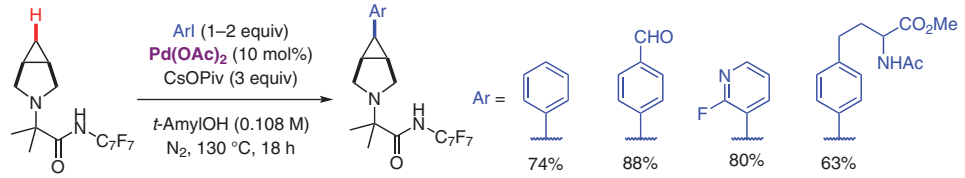
Piperidines with C3-AQ amide directing group

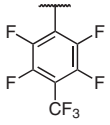


(13r) Bull, *Org. Lett.* **2018**, *20*, 3948.

Transannular C–H bond functionalization

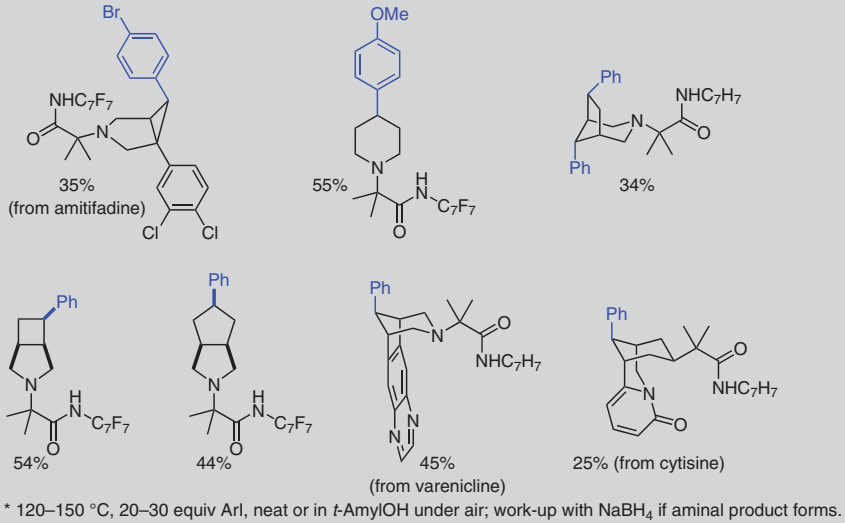


C_7F_7 =



Upon completion of the reactions, hydrazine water solution or methanol is added and the reaction mixtures are heated at 60 °C to remove the ligated Pd from products.

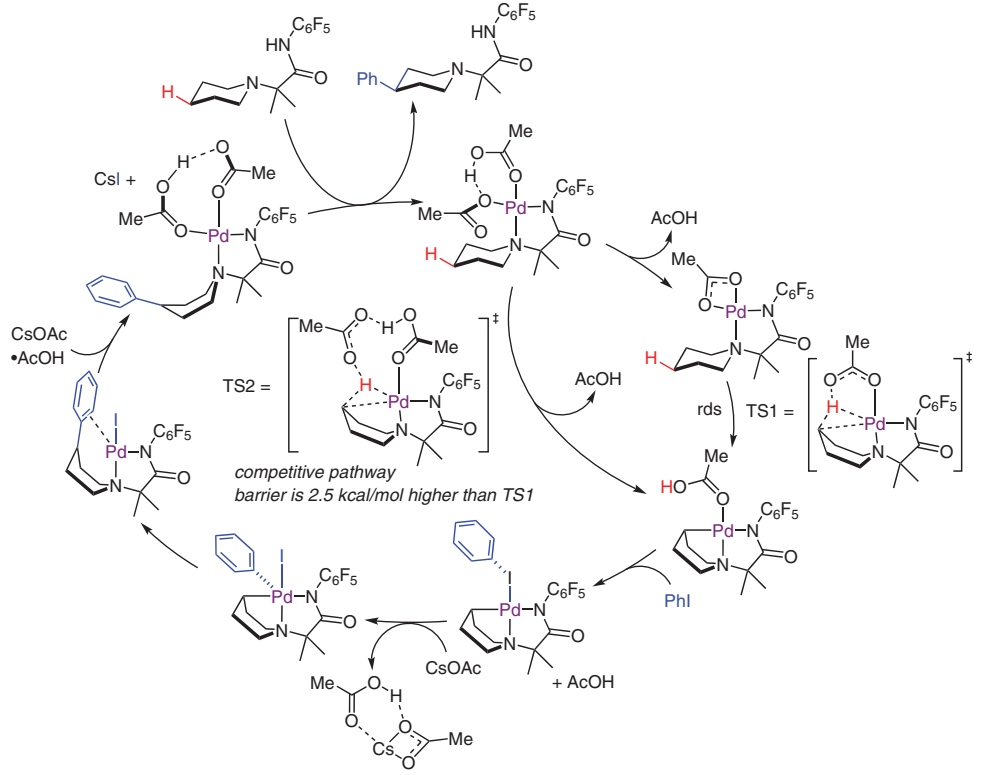
Selected scope of other alicyclic amines*



* 120–150 °C, 20–30 equiv ArI, neat or in *t*-AmylOH under air; work-up with $NaBH_4$ if aminal 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 $Pd(OAc)_2$ 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 γ- and more remote C–H bond activation of cyclic amines, part I[14]

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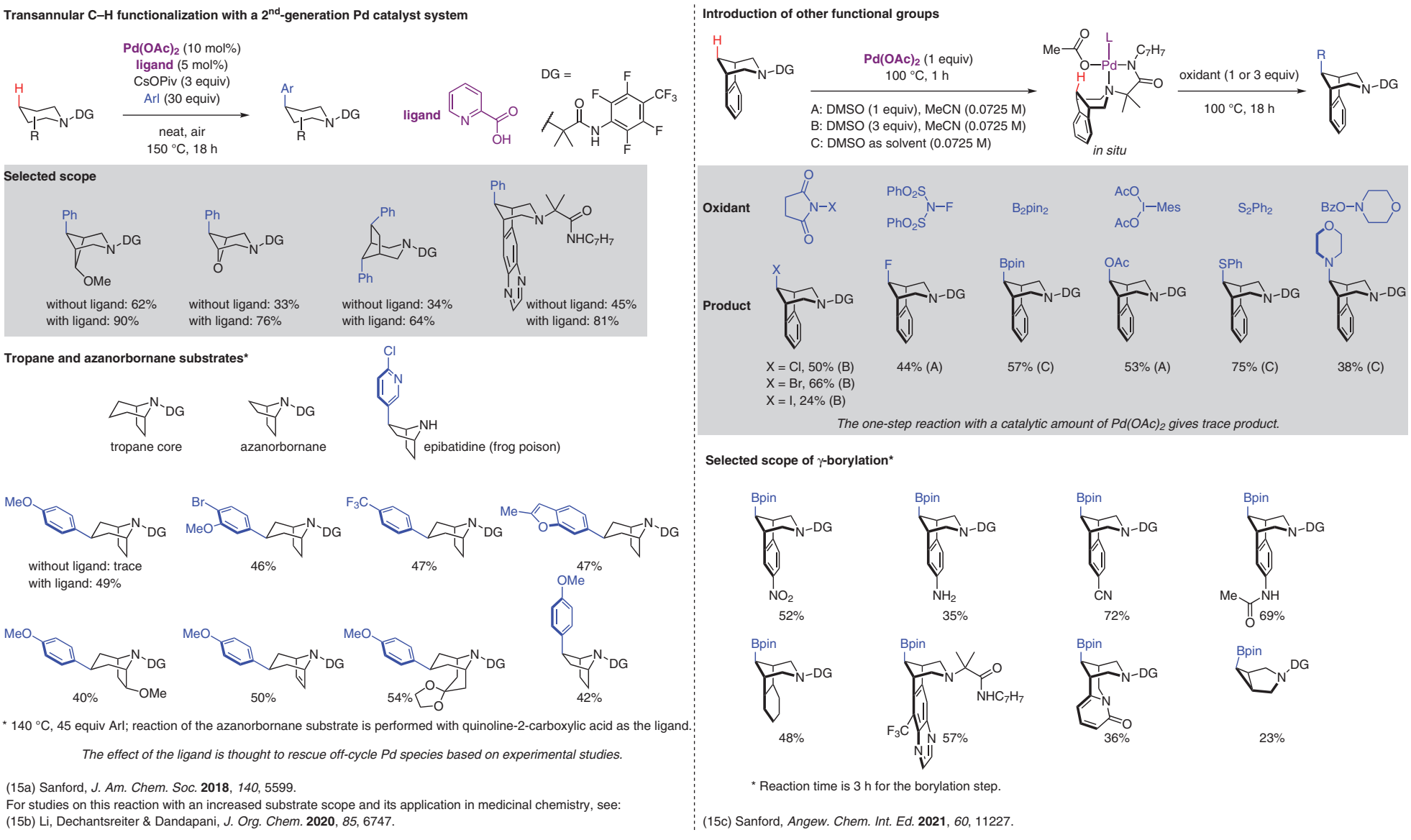

Figure 15 Directed γ- and more remote C–H bond activation of cyclic amines, part II[15]

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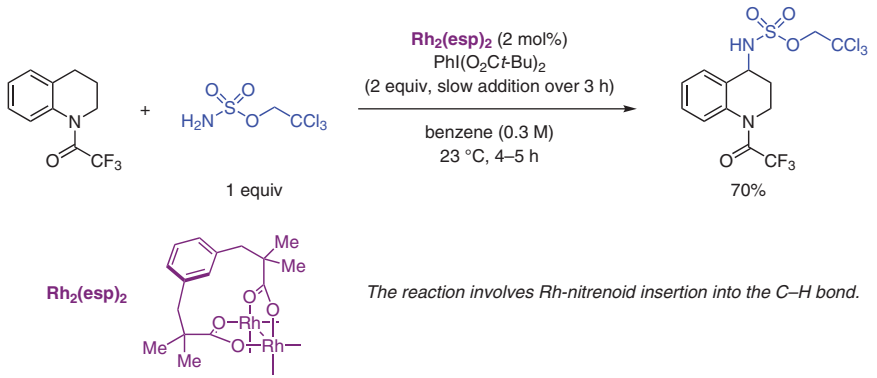
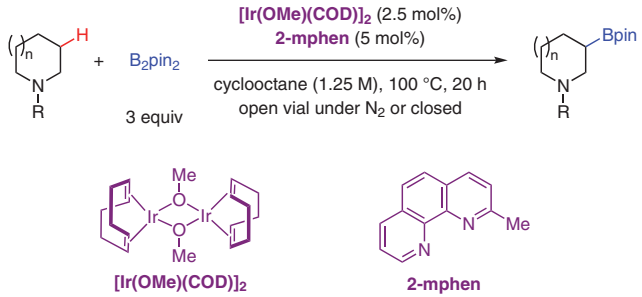
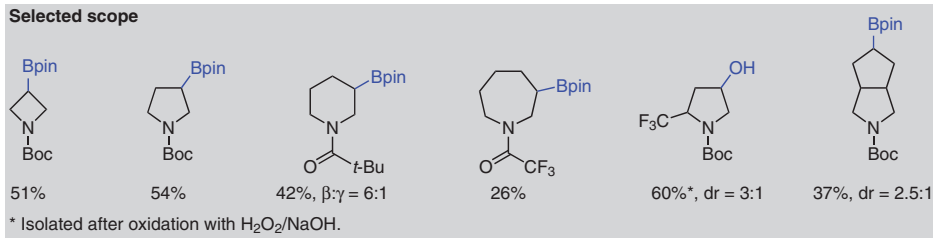
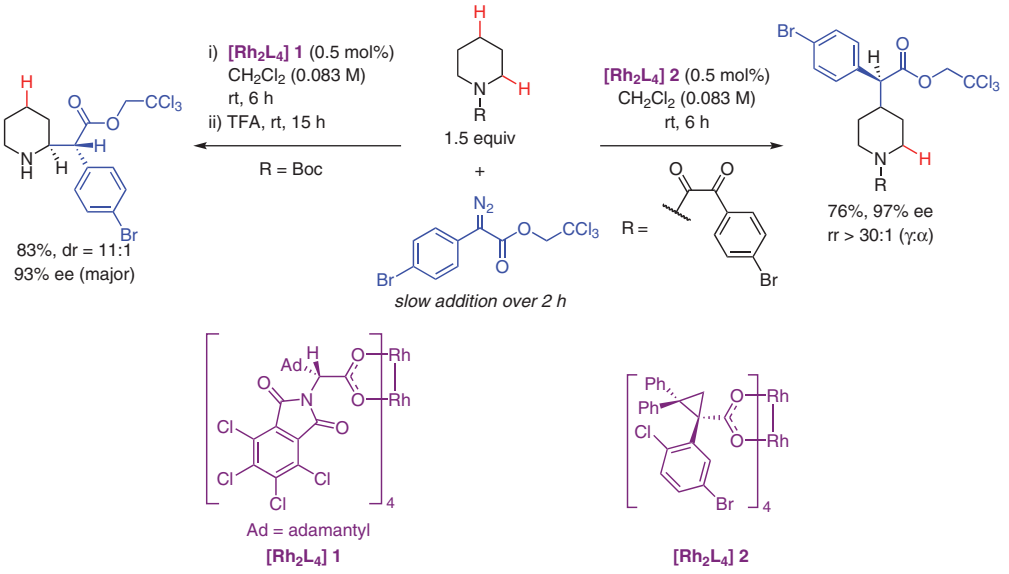


(16a) Du Bois, *J. Am. Chem. Soc.* **2007**, *129*, 562.

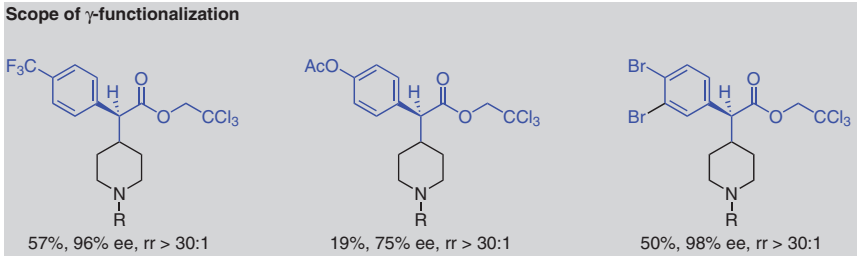




(16b) Hartwig, *Science* **2020**, *368*, 736.



A stronger electron-withdrawing protecting group and a sterically more demanding catalyst improves γ- over α-selectivity.



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

Figure 16 Undirected remote C–H bond activation of cyclic amines[16]

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Conflict of Interest

The authors declare no conflict of interest.

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