

# C–H Bond Functionalization of Amines: A Graphical Overview of Diverse Methods

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Received: 10.06.2021

Accepted: 18.06.2021

Published online: 12.08.2021

DOI: 10.1055/s-0040-1706051; Art ID: so-2021-d0031-gr

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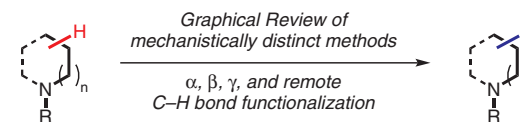
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**Abstract** This Graphical Review provides a concise overview of the manifold and mechanistically diverse methods that enable the functionalization of  $sp^3$  C–H bonds in amines and their derivatives.

**Key words** C–H bond functionalization, amines, heterocycles, catalysis, synthesis

## 1 Introduction

The development of methods for the C–H bond functionalization of amines continues to be a topic of significant interest. Given the potential to lead to real-world applications, coupled with the intellectually stimulating nature of the field, this sustained high level of interest is hardly surprising. A plethora of approaches have emerged over the years, exhibiting significant mechanistic diversity. In addition, an almost overwhelming number of contributions continue to be published at an ever-accelerating pace, making it challenging to keep up with what has already been accomplished, and to put new discoveries into perspective. The rapid speed of development can also obscure what has already been done well versus which transformations need further improvement (regarding scope, ease of use, cost, scalability, etc.), and which worthwhile unsolved challenges remain to be addressed. The goal of this Graphical Review is to provide a concise overview of the manifold methods that achieve the functionalization of  $sp^3$  C–H



bonds in amines and their protected derivatives (e.g., amides, carbamates, *N*-aryl amines, etc.). We aim to cover the most important methods while highlighting the underlying mechanisms. Throughout, we have attempted to trace the origin of each approach back to a seminal report or important literature precedent. A focus is placed on historical contributions, key innovations, and the most recent cutting-edge advances. While reactions are grouped by mechanism, clear categorization of a given process is not always possible. Clearly, certain transformations would fit well into different categories. Due to the format of this review and the vast number of contributions published to date, this overview could not possibly be comprehensive, nor does it aim to be. Coverage extends to the end of 2020, with selected contributions from early 2021. We hope that this review will offer something of value to novices and experts alike. Feedback from the community is welcomed, so that a future, updated version of this review can be improved upon.

Regarding the structure of this Graphical Review, abbreviated references including prior reviews are provided within the Figures at the appropriate places. Full references are shown in the reference section and are grouped by Figure number. A note on the use of color: Amine substrates are shown in black, while groups that are being added are colored in light or dark blue. Catalysts are shown in purple or green. Other colors are used on occasion to highlight certain aspects (e.g., green for directing groups, red for hydrogens that are being functionalized, and orange for curly arrows).



(from left to right) **Subhradeep Dutta** was born and raised in West Bengal, India. He earned a B.Sc. degree in chemistry from Calcutta University (India) in 2016 and an M.Sc. degree in chemistry from the Indian Institute of Technology Kanpur (IITK) in 2018 under the guidance of Prof. Basker Sundararaju. In August 2018, he moved to the University of Florida (USA) for his graduate studies, joining the group of Prof. Daniel Seidel. His research focuses on developing methods towards the C–H bond functionalization of cyclic amines.

**Bowen Li** was born and raised in Shandong, P. R. of China. He earned a B.Sc. degree in the School of Chemistry and Chemical Engineering at Shanghai Jiao Tong University (P. R. of China) working with Prof. Wanbin Zhang. In 2019, he moved to the University of Florida (USA) for his graduate studies, joining the group of Prof. Daniel Seidel. His research focuses on asymmetric catalysis and C–H bond functionalization.

**Dillon Rickertsen** was born in Denver, Colorado, USA. He earned a B.Sc. degree in the Department of Chemistry at the University of Colorado, Denver (USA), working with Prof. Scott Reed. In 2019, he moved to the University of Florida for his graduate studies, joining the group of Prof. Daniel Seidel. His research is focused on developing methodologies for the C–H bond functionalization of amines.

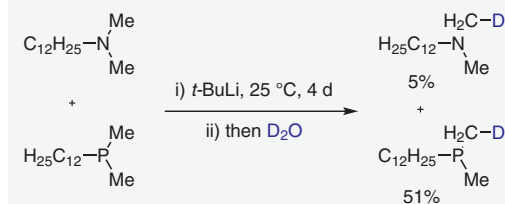
**Daniel Valles** was born in Caracas, Venezuela and raised in Weston, Florida, USA. He attended the California Institute of Technology (Caltech) (USA) working with Prof. Peter Dervan, Prof. Sarah Reisman, and Dr. Scott Virgil. In 2018, he started his Ph.D. research at the University of Florida under the direction of Prof. Daniel Seidel. His research focuses on the functionalization of C–H bonds on cyclic amines.

**Daniel Seidel** studied chemistry at the Friedrich-Schiller-Universität Jena (Germany) and at the University of Texas at Austin (USA) (Diplom 1998). He performed his graduate studies in the lab of Prof. Jonathan L. Sessler, obtaining his Ph.D. in 2002. From 2002–2005, he was an Ernst Schering Postdoctoral Fellow in the group of Prof. David A. Evans at Harvard University (USA). He started his independent career at Rutgers University (USA) in 2005 and was promoted to Associate Professor in 2011 and Full Professor in 2014. In the summer of 2017, his research group moved to the University of Florida (USA).

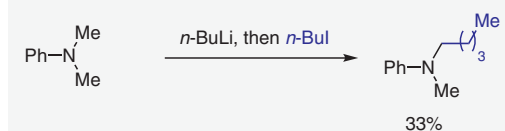
## Notable features

- No protection and deprotection steps required.
- Regioselectivity controlled by the base.
- For Lewis acid activated tertiary amines, deprotonation, electrophile capture, and decomplexation are generally carried out in one pot.

## Seminal studies



(1a) Peterson, *J. Org. Chem.* **1965**, *30*, 1939.



(1b) Lepley, *J. Org. Chem.* **1966**, *31*, 2055.

## Further reading

Additional seminal work:

(1i) Lepley, *J. Org. Chem.* **1966**, *31*, 2061.

(1j) Lepley, *Chem. Commun. (London)* **1967**, 1198.

Reviews on  $\alpha$ -deprotonation and functionalization:

(1k) Kessar, *Chem. Rev.* **1997**, *97*, 721.

(1l) Katritzky, *Tetrahedron* **1998**, *54*, 2647.

Deprotonation and functionalization of other Lewis acid amine complexes:

(1m) Mioskowski, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 430.

(1n) Vedejs, *J. Am. Chem. Soc.* **1997**, *119*, 6941.

(1o) Simpkins, *Tetrahedron* **1998**, *54*, 12923.

(1p) Kessar, *J. Am. Chem. Soc.* **2007**, *129*, 4506.

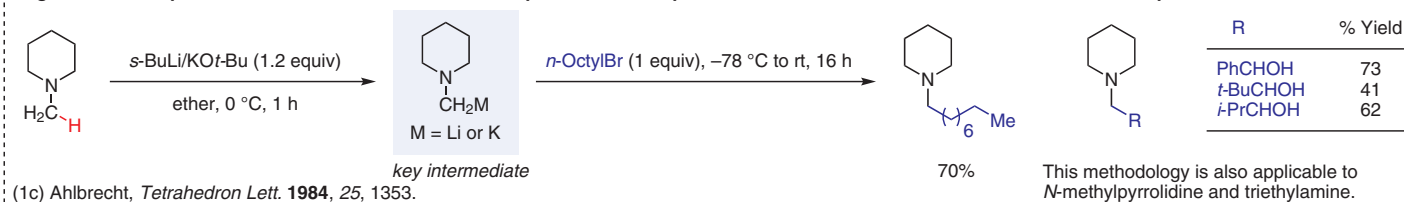
Other applications of the deprotonation methodology:

(1q) Harmata, *Tetrahedron Lett.* **1996**, *37*, 6267.

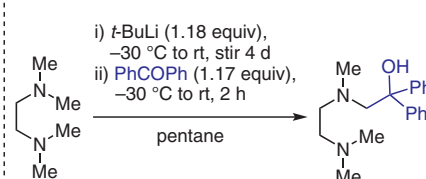
(1r) Kovács, *J. Org. Chem.* **2019**, *84*, 7100.

(1s) Kovács, *J. Org. Chem.* **2020**, *85*, 11226.

## Regioselective deprotonation and functionalization in the presence of a superbases

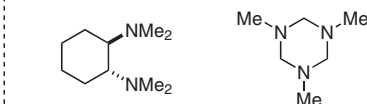


## Intramolecular activation of amines containing a second donor atom

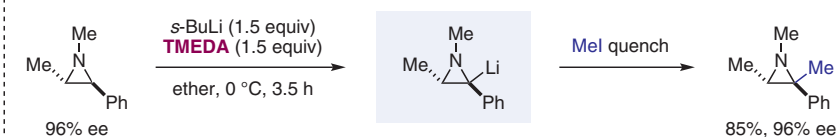


(1d) Strohmann, *J. Am. Chem. Soc.* **2008**, *130*, 14412.

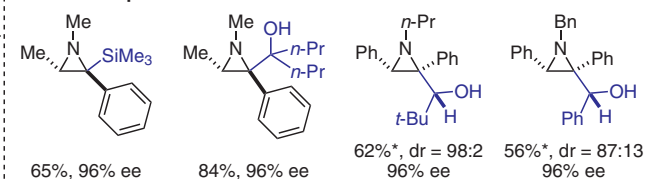
Other systems where similar deprotonation and trapping is observed:



## Functionalization of enantioenriched aziridines

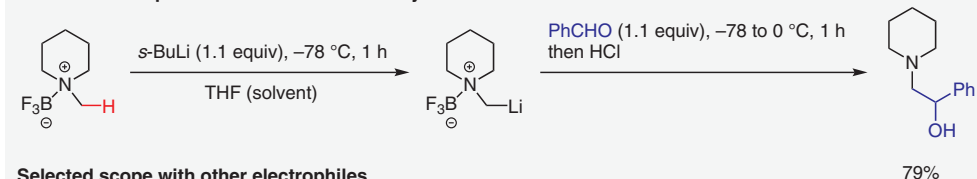


## Selected scope

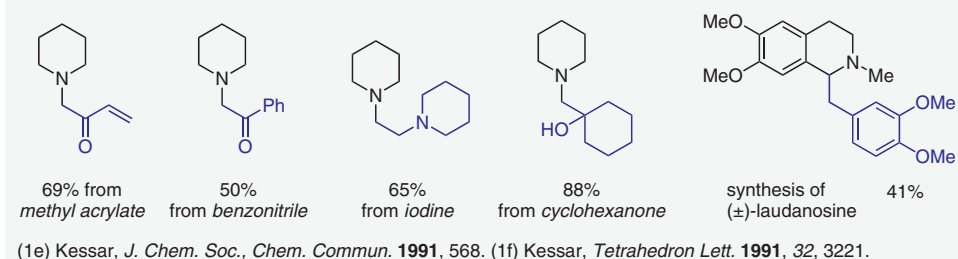
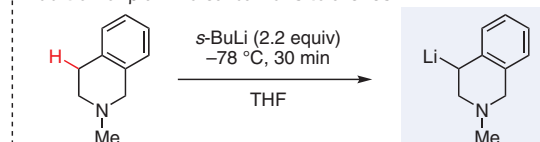


(1g) Luisi, *Chem. Eur. J.* **2011**, *17*, 286.

(\* THF was used as the solvent)

Lewis acid complexed  $\alpha$ -metalation of tertiary amines

## Selected scope with other electrophiles

Addition of  $\beta$ -amino carbanions to arenes

## Selected scope

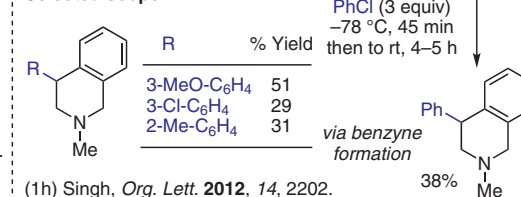
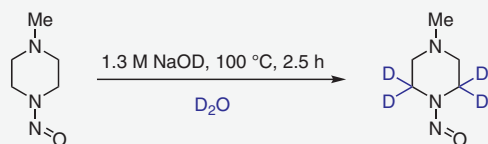


Figure 1 Deprotonation of tertiary amines.<sup>1</sup>

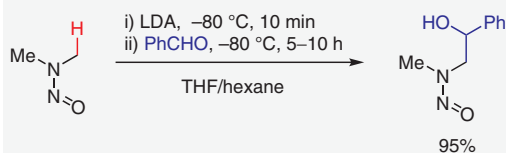
## Notable features

- Rate of deprotonation depends on stabilization of the electron-rich C–Li bond by a nearby empty orbital or electron-withdrawing group.
- Precomplexation of the substrate with the organolithium occurs prior to deprotonation.
- Lithiate stabilized by dipoles of amide (or similar functional groups) and hence termed "dipole stabilized carbanions".

## Seminal discovery

(2a) Keefer, *J. Am. Chem. Soc.* **1970**, *92*, 5747.

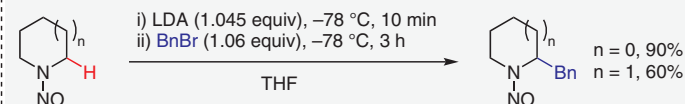
## First example of C–C bond formation

(2b) Seebach, *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 301.

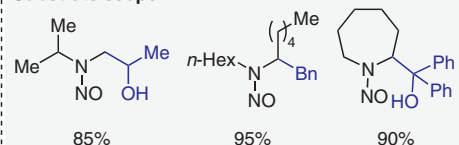
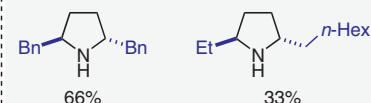
## Further reading

- Reviews:
- (2p) Seebach, *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 15.  
 (2q) Beak, *Chem. Rev.* **1978**, *78*, 275.  
 (2r) Beak, *Chem. Rev.* **1984**, *84*, 471.  
 (2s) Clayden, *Tetrahedron Organic Chemistry Series* **2002**, *23*, 9.
- Seminal work and other directing groups:
- (2t) Fraser, *Can. J. Chem.* **1973**, *51*, 1109.  
 (2u) Lyle, *Tetrahedron Lett.* **1976**, *17*, 4431.  
 (2v) Seebach, *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 313.  
 (2w) Seebach, *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 274.  
 (2x) Meyers, *J. Am. Chem. Soc.* **1980**, *102*, 7125.  
 (2y) Seebach, *Tetrahedron* **1983**, *39*, 1963.  
 (2z) Gawley, *J. Org. Chem.* **1986**, *51*, 3076.  
 (2aa) Gawley, *J. Org. Chem.* **1989**, *54*, 3002.  
 (2ab) Meyers, *J. Org. Chem.* **1993**, *58*, 6538.  
 (2ac) Singh, *Synth. Commun.* **2006**, *36*, 3339.

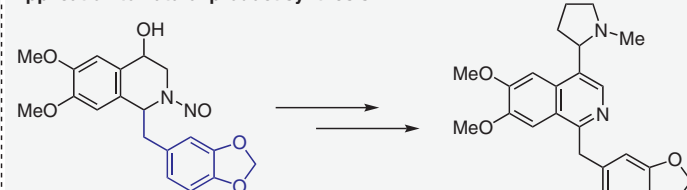
## Functionalization of cyclic and open-chain nitrosamines



## Substrate scope

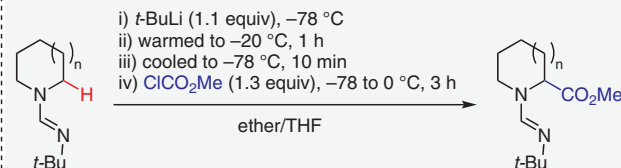
(2c) Seebach, *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1101.(2d) Seebach, *Synthesis* **1979**, 423.See also: (2e) Seebach, *J. Med. Chem.* **1974**, *17*, 1225.Access to  $\alpha,\alpha'$ -difunctionalized pyrrolidinesKey constituents of the venom of the South African fire ant, *Solenopsis punctaticeps*.(2f) Fraser, *Synthesis* **1976**, 540.

## Application to natural product synthesis

(2g) Seebach, *Tetrahedron Lett.* **1980**, *21*, 1927.

(±)-macrostomine

## Formamidines as substrates



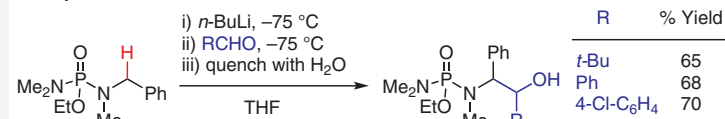
Other electrophiles used:

PhCHO, PhSeSePh, Br(CH<sub>2</sub>)<sub>3</sub>Cl, *n*-BuI

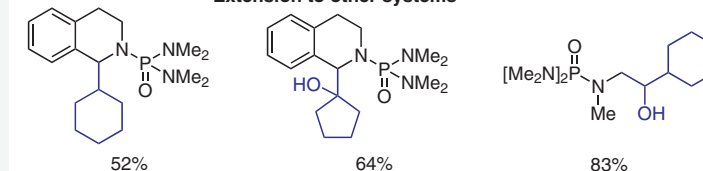
*n* = 0, 85%  
*n* = 1, 87%  
*n* = 2, 91%

(2m) Meyers, *J. Am. Chem. Soc.* **1984**, *106*, 3270.

## Phosphoramides as substrates

(2h) Savignac, *Tetrahedron Lett.* **1974**, *15*, 2651. (2i) Savignac, *J. Organomet. Chem.* **1973**, *57*, C47. See also: (2j) Magnus, *Synthesis* **1980**, 575. (2k) Seebach, *Helv. Chim. Acta* **1981**, *64*, 643.

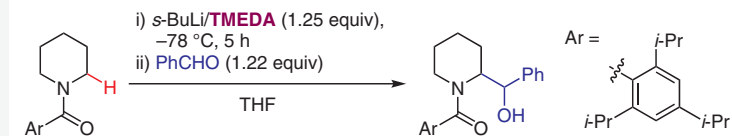
## Extension to other systems



(from cyclohexyl iodide)

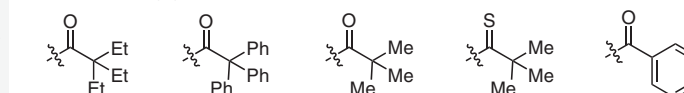
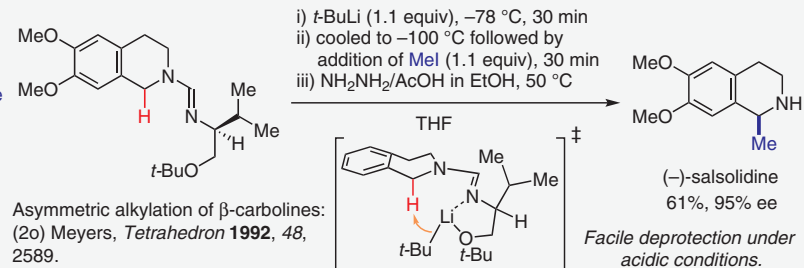
Deprotection is facile by refluxing with aqueous methanolic hydrochloric acid.

## Amides as substrates

(2l) Beak, *J. Am. Chem. Soc.* **1984**, *106*, 1010.

Disadvantage: Harsh deprotection conditions required.

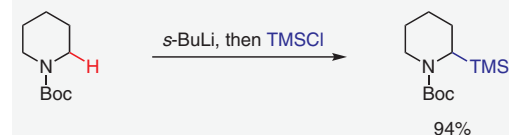
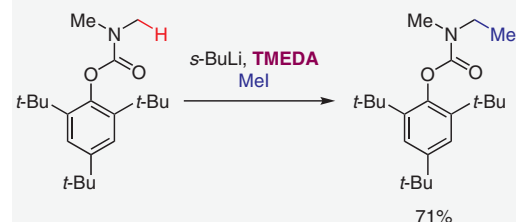
## Other protecting groups used

Chiral Formamidines in asymmetric synthesis (2n) Meyers, *Tetrahedron* **1987**, *43*, 5095.Asymmetric alkylation of  $\beta$ -carboline:  
(2o) Meyers, *Tetrahedron* **1992**, *48*, 2589.(-)-salsolidine  
61%, 95% ee  
Facile deprotection under acidic conditions.Figure 2 Deprotonation of protected amines, part I.<sup>2</sup>

## Notable features

- Boc group is easy to install and remove.
- Stabilization of the organometallic intermediate through chelation.
- Lithiation trapping of *N*-Boc heterocycles is amenable to scale-up through a flow process.

## Historical precedent



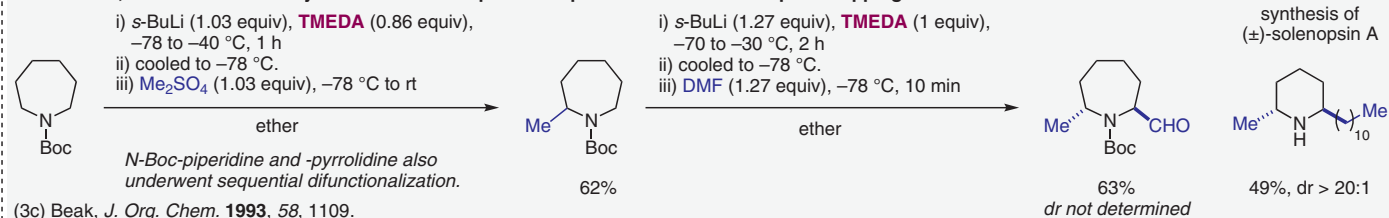
## Further reading

Extension of lithiation trapping to other systems:  
 (3n) O'Brien, *Org. Lett.* **2005**, *7*, 4459.  
 (3o) van Maarseveen, *Tetrahedron Lett.* **2005**, *46*, 2369.  
 (3p) Hodgson, *Angew. Chem. Int. Ed.* **2007**, *46*, 2245.  
 (3q) Coldham, *Chem. Eur. J.* **2013**, *19*, 7724.

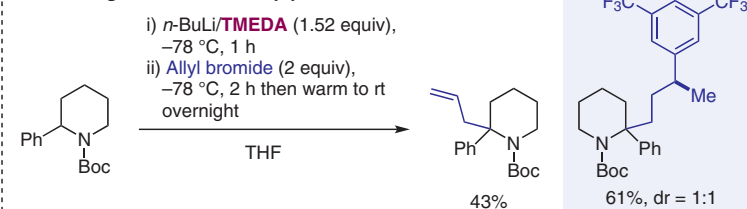
Application to natural product synthesis:  
 (3r) Feringa, *Org. Biomol. Chem.* **2008**, *6*, 3464.  
 (3s) Stoltz, *J. Am. Chem. Soc.* **2008**, *130*, 13745.

Transmetalation to organocuprates:  
 (3t) Dieter, *Tetrahedron Lett.* **1997**, *38*, 783.  
 (3u) Dieter, *J. Org. Chem.* **2002**, *67*, 847.

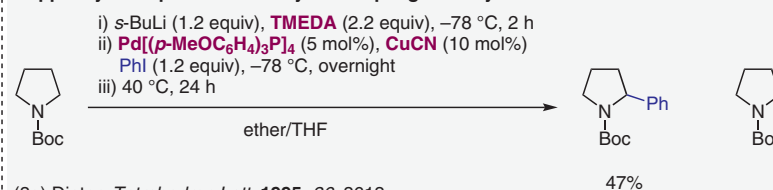
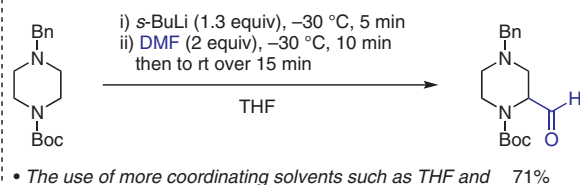
Transmetalation to organozinc species:  
 (3v) Coldham, *Org. Lett.* **2008**, *10*, 3923.

Access to  $\alpha,\alpha'$ -difunctionalized cyclic amines via sequential deprotonation and electrophile trapping

## Access to gem-disubstituted piperidines

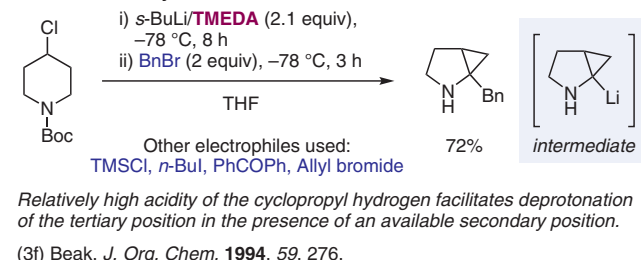
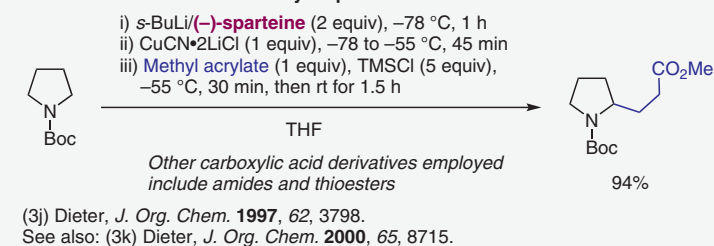
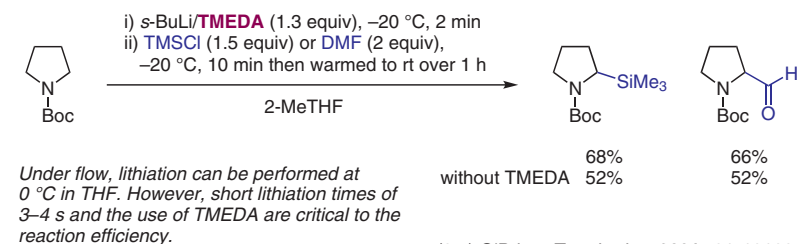


## Copper cyanide/palladium-catalyzed coupling with aryl iodides

TMEDA-free lithiation trapping of *N*-Boc heterocycles

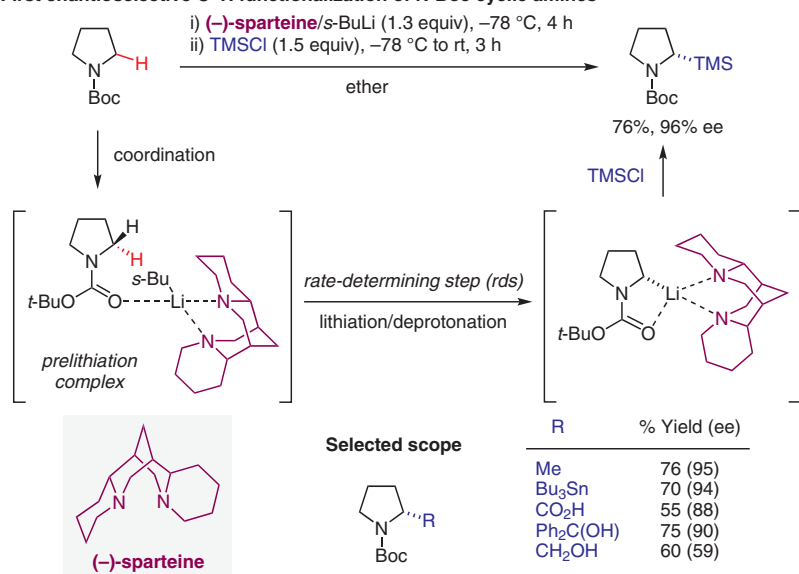
- The use of more coordinating solvents such as THF and 2-MeTHF is crucial in absence of TMEDA.
- *N*-Boc-piperidine and -azepine do not react.

## Intramolecular cyclization

Transmetalation to  $\alpha$ -aminoalkyl cupratesHigh temperature batch and flow lithiation trapping of *N*-Boc-pyrrolidineFigure 3 Deprotonation of protected amines, part II.<sup>3</sup>

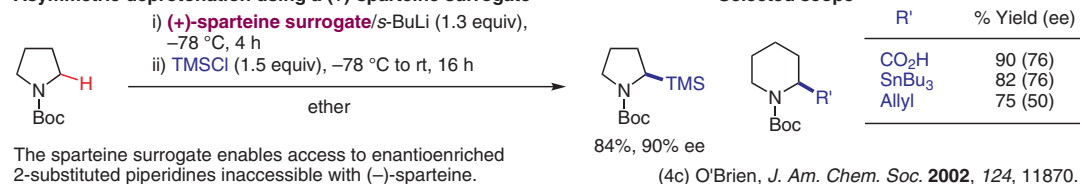


### First enantioselective C–H functionalization of *N*-Boc cyclic amines



(4a) Beak, *J. Am. Chem. Soc.* **1991**, 113, 9708.  
See also: (4b) Beak, *J. Am. Chem. Soc.* **1994**, 116, 3231.

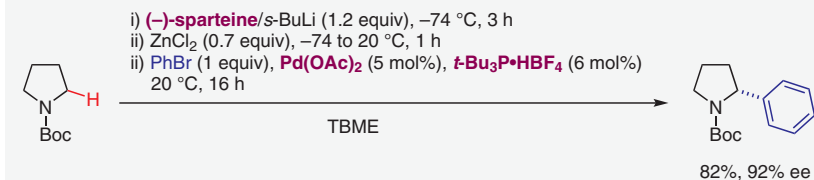
### Asymmetric deprotonation using a (+)-sparteine surrogate



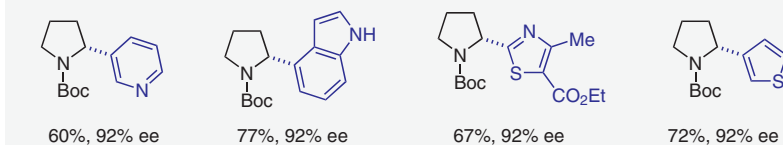
Inaccessibility of (+)-sparteine motivated the development of a surrogate by O'Brien and co-workers.

Enantiocomplementary selectivity to (–)-sparteine was observed.

### Palladium-catalyzed $\alpha$ -arylation of *N*-Boc-pyrrolidine



### Selected scope with other electrophiles



(4d) Campos, *J. Am. Chem. Soc.* **2006**, 128, 3538.

### Further reading

#### Reviews:

(2r) Beak, *Chem. Rev.* **1984**, 84, 471.  
(4f) O'Brien, *Org. React.* **2019**, 100, 255.  
(4g) Barker, *Tetrahedron* **2020**, 76, 131704.

#### Other selected contributions:

(4h) Beak, *J. Org. Chem.* **1995**, 60, 7092.  
(4i) Beak, *Org. Lett.* **2000**, 2, 155.  
(4j) Kozłowski, *J. Am. Chem. Soc.* **2004**, 126, 15473.  
(4k) Coldham, *J. Org. Chem.* **2010**, 75, 4069.  
(4l) Coldham, *J. Am. Chem. Soc.* **2012**, 134, 5300.

#### Use of other chiral ligands:

(4m) Alexakis, *Tetrahedron Lett.* **2003**, 44, 8893.  
(4n) O'Brien, *Org. Biomol. Chem.* **2003**, 1, 3977.  
(4o) O'Brien, *Chem. Commun.* **2006**, 2607.

#### Catalytic asymmetric deprotonation with a "dummy" ligand:

(4p) O'Brien, *J. Am. Chem. Soc.* **2005**, 127, 16378.

### Diastereoselective arylation of substituted piperidines

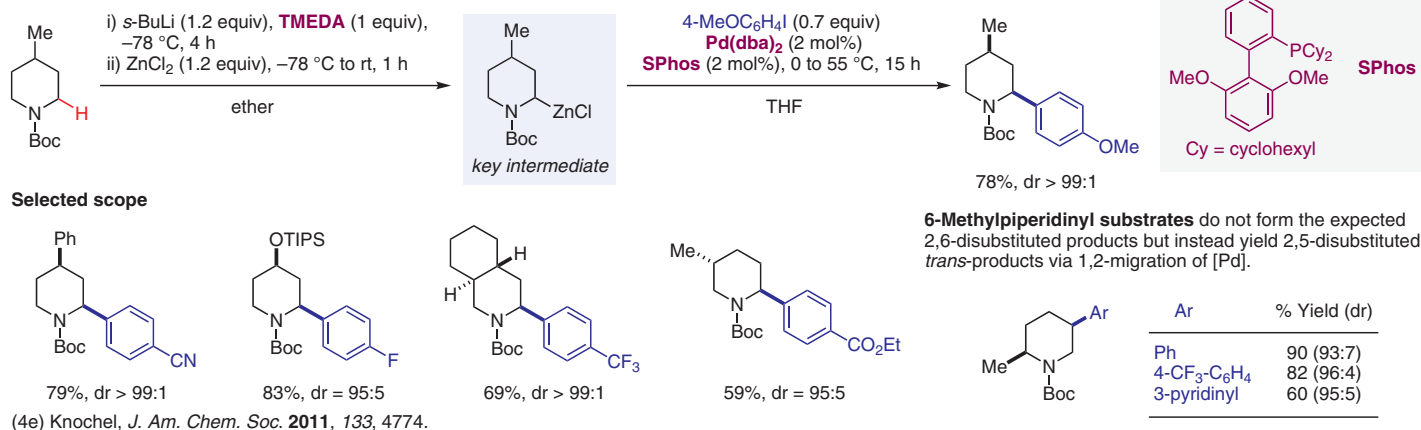
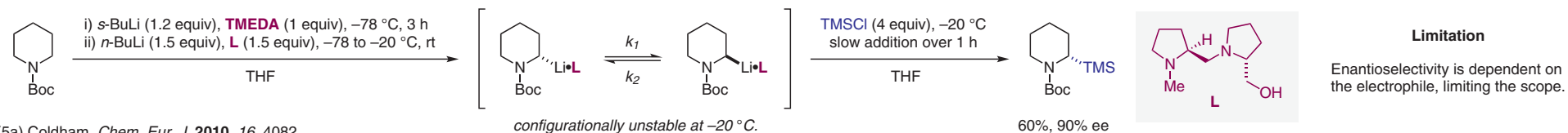
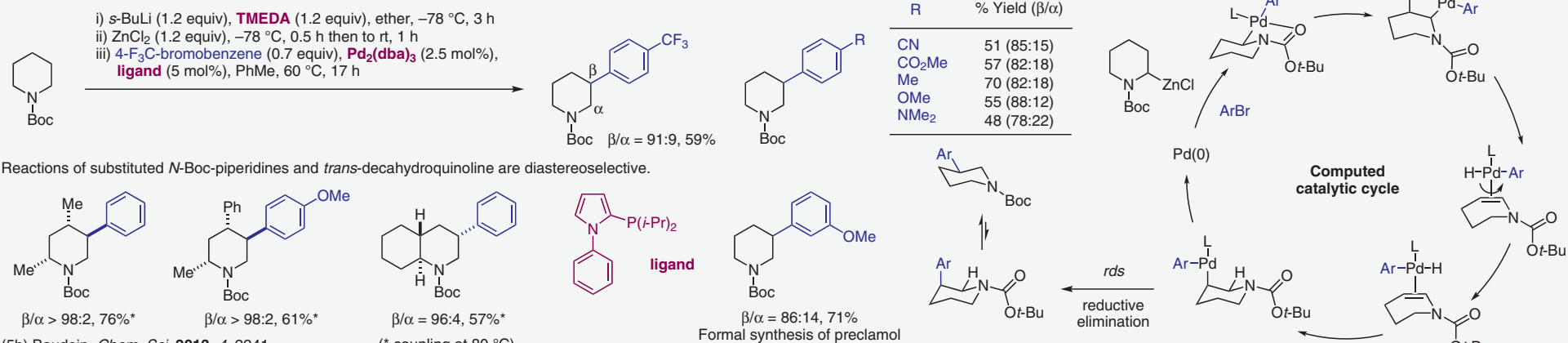
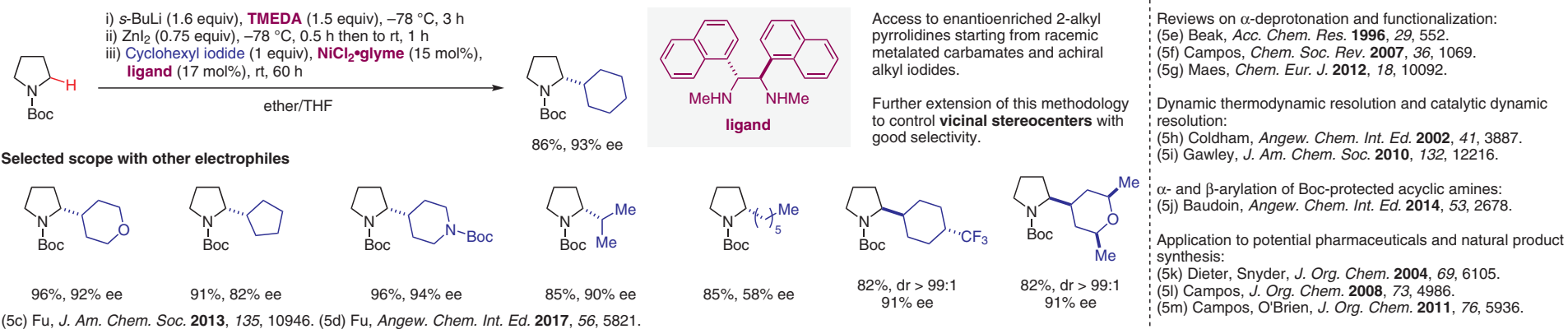


Figure 4 Deprotonation of protected amines, part III.<sup>4</sup>

## Asymmetric substitution of Boc-protected cyclic amines via Dynamic Kinetic Resolution

(5a) Coldham, *Chem. Eur. J.* **2010**, *16*, 4082. $\beta$ -C-H Arylation of *N*-Boc-piperidines

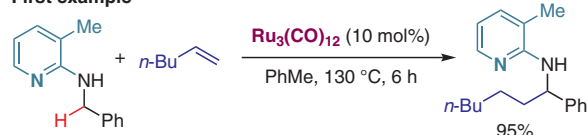
## Enantioconvergent Negishi cross-coupling with unactivated secondary alkyl electrophiles

Figure 5 Deprotonation of protected amines, part IV.<sup>5</sup>

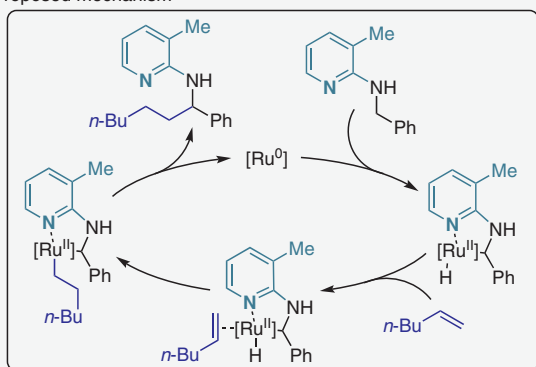
## Notable features

- Functionalization of relatively unactivated C–H bonds is enabled by various directing groups.
- Intermediates with discrete carbon–metal bonds allow for diverse transformations.
- Fine-tuning of outcomes is possible through the use of additives.

## First example



## Proposed mechanism

(6a) Jun, *Chem. Commun.* **1998**, 1405.

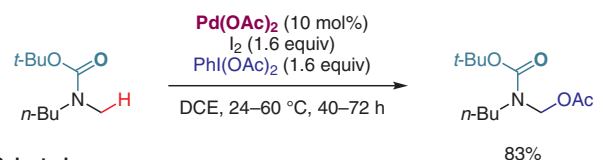
## Further reading

Other selected contributions:

- (6f) Murai, *J. Am. Chem. Soc.* **2001**, *123*, 10935.  
 (6g) Shibata, *Org. Lett.* **2009**, *11*, 1821.  
 (6h) Ackermann, *Org. Lett.* **2014**, *16*, 1876.  
 (6i) Opatz, *Org. Lett.* **2014**, *16*, 4201.  
 (6j) Yu, *J. Am. Chem. Soc.* **2015**, *137*, 11876.  
 (6k) Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 10530.  
 (6l) Bull, *Org. Lett.* **2018**, *20*, 3948.  
 (6m) Sawamura, *J. Am. Chem. Soc.* **2020**, *142*, 589.  
 (6n) Hartwig, *J. Am. Chem. Soc.* **2020**, *142*, 7912.  
 Reviews on transition-metal-catalyzed amine functionalization:  
 (5g) Maes, *Chem. Eur. J.* **2012**, *18*, 10092.  
 (6o) Yu, *Chem. Rev.* **2017**, *117*, 8754.  
 (6p) Schnürch, *Chem. Soc. Rev.* **2018**, *47*, 6603.  
 (6q) Zhang, *Chem. Commun.* **2019**, *55*, 13048.  
 (6r) Hsu, *Adv. Synth. Catal.* **2020**, *362*, 4513.

## Seminal work with different metal catalysts

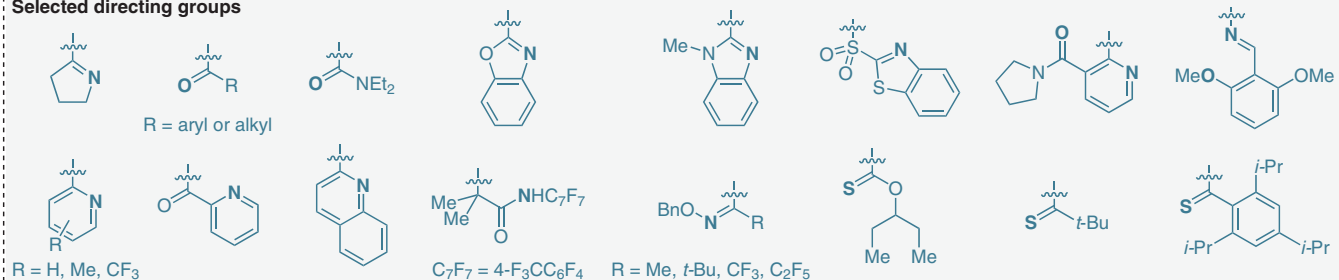
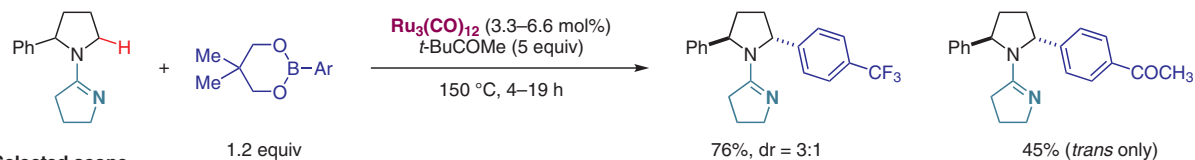
## Palladium



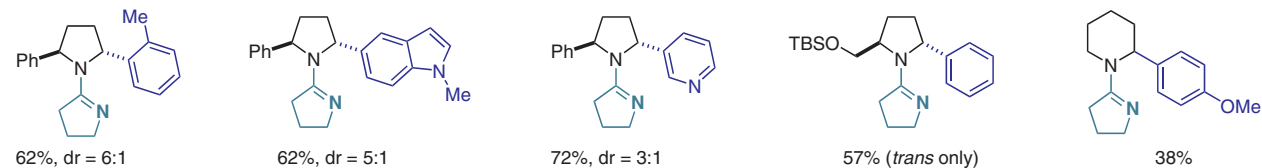
## Selected scope

(6b) Yu, *Org. Lett.* **2006**, *8*, 3387.

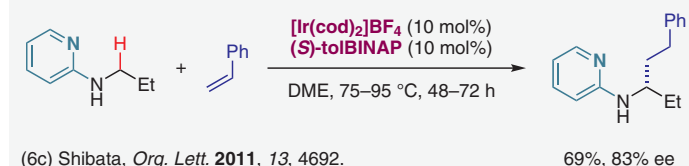
## Selected directing groups

Ru-catalyzed  $\alpha$ -C–H arylation

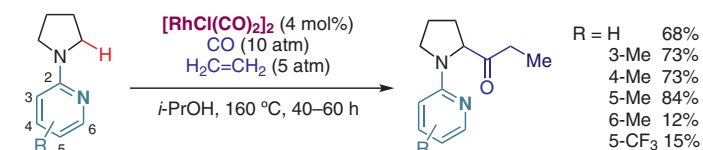
## Selected scope

(6e) Sames, *J. Am. Chem. Soc.* **2006**, *128*, 14220.

## Iridium

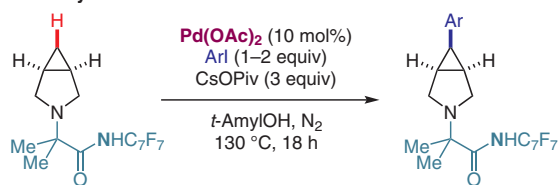
(6c) Shibata, *Org. Lett.* **2011**, *13*, 4692.

## Rhodium

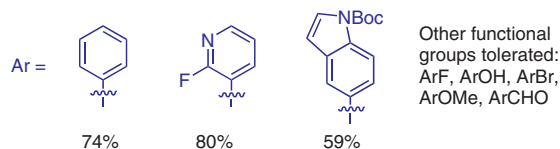
(6d) Murai, *J. Am. Chem. Soc.* **2000**, *122*, 12882.Figure 6 Transition-metal-catalyzed reactions with substrates containing directing groups, part I.<sup>6</sup>



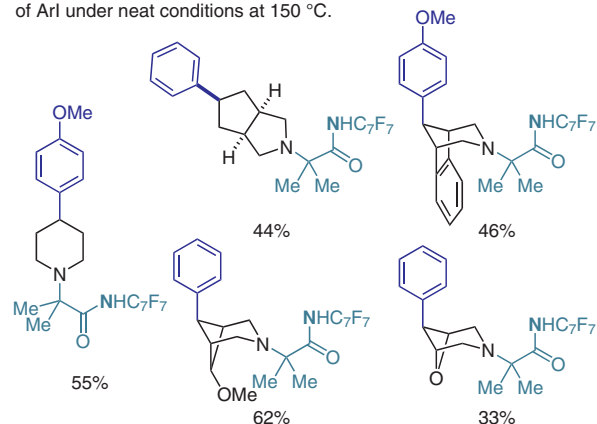
## Pd-catalyzed transannular C–H functionalization



## Selected scope



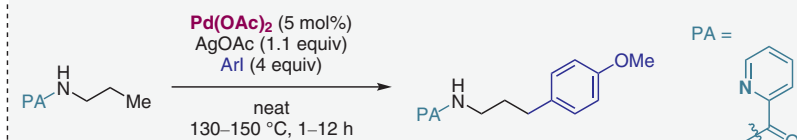
For products shown below, reactions were performed with 30 equiv of ArI under neat conditions at 150 °C.



(7a) Sanford, *Nature* **2016**, 531, 220.  
(7b) Sanford, *J. Am. Chem. Soc.* **2018**, 140, 5599.  
(7c) Sanford, *Angew. Chem. Int. Ed.* **2021**, 60, 11227.

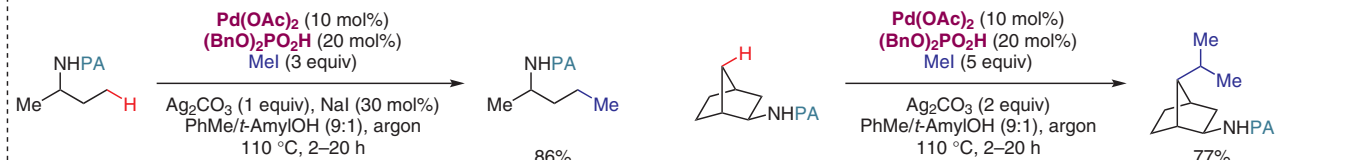
## Further reading

(7j) Daugulis, *J. Am. Chem. Soc.* **2012**, 134, 7.  
(7k) Shi, *Chem. Sci.* **2013**, 4, 3712.  
(7l) Chen, *Adv. Synth. Catal.* **2014**, 356, 1544.  
(7m) Wang, *Org. Lett.* **2015**, 17, 3698.  
(7n) Dong, *Angew. Chem. Int. Ed.* **2016**, 55, 5299.  
(7o) Sheppard, *J. Org. Chem.* **2018**, 83, 2495.

Picolinamide-directed  $\gamma$ -C–H arylation

(7d) Daugulis, *J. Am. Chem. Soc.* **2005**, 127, 13154.

76%

Picolinamide-directed  $\gamma$ -C–H alkylation

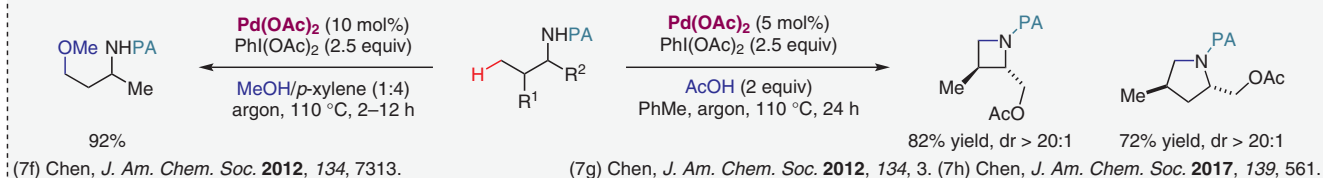
(7e) Chen, *J. Am. Chem. Soc.* **2013**, 135, 2124.

86%

77%

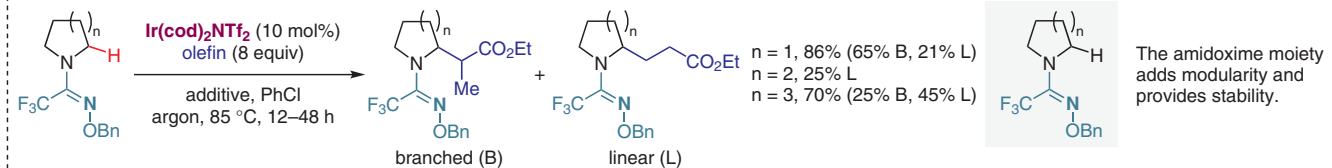
Norbornene substrates provide isopropyl-substituted products via multiple methylations.

## Picolinamide-directed intermolecular alkoxylation &amp; intramolecular amination



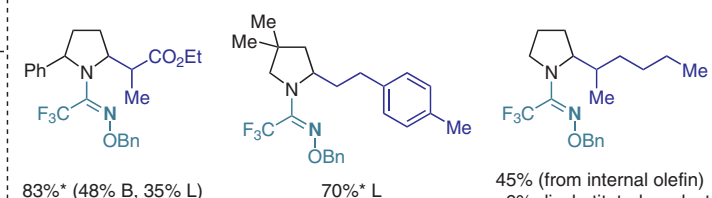
(7f) Chen, *J. Am. Chem. Soc.* **2012**, 134, 7313.

(7g) Chen, *J. Am. Chem. Soc.* **2012**, 134, 3. (7h) Chen, *J. Am. Chem. Soc.* **2017**, 139, 561.

Amidoxime-directed  $\alpha$ -C–H Alkylation

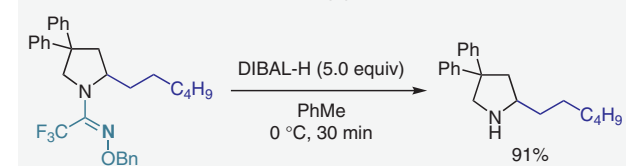
(\* 0.1 equiv of AgSbF<sub>6</sub> or HBF<sub>4</sub>•Et<sub>2</sub>O as additive)

## Selected scope



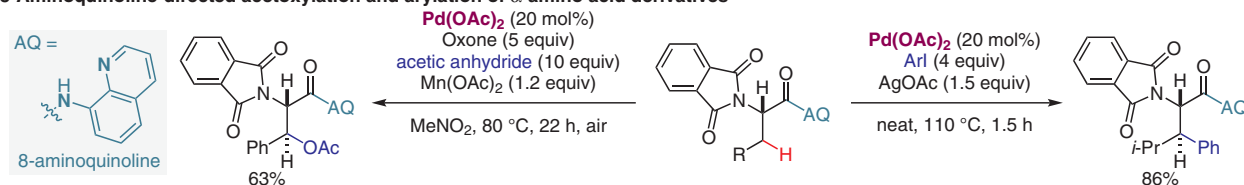
(7i) Yu, *J. Am. Chem. Soc.* **2020**, 142, 5117.

## Facile removal of amidoxime directing group

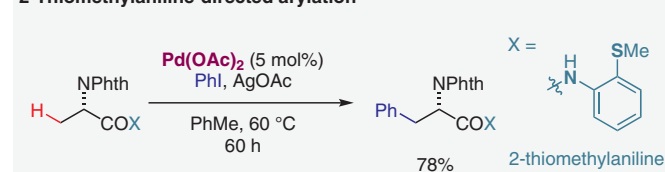
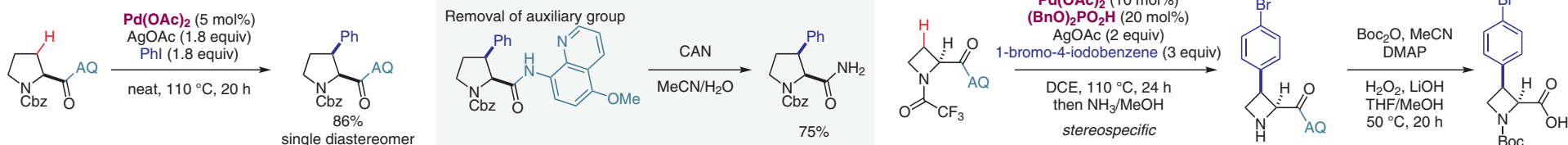
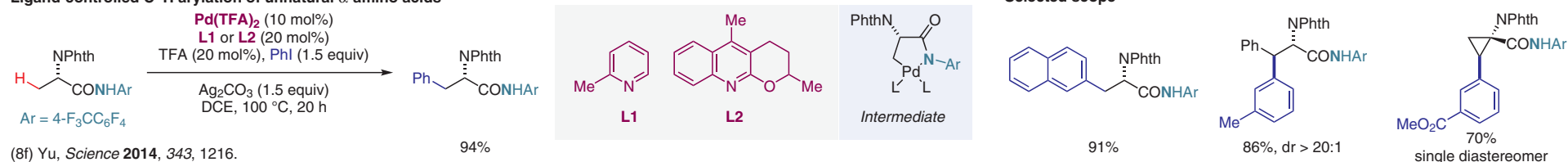


$\alpha$ -Substituent restricts free rotation of DG.

Figure 7 Transition-metal-catalyzed reactions with substrates containing directing groups, part II.<sup>7</sup>

8-Aminoquinoline-directed acetoxylation and arylation of  $\alpha$ -amino acid derivatives(8a) Corey, *Org. Lett.* **2006**, *8*, 3391.

## 2-Thiomethylaniline-directed arylation

(8b) Daugulis, *Angew. Chem. Int. Ed.* **2012**, *51*, 5188.8-Aminoquinoline-directed  $\beta$ -C-H arylation of proline and azetidine-2-carboxylic acid derivatives(8c) Bull, *Org. Lett.* **2014**, *16*, 4956. (8d) Bull, *Eur. J. Org. Chem.* **2016**, 139.(8e) Schreiber, *J. Am. Chem. Soc.* **2017**, *139*, 11300. 57%Ligand-controlled C-H arylation of unnatural  $\alpha$ -amino acids(8f) Yu, *Science* **2014**, *343*, 1216.

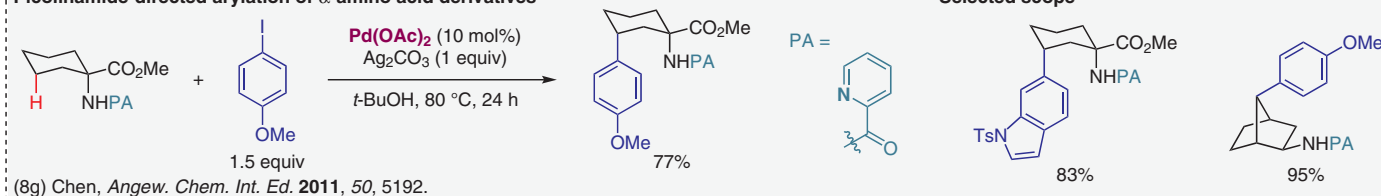
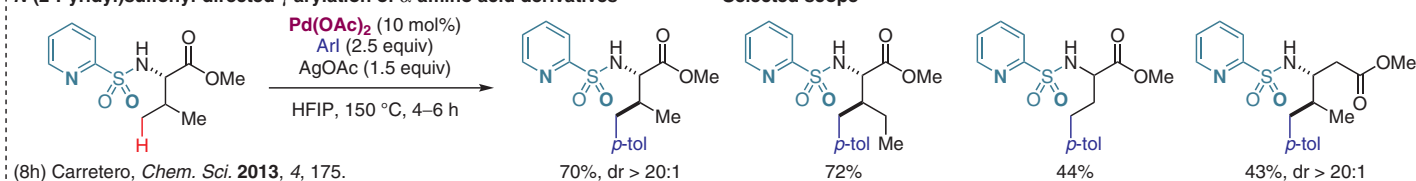
## Further reading

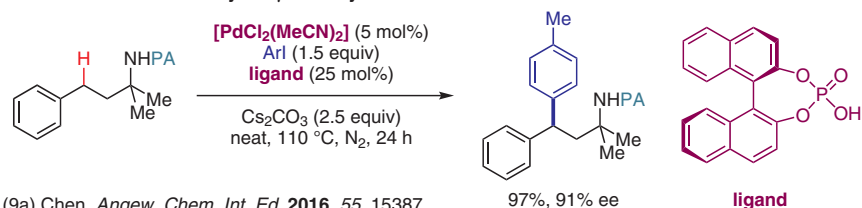
Other selected contributions:

- (8i) Shi, *Chem. Sci.*, **2013**, *4*, 3906.  
 (8j) Chen, *J. Am. Chem. Soc.* **2013**, *135*, 12135.  
 (8k) Chen, *Chem. Sci.* **2014**, *5*, 3952.  
 (8l) Yu, *J. Am. Chem. Soc.* **2014**, *136*, 16940.  
 (8m) Shi, *Angew. Chem. Int. Ed.* **2014**, *53*, 3899.  
 (8n) Shi, *J. Am. Chem. Soc.* **2015**, *137*, 8219.  
 (8o) Yu, *Chem. Eur. J.* **2016**, *22*, 4748.  
 (8p) Shi, *J. Am. Chem. Soc.* **2016**, *138*, 10750.  
 (8q) Shi, *Angew. Chem. Int. Ed.* **2018**, *57*, 5858.

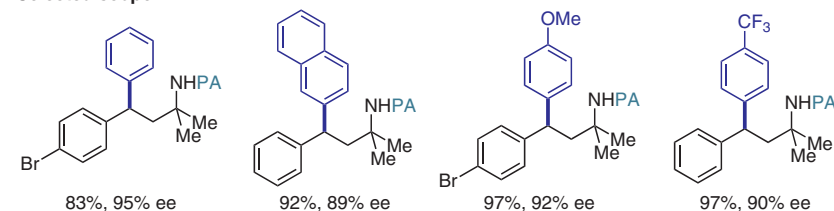
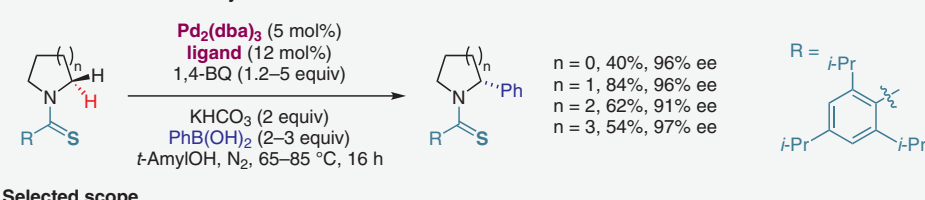
Reviews on directing-group-based C-H functionalization of amino acid derivatives:

- (8r) Brimble, *Chem. Rev.* **2014**, *114*, 8775.  
 (8s) Chen, *Acc. Chem. Res.* **2016**, *49*, 635.  
 (8t) Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 14700.  
 (8u) Chen, *CCS Chem.* **2020**, *2*, 1797.

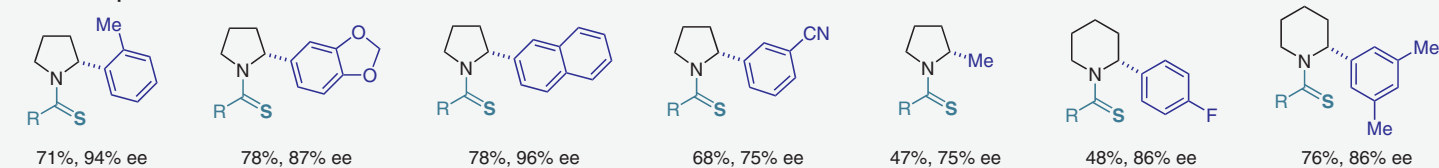
Picolinamide-directed arylation of  $\alpha$ -amino acid derivatives(8g) Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 5192.N-(2-Pyridyl)sulfonyl-directed  $\gamma$ -arylation of  $\alpha$ -amino acid derivatives(8h) Carretero, *Chem. Sci.* **2013**, *4*, 175.Figure 8 Transition-metal-catalyzed reactions with substrates containing directing groups, functionalization of amino acid derivatives.<sup>8</sup>

Enantioselective Pd-catalyzed  $\gamma$ -C-H arylation(9a) Chen, *Angew. Chem. Int. Ed.* **2016**, *55*, 15387.

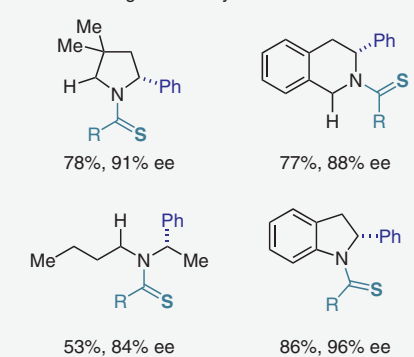
## Selected scope

Enantioselective Pd-catalyzed  $\alpha$ -C-H functionalization

## Selected scope

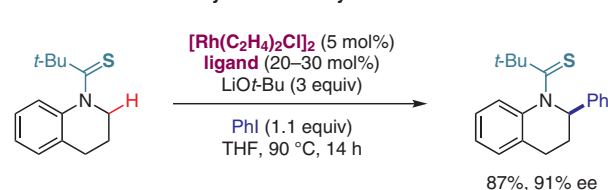
(9b) Yu, *Nat. Chem.* **2017**, *9*, 140.See also: (9c) Gong, *Angew. Chem. Int. Ed.* **2019**, *58*, 1803.

## Exclusive regioselectivity in steric environments

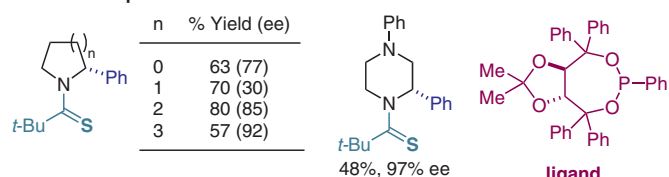
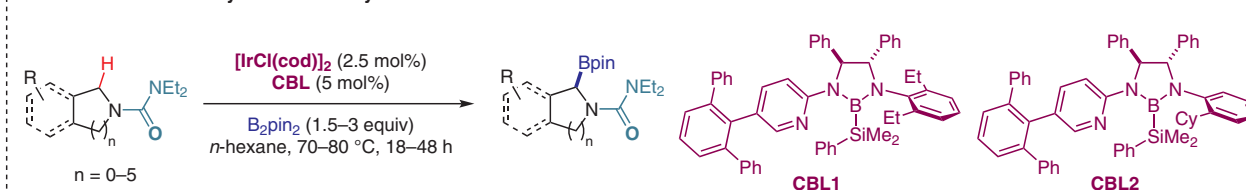


## Other functional groups tolerated:

ArF, ArCl, ArBr, ArOMe, ArCHO, ArCOMe, ArCOOMe.

Enantioselective Rh-catalyzed  $\alpha$ -C-H arylation

## Selected scope

(9d) Glorius, *Angew. Chem. Int. Ed.* **2018**, *57*, 9950.Enantioselective Ir-catalyzed  $\alpha$ -C-H borylation

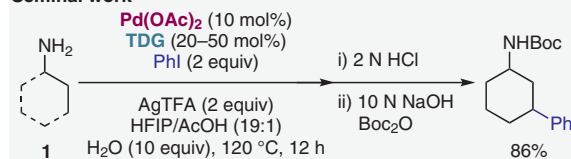
## Selected scope

(9e) Xu, *J. Am. Chem. Soc.* **2020**, *142*, 12062.Figure 9 Transition-metal-catalyzed reactions with substrates containing directing groups, catalytic enantioselective approaches.<sup>9</sup>

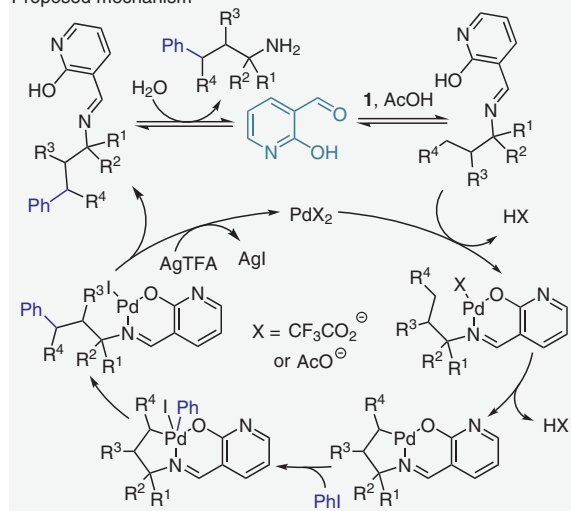
## Notable features

- Installation and removal of directing groups occurs in situ.
- Selective  $\gamma$ -C-H activation dominates due to facile formation of five-membered metallocycles.
- Pd(II)/Pd(IV) catalysis is typically involved.

## Seminal work



## Proposed mechanism

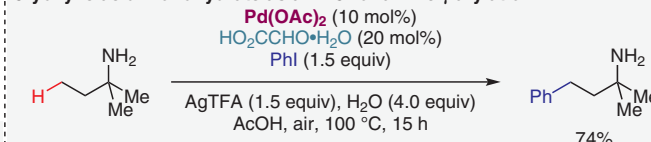
(10a) Yu, *J. Am. Chem. Soc.* **2016**, *138*, 14554.

## Further reading

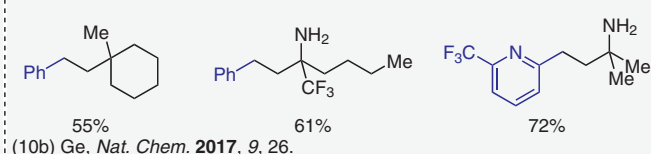
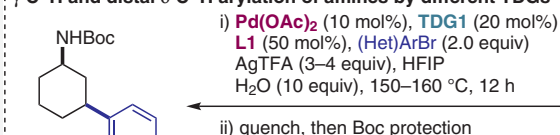
- Bulky salicylaldehydes and alkyl acetals as TDGs:  
(10f) Murakami, *Angew. Chem. Int. Ed.* **2017**, *56*, 1073.  
(10g) Bull, *Chem. Eur. J.* **2018**, *24*, 17838.

## Reviews:

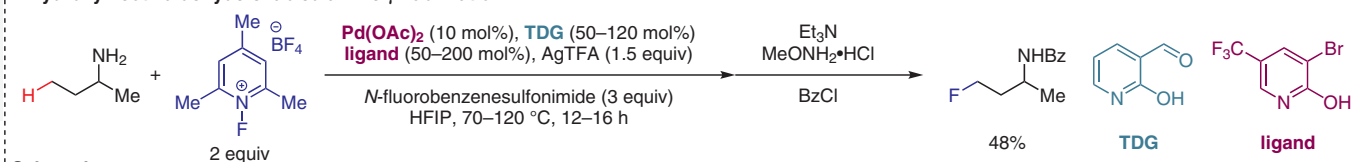
- (10h) Bull, *Org. Biomol. Chem.* **2018**, *16*, 4582.  
(10i) Ge, *ChemSusChem* **2019**, *12*, 2955.  
(10j) Gaunt, *Chem. Rev.* **2020**, *120*, 2613.

Glyoxylic acid monohydrate as a TDG for amine  $\gamma$ -arylation

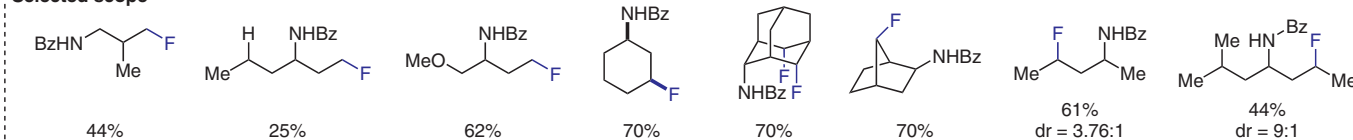
## Selected scope

 $\gamma$ -C-H and distal  $\delta$ -C-H arylation of amines by different TDGs

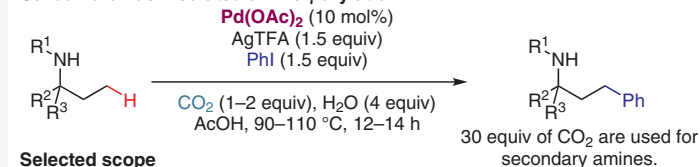
R	% Yield
H	65
6-CF <sub>3</sub>	73
6-Me	61
5-Me	72
4-CF <sub>3</sub>	50

(10d) Yu, *J. Am. Chem. Soc.* **2018**, *140*, 17884.2-Hydroxynicotinaldehyde-enabled amine  $\gamma$ -fluorination

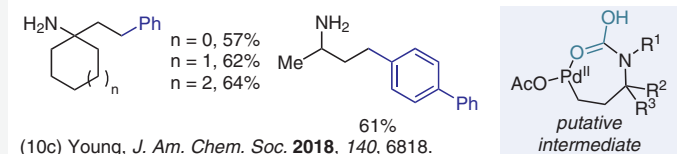
## Selected scope

(10e) Yu, *J. Am. Chem. Soc.* **2020**, *142*, 9966.

Ag salts must be present for methylene fluorination and absent for methyl fluorination.

Carbon dioxide mediated amine  $\gamma$ -arylation

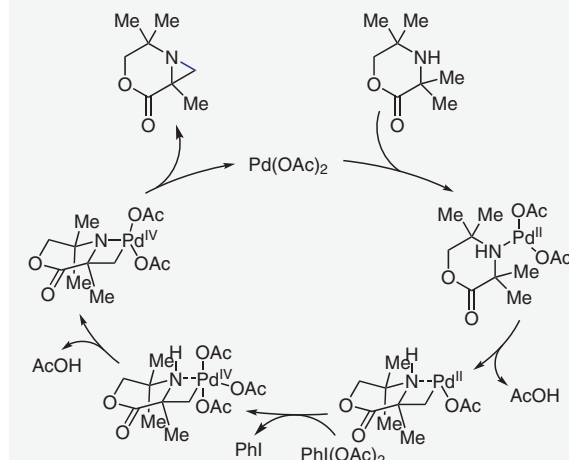
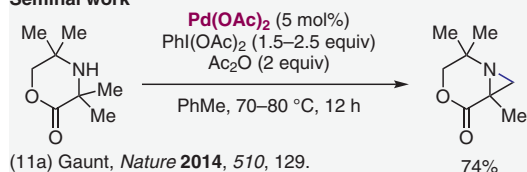
## Selected scope

(10c) Young, *J. Am. Chem. Soc.* **2018**, *140*, 6818.Figure 10 Transition-metal-catalyzed reactions involving transient directing groups (TDGs).<sup>10</sup>

## Notable features

- Native-amine-directed transformations typically take place in a single step and without the addition of exogenous DGs, exploiting the innate coordinating ability of the nitrogen atom.
- Methods minimize the formation of stable and unreactive bis(amine) complexes and  $\beta$ -hydride elimination.

## Seminal work



## Further reading

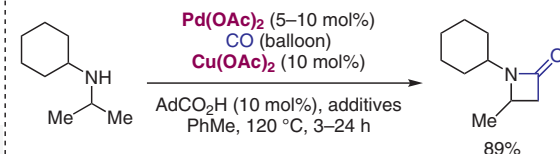
Other selected contributions:

- (11g) Gaunt, *Nat. Chem.* **2015**, *7*, 1009.  
 (11h) Gaunt, *Angew. Chem. Int. Ed.* **2017**, *56*, 11958.  
 (11i) Shi, *Org. Chem. Front.* **2017**, *4*, 2097.  
 (11j) Gaunt, *Chem. Sci.* **2018**, *9*, 7628.  
 (11k) Bannister, *ACS Catal.* **2019**, *9*, 4887.  
 (11l) Gaunt, *Nat. Chem.* **2020**, *12*, 76.

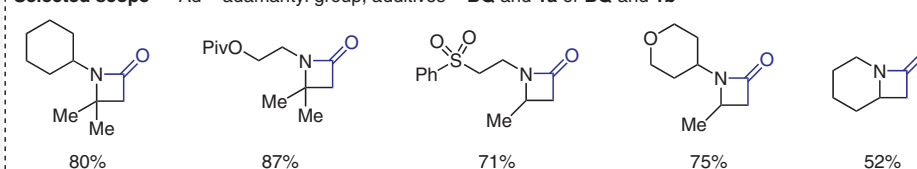
Reviews:

- (11m) Gaunt, *Chem* **2019**, *5*, 1031.  
 (10j) Gaunt, *Chem. Rev.* **2020**, *120*, 2613.

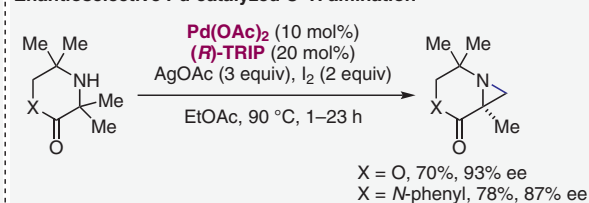
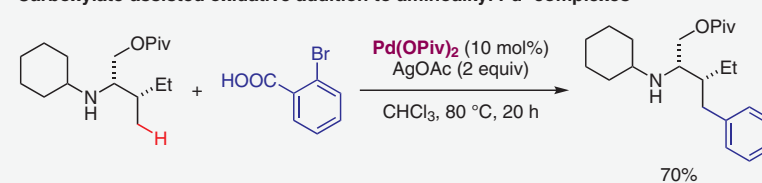
## C–H carbonylation of unhindered aliphatic amines



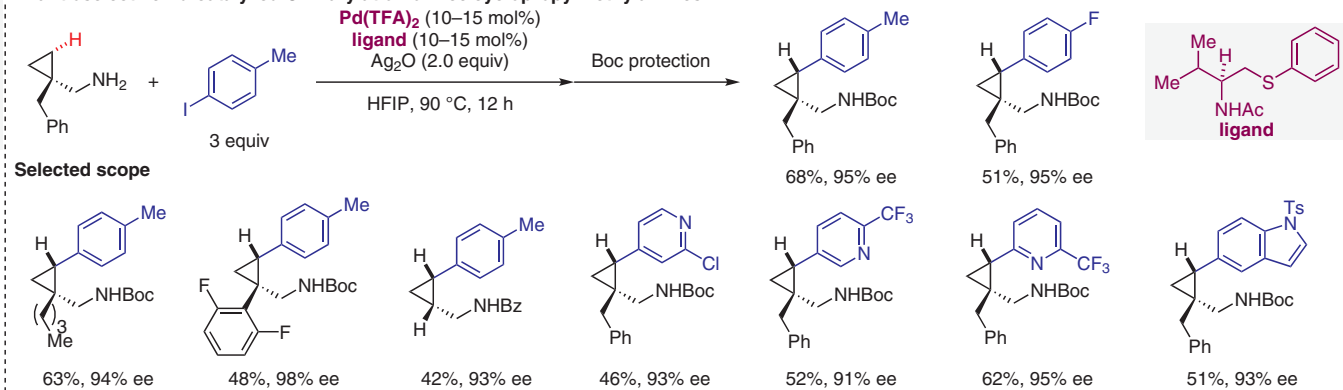
## Selected scope

(11c) Gaunt, *Science* **2016**, *354*, 851.

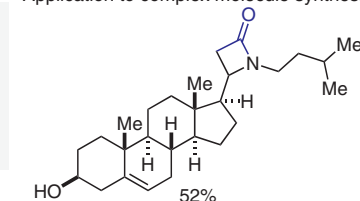
## Enantioselective Pd-catalyzed C–H amination

(11d) Gaunt, *J. Am. Chem. Soc.* **2017**, *139*, 1412.Carboxylate-assisted oxidative addition to aminoalkyl Pd<sup>II</sup> complexes(11e) Gaunt, *Angew. Chem. Int. Ed.* **2019**, *58*, 9054.

## Enantioselective Pd-catalyzed C–H arylation of free cyclopropylmethylamines

(11f) Yu, *J. Am. Chem. Soc.* **2020**, *142*, 12015.

## Application to complex molecule synthesis

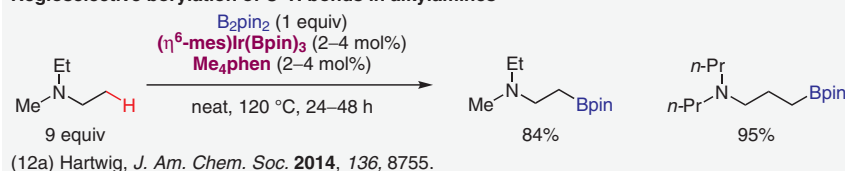
Figure 11 Native-amine-directed transition-metal-catalyzed reactions.<sup>11</sup>



## Notable features

- Cleavage of the C–H bond does not rely on coordination of the metal catalyst with the substrate.
- Regioselectivity is based on reactivity differences of C–H bonds.

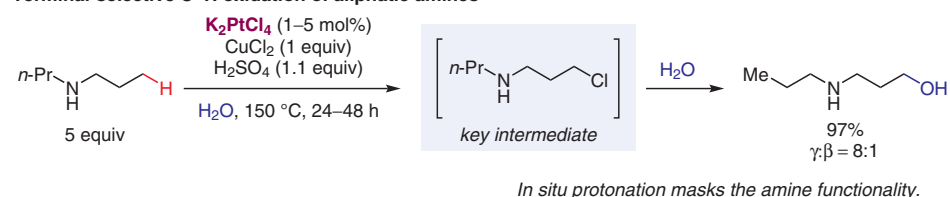
## Regioselective borylation of C–H bonds in alkylamines



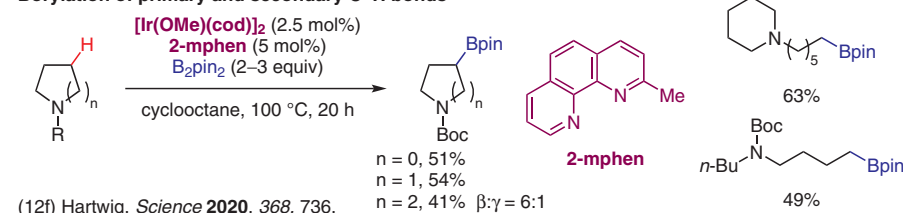
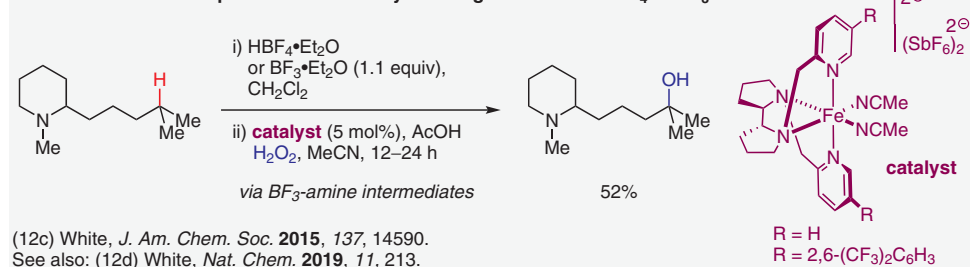
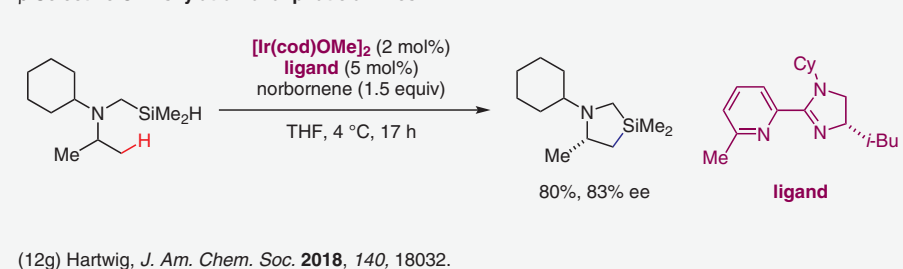
## Further reading

- Other selected contributions:  
 (12i) Sanford, *Org. Lett.* **2016**, *18*, 4258.  
 (12j) White, *J. Am. Chem. Soc.* **2017**, *139*, 14586.
- Reviews:  
 (12k) Hartwig, *ACS Cent. Sci.* **2016**, *2*, 281.  
 (12l) Glorius, *ACS Cent. Sci.* **2021**, *7*, 245.

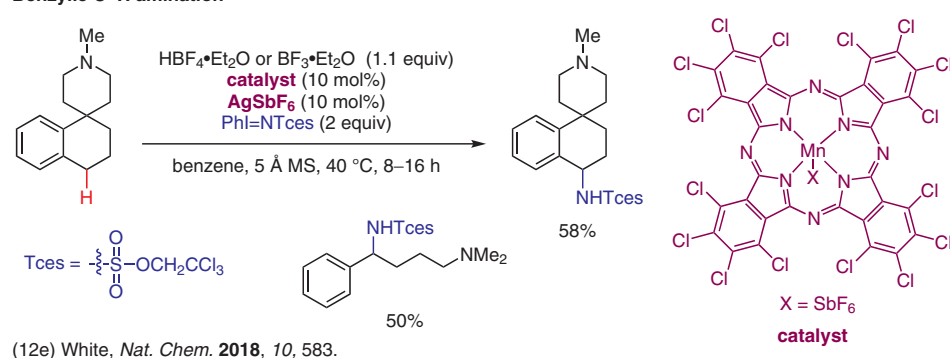
## Terminal-selective C–H oxidation of aliphatic amines



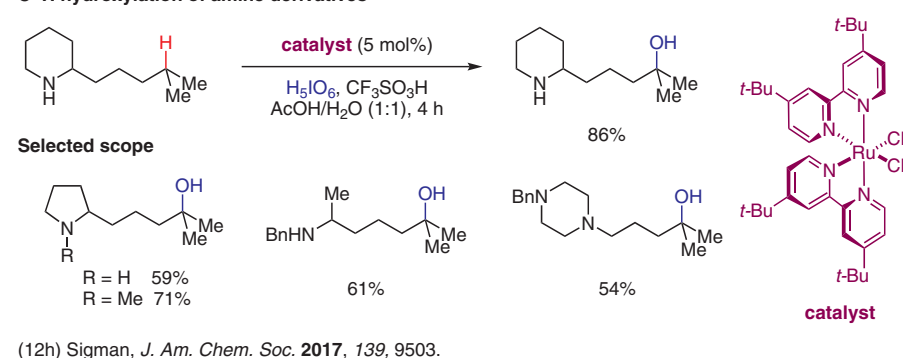
## Borylation of primary and secondary C–H bonds

Remote oxidation of aliphatic C–H bonds by masking amines with  $\text{HBF}_4$  or  $\text{BF}_3$  $\beta$ -Selective C–H silylation of aliphatic amines

## Benzylic C–H amination



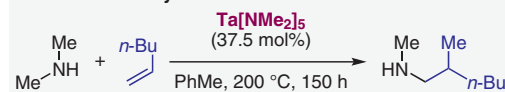
## C–H hydroxylation of amine derivatives

Figure 12 Undirected transition-metal-catalyzed reactions.<sup>12</sup>

## Notable features

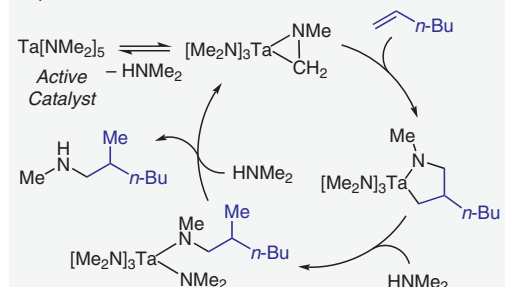
- Atom-economical process using early transition metals that are abundant and exhibit low toxicity.
- Reactions proceed through metalaziridine intermediates.

## Seminal discovery



(13a) Maspero, *Synthesis* **1980**, 305.

Proposed mechanism:



(13b) Nugent, *Organometallics* **1983**, 2, 161.  
Also see Refs 13d and 13h.

## Further reading

Reviews:

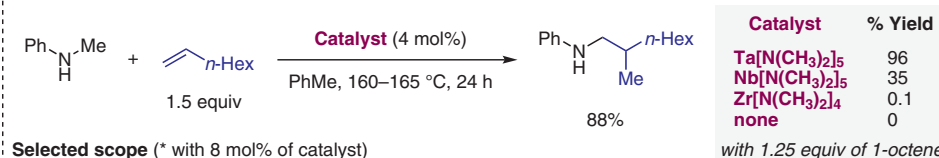
- (13i) Roesky, *Angew. Chem. Int. Ed.* **2009**, 48, 4892.  
 (13j) Beller, *ChemSusChem* **2009**, 2, 715.  
 (13k) Schafer, *Synthesis* **2014**, 46, 2884.  
 (13l) Schulz, *Organometallics* **2018**, 37, 4313.  
 (13m) Schafer, *Chem. Commun.* **2018**, 54, 12543.

An early example of a catalytic asymmetric reaction:  
 (13n) Schafer, *Angew. Chem. Int. Ed.* **2009**, 48, 8361.

Other selected contributions:

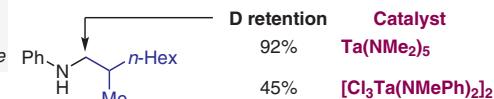
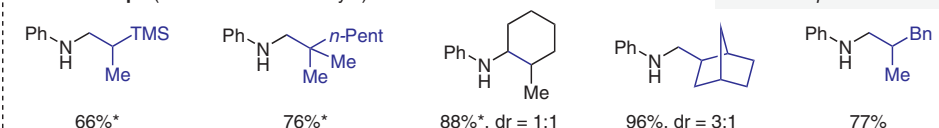
- (13o) Doye, *Eur. J. Org. Chem.* **2001**, 4411.  
 (13p) Odom, *J. Am. Chem. Soc.* **2006**, 128, 9344.  
 (13q) Zi, *Chem. Commun.* **2010**, 46, 6296.  
 (13r) Hultsch, *Organometallics* **2011**, 30, 921.  
 (13s) Schafer, *Org. Lett.* **2013**, 15, 2182.  
 (13t) Doye, *Chem. Eur. J.* **2017**, 23, 4197.  
 (13u) Doye, *Angew. Chem. Int. Ed.* **2021**, 60, 9936.

**Application of group V metals to amine  $\alpha$ -functionalization** (13c) Hartwig, *J. Am. Chem. Soc.* **2007**, 129, 6690. (13d) Hartwig, *J. Am. Chem. Soc.* **2008**, 130, 14940.

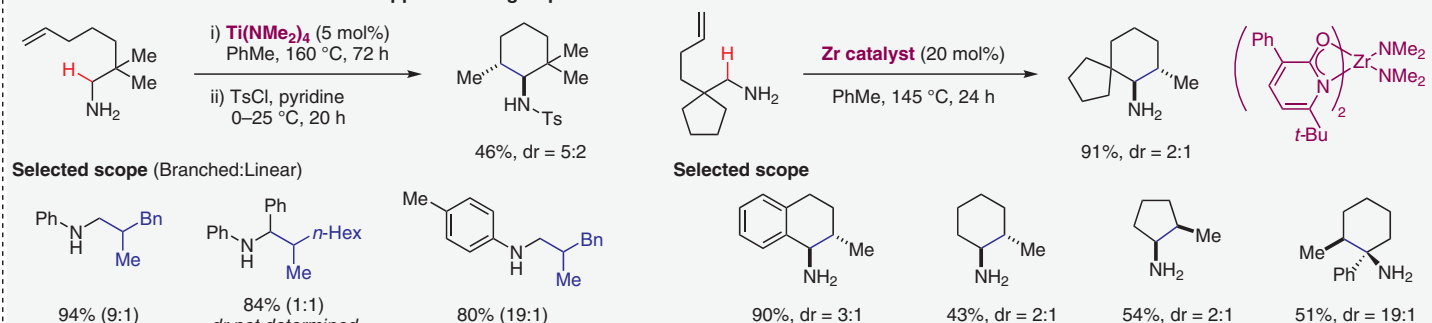


The chloroamido complex  $[\text{Cl}_3\text{Ta}(\text{NMePh})_2]_2$  catalyzes the same reaction effectively at 90 °C while  $\text{Ta}(\text{NMe}_2)_5$  shows no activity at this temperature.

**Selected scope** (\* with 8 mol% of catalyst)



A mechanistic study suggests formation of an azametallacyclopropane ( $\eta^2$ -imine complex) as the turnover-limiting step.

Application of group IV metals to intramolecular amine  $\alpha$ -functionalization

(13e) Doye, *Angew. Chem. Int. Ed.* **2009**, 48, 1153.

(13f) Schafer, *J. Am. Chem. Soc.* **2009**, 131, 2116.

## Intermolecular hydroaminoalkylation with group III metals

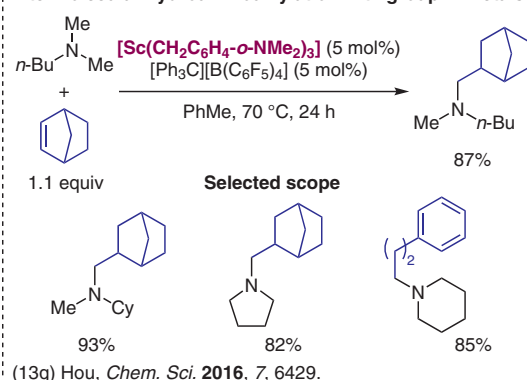
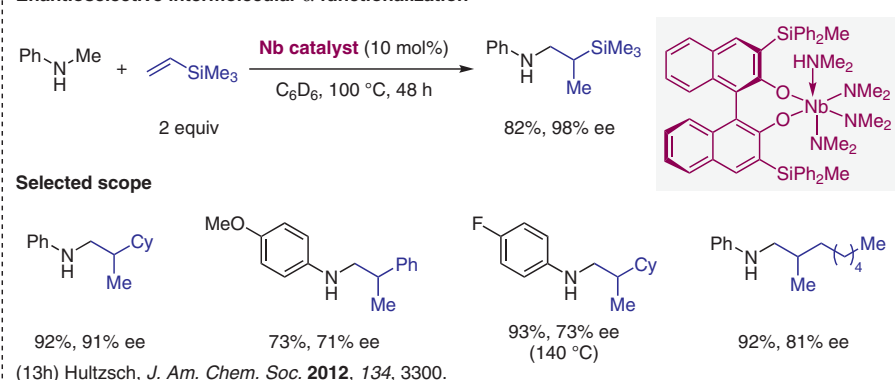
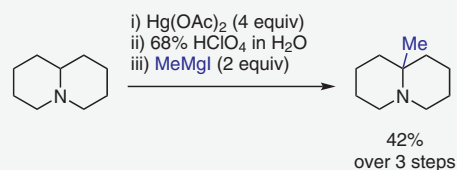
Enantioselective intermolecular  $\alpha$ -functionalization

Figure 13 Hydroaminoalkylation.<sup>13</sup>

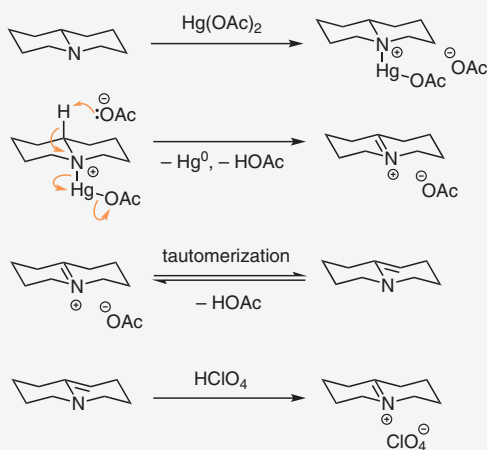
## Notable features

- Operationally simple approach to access iminium ions.
- Mostly applicable to tertiary amines.
- Substrate dimerization can occur via enamine intermediates.
- Compatible with a range of different nucleophiles.
- Yields are typically moderate to low.

## Seminal example

(14a) Leonard, *J. Am. Chem. Soc.* **1955**, 77, 439.

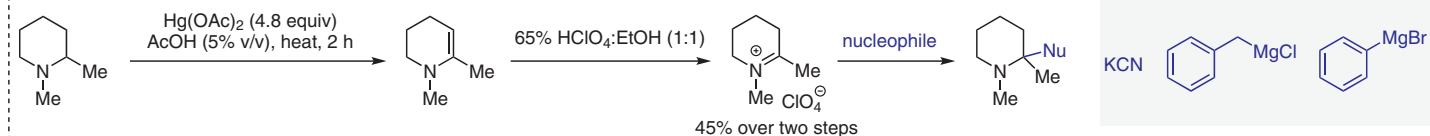
## Proposed mechanism

(14b) Morrow, *J. Am. Chem. Soc.* **1958**, 80, 371.

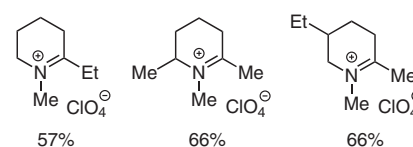
## Further reading

- (14i) Haginiwa, *Tetrahedron Lett.* **1969**, 19, 1485.  
(14j) Butler, *Chem. Rev.* **1984**, 84, 249.

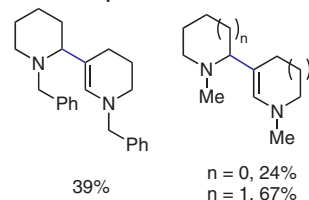
## Mercury-promoted formation of enamines and subsequent transformations



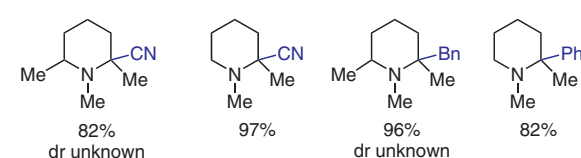
## Iminium salts, selected scope

(14c) Leonard, *J. Am. Chem. Soc.* **1957**, 79, 5279.

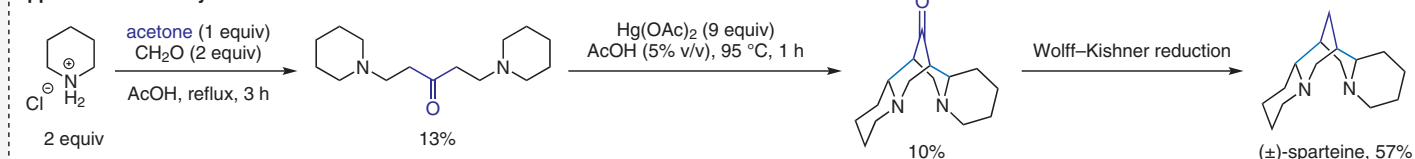
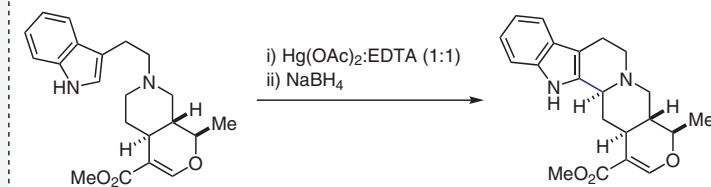
## Dimerized products



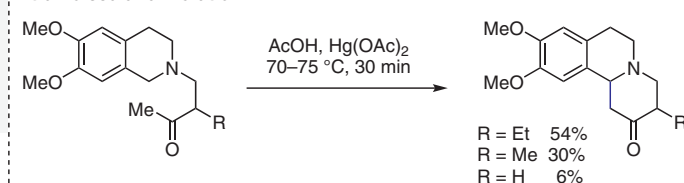
## Selected nucleophile scope



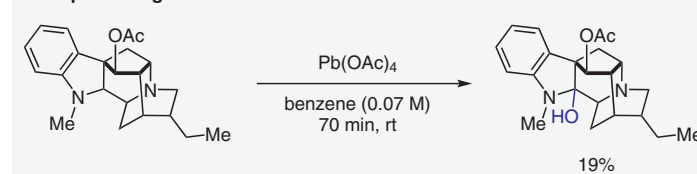
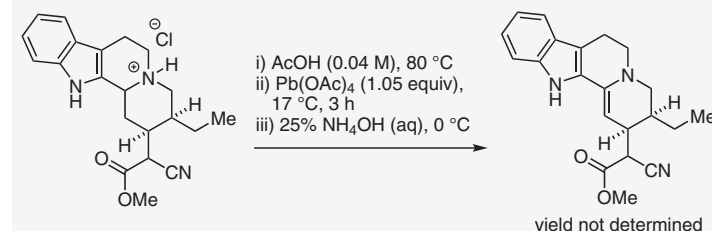
## Application in total synthesis

(14d) Tamelen, *J. Am. Chem. Soc.* **1969**, 91, 7372.(14e) Uskoković, *J. Am. Chem. Soc.* **1971**, 93, 5907.

## Intramolecular annulation

With  $\text{R} = \text{H}$ , competing Hofmann-type elimination is observed.(14f) Whittaker, *J. Chem. Soc.* **1963**, 1449.

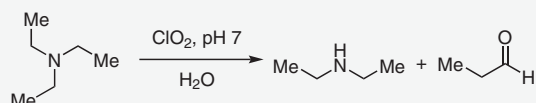
## Examples using lead tetraacetate as an oxidant

(14g) Taylor, *J. Am. Chem. Soc.* **1964**, 86, 729.(14h) Szantay, *Tetrahedron* **1976**, 32, 1019.Figure 14 Oxidative methods, stoichiometric metal-based oxidants.<sup>14</sup>

### Notable features

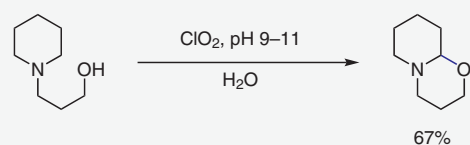
- Various nonmetallic reagents are suitable for amine oxidation.
- Typically, no catalyst is required.

### Early examples with stoichiometric oxidants

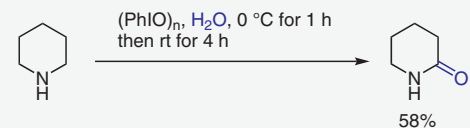
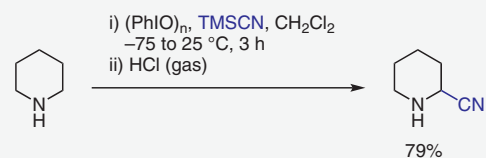


Formation of an iminium species is followed by hydrolysis.

(15a) Rosenblatt, *J. Org. Chem.* **1963**, *28*, 2790.



(15b) Hortmann, *J. Am. Chem. Soc.* **1988**, *110*, 4829.

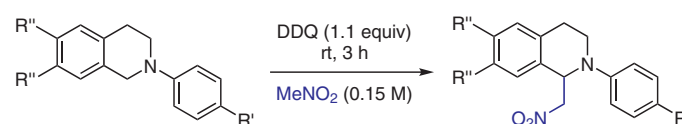


(15c) Moriarty, Ochiai, Nagao, *Tetrahedron Lett.* **1988**, *29*, 6913.  
See also: (15d) Xiong, *Tetrahedron Lett.* **2015**, *56*, 5628.

### Further reading

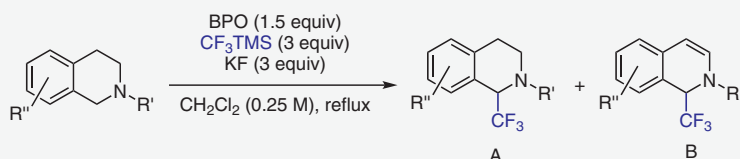
- (15k) Zhdankin, *Tetrahedron Lett.* **1995**, *36*, 7975.  
 (15l) Hu, *New J. Chem.* **2013**, *37*, 1684.  
 (15m) Nguyen, *J. Org. Chem.* **2018**, *83*, 1000.  
 (15n) Zhang, Luo, *J. Org. Chem.* **2019**, *84*, 2542.  
 (15o) Li, *Eur. J. Org. Chem.* **2020**, 103.  
 (15p) Singh, *Synthesis* **2021**, *53*, 1556.

### Oxidation with DDQ



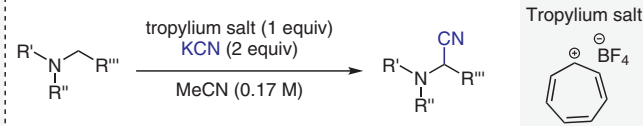
(15e) Todd, *Tetrahedron Lett.* **2009**, *50*, 1199.

### Oxidation with BPO



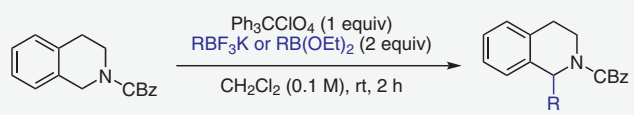
(15f) Qing, *Chem. Commun.* **2010**, *46*, 6285.

### Oxidation with tropylium tetrafluoroborate



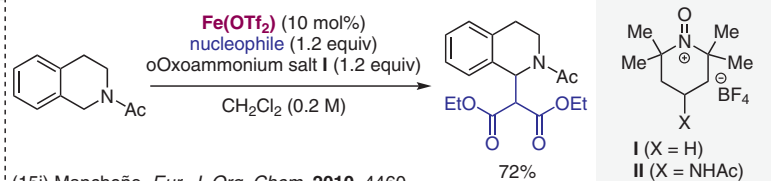
(15g) Lambert, *J. Am. Chem. Soc.* **2011**, *133*, 1260.

### Oxidation with trityl perchlorate



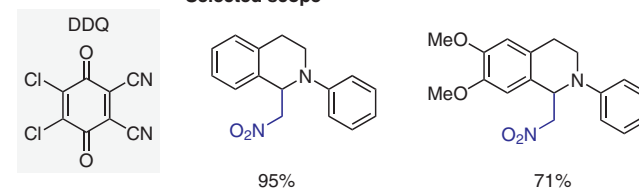
(15h) Lou, Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 3904.

### Oxidation with oxoammonium salts

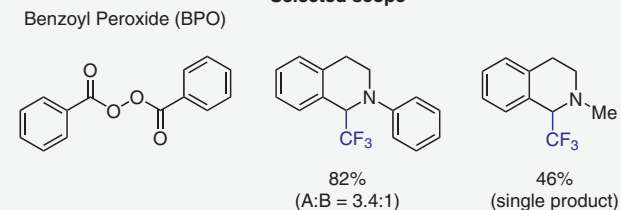


(15i) Mancheño, *Eur. J. Org. Chem.* **2010**, 4460.

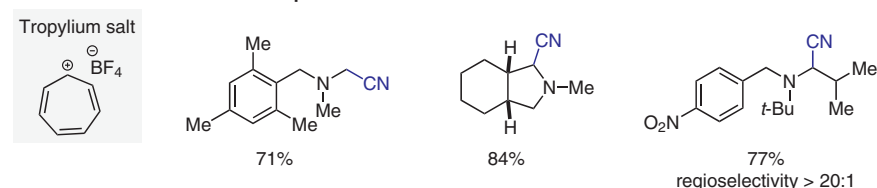
### Selected scope



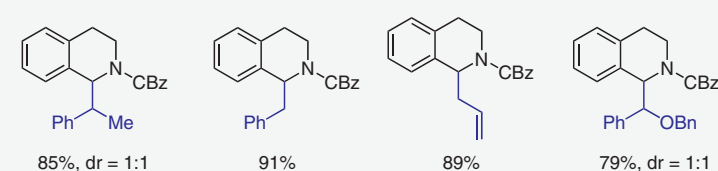
### Selected scope



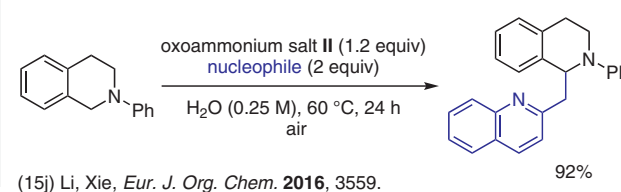
### Selected scope



### Selected scope



### Oxoammonium salts



(15j) Li, Xie, *Eur. J. Org. Chem.* **2016**, 3559.

Figure 15 Oxidative methods, stoichiometric nonmetallic oxidants.<sup>15</sup>

## Notable features

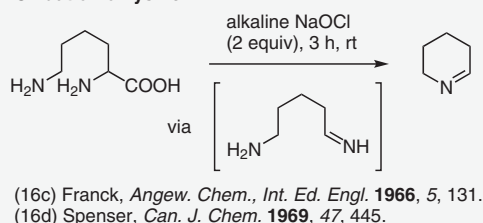
- Oxidation of typically unprotected amines to access versatile synthetic building blocks that can be further functionalized.

## Reviews

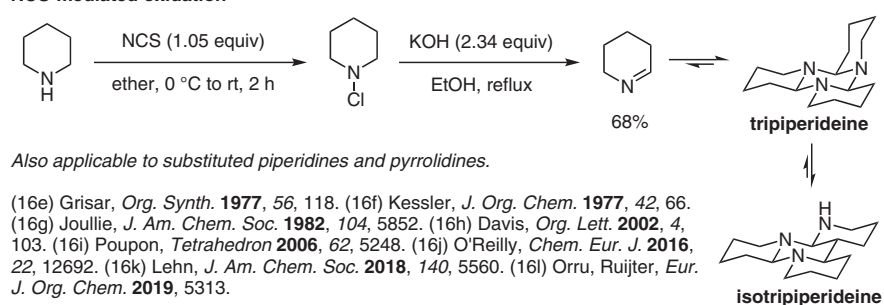
(16a) Murahashi, *Chem. Rev.* **2019**, *119*, 4684.

(16b) Largeron, *Eur. J. Org. Chem.* **2013**, 5225.

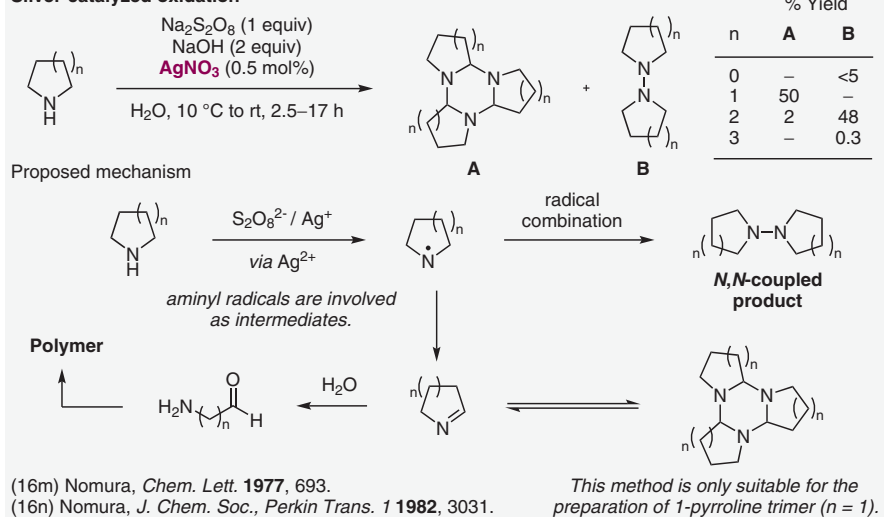
## Oxidation of lysine



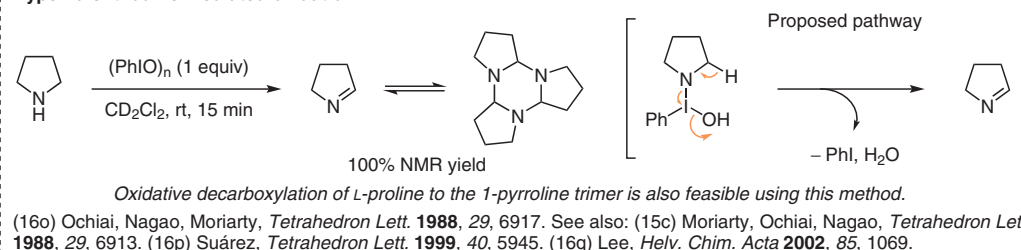
## NCS-mediated oxidation



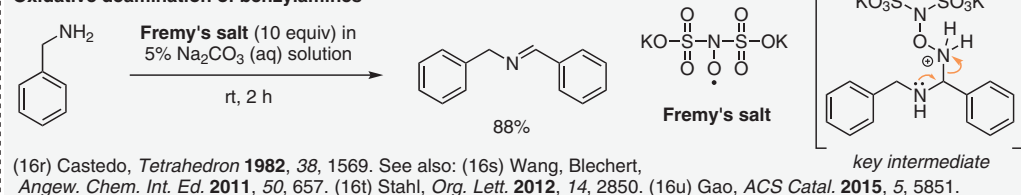
## Silver-catalyzed oxidation



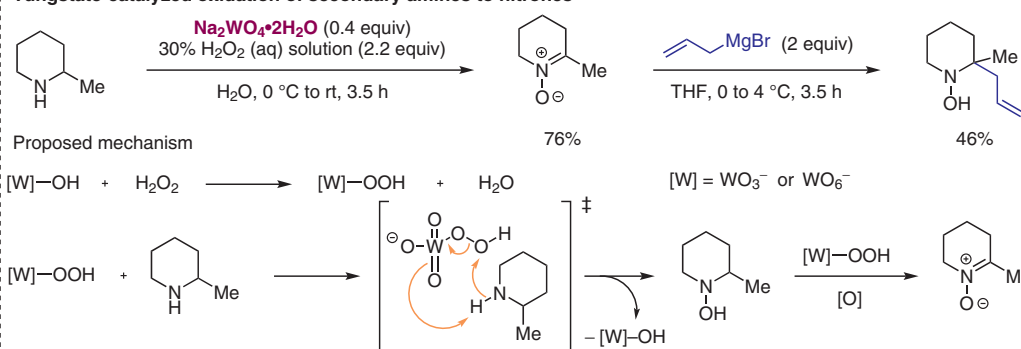
## Hypervalent iodine mediated oxidation



## Oxidative deamination of benzylamines



## Tungstate-catalyzed oxidation of secondary amines to nitrones



## Nitrones from hydroxylamine

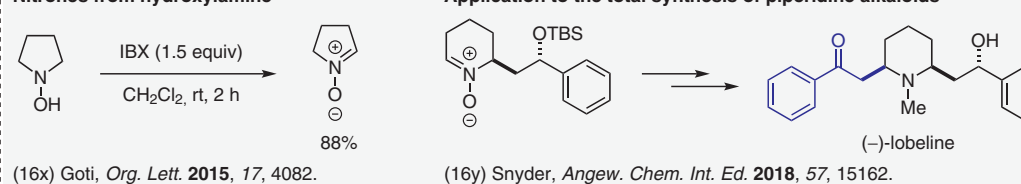


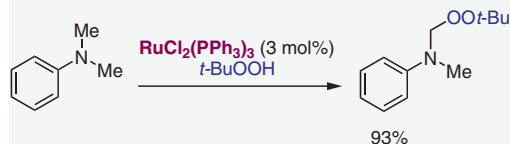
Figure 16 Oxidative preparation of building blocks.<sup>16</sup>



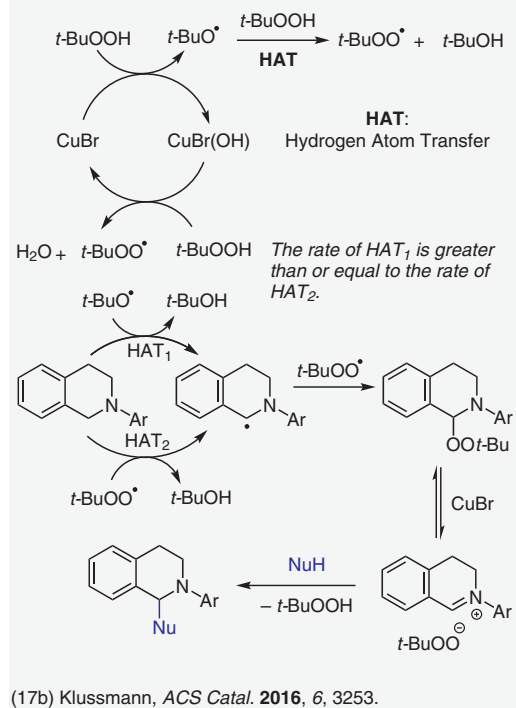
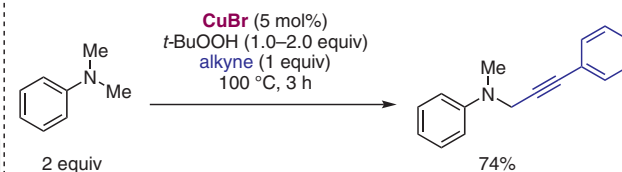
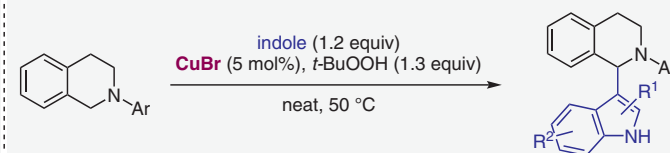
## Notable features

- Metal catalysis enables the use of readily available oxidants such as peroxides in the oxidation of amines.
- Radical intermediates are involved in some if not most reactions.
- Substrate scope is often limited to *N*-arylamines.

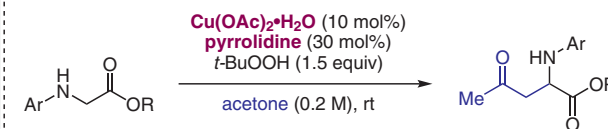
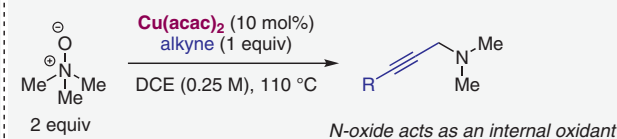
## Seminal work



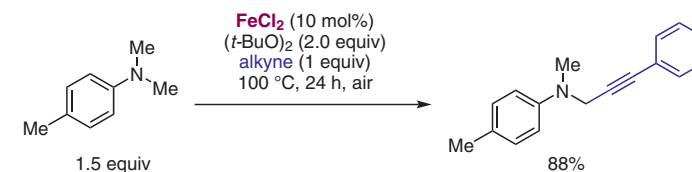
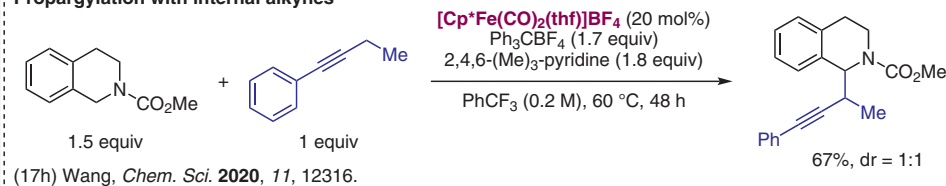
## Proposed mechanism

Alkynylation of *N,N*-dimethylanilinesArylation of *N*-aryltetrahydroisoquinolines

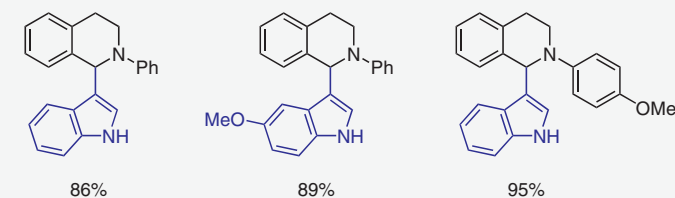
## Alkylation of secondary amino esters

Alkynylation of *N*-oxides

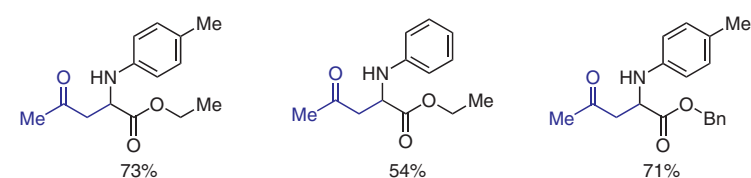
## Propargylation with internal alkynes



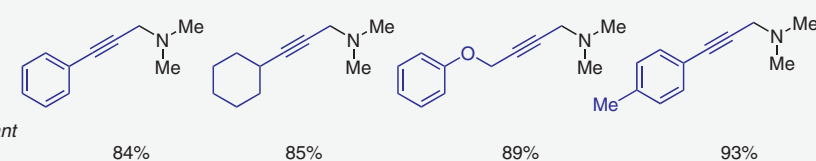
## Selected scope



## Selected scope



## Selected scope



## Further reading

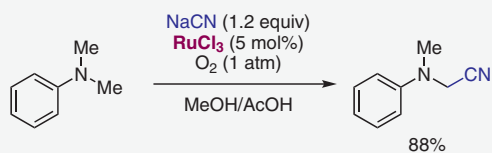
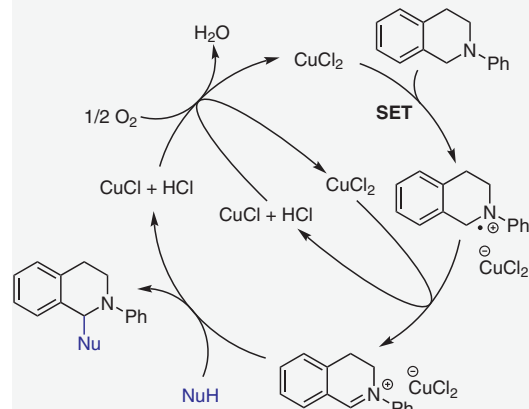
- (17i) Li, *Acc. Chem. Res.* **2009**, *42*, 335.
- (17j) Dong, *Chem. Rev.* **2011**, *11*, 1215.
- (17k) Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3464.
- (17l) Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74.
- (17m) Luo, *Chem. Rev.* **2017**, *117*, 9433.
- (17n) Li, *J. Org. Chem.* **2019**, *84*, 12705.
- (17o) Chen, *ChemSusChem* **2020**, *13*, 4776.

Figure 17 Metal-catalyzed cross-dehydrogenative-coupling (CDC) reactions.<sup>17</sup>

## Notable features

- Metal catalysis enables the use of oxygen as the terminal oxidant.
- Substrate scope is often limited to *N*-arylamines.

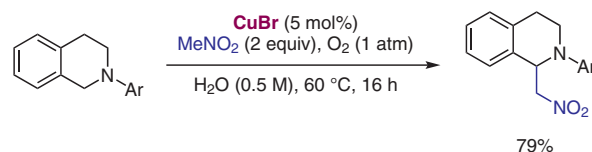
## Seminal example

(18a) Murahashi, *J. Am. Chem. Soc.* **2003**, *125*, 15312.Proposed mechanism of CuCl<sub>2</sub>-catalyzed reactions(18b) Klussmann, *J. Org. Chem.* **2014**, *79*, 12033.

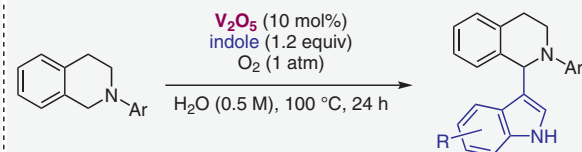
## Further reading

- (18i) Yang, *Green Chem.* **2014**, *16*, 2428.  
 (18j) Polyzos, *Chem. Commun.* **2015**, *51*, 334.  
 (18k) Gogoi, *ChemistrySelect* **2016**, *1*, 4620.  
 (18l) Schnürch, *Monatsh. Chem.* **2017**, *148*, 91.  
 (18m) Zhang, *RSC Adv.* **2017**, *7*, 1229.  
 (18n) Le, Zhu, *Synthesis* **2018**, *50*, 2775.  
 (18o) Chandrasekharam, *Adv. Synth. Catal.* **2018**, *360*, 4080.  
 (18p) Turner, Greaney, *ACS Catal.* **2018**, *8*, 10032.  
 (18q) Dong, *Adv. Synth. Catal.* **2021**, *363*, 1185.  
 (18r) Anilkumar, *Eur. J. Org. Chem.* **2021**, 1776.

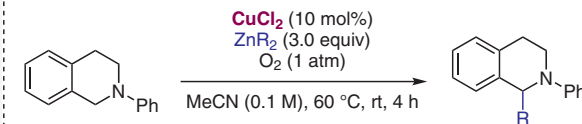
## Copper-catalyzed aza-Henry reaction

(18c) Li, *Green Chem.* **2007**, *9*, 1047.

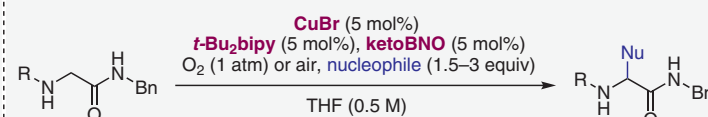
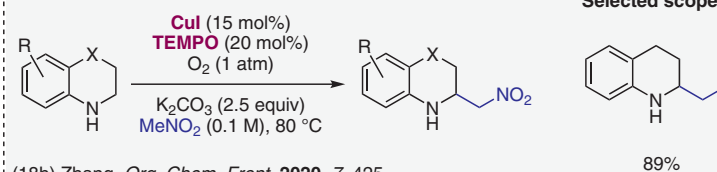
## Vanadium-catalyzed arylation

(18e) Prabhu, *Chem. Commun.* **2011**, *47*, 11787.

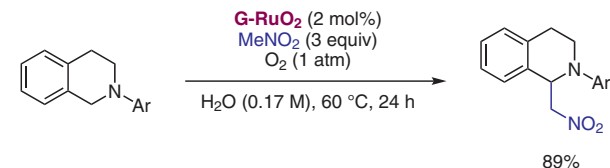
## Copper-catalyzed alkylation with organozinc reagents

(18f) Menche, *Org. Lett.* **2015**, *17*, 3982.

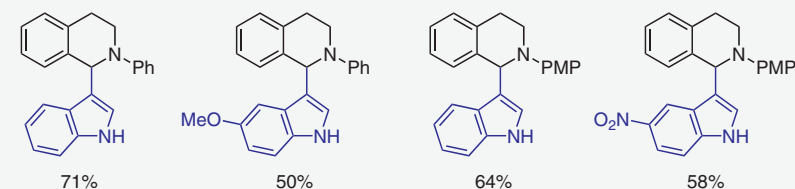
## Examples of dual catalysis involving aminoxy radicals

(18g) Kanai, *Chem. Sci.* **2012**, *3*, 3249.(18h) Zhang, *Org. Chem. Front.* **2020**, *7*, 425.

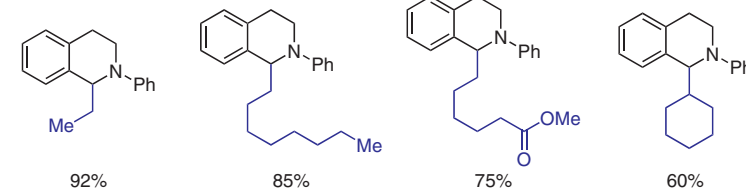
## Ruthenium-catalyzed aza-Henry reaction

(18d) Wu, *Org. Lett.* **2012**, *14*, 5992.

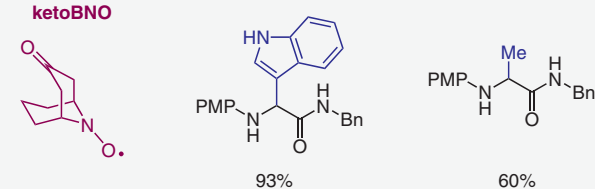
## Selected scope



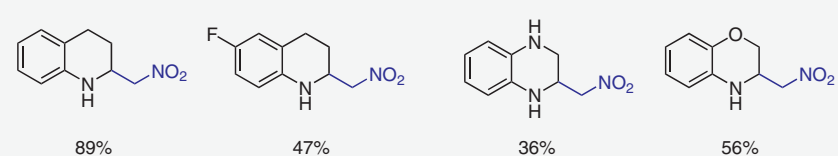
## Selected scope



## Selected scope



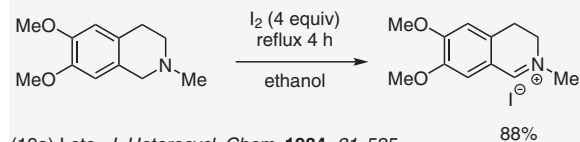
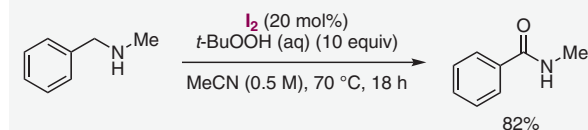
## Selected scope

Figure 18 Metal-catalyzed cross-dehydrogenative-coupling (CDC) reactions with oxygen as the terminal oxidant.<sup>18</sup>

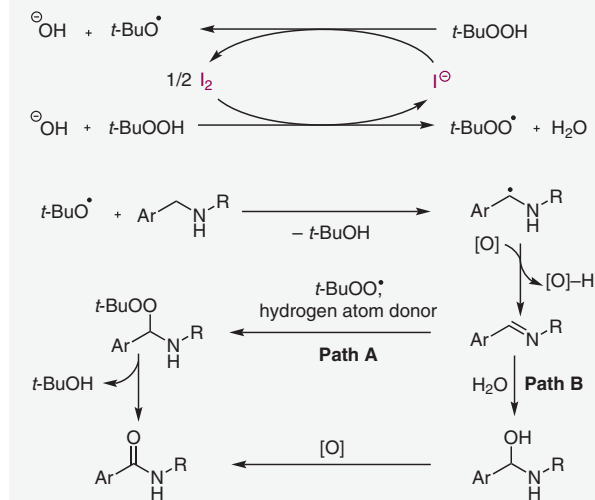
## Notable features

- Its low toxicity renders iodine an ideal catalyst.
- Peroxides or oxygen act as terminal oxidants.

## Historical precedent with stoichiometric iodine

Oxidation of benzylamines with I<sub>2</sub>

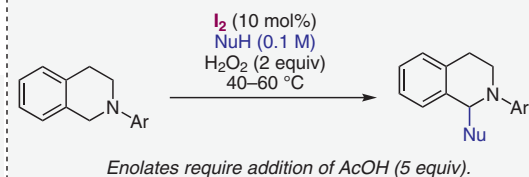
## Proposed mechanism



## Further reading

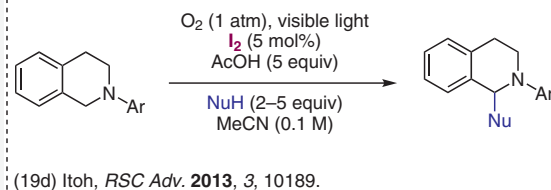
- (19h) Lei, *Chem. Asian J.* **2015**, *10*, 806.  
 (19i) Baruah, *Synlett* **2017**, *28*, 461.  
 (19j) Maiti, *ACS Omega* **2019**, *4*, 20410.

## Iodine-catalyzed alkylation



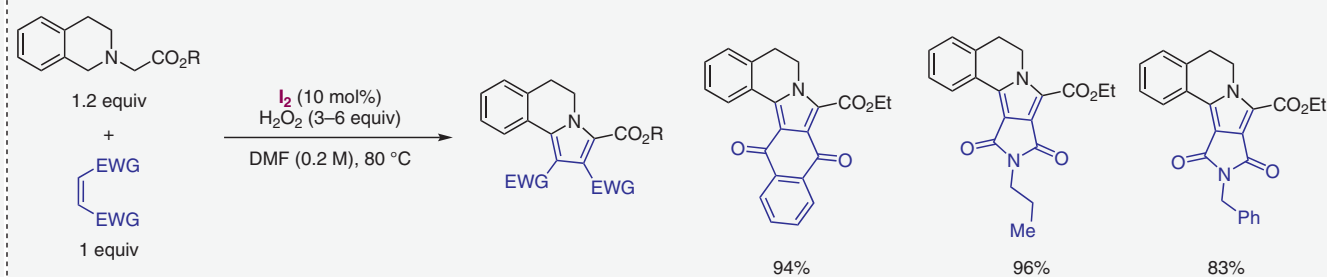
(19c) Itoh, *Org. Lett.* **2013**, *15*, 574.

## Oxygen as the terminal oxidant



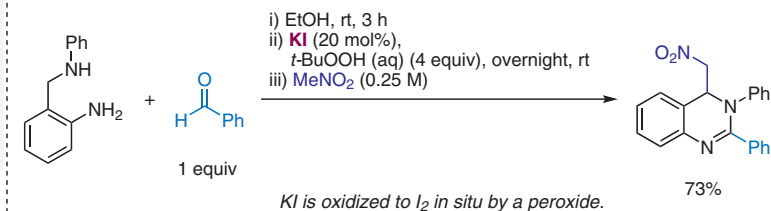
(19d) Itoh, *RSC Adv.* **2013**, *3*, 10189.

## Oxidative 1,3-dipolar cyclization



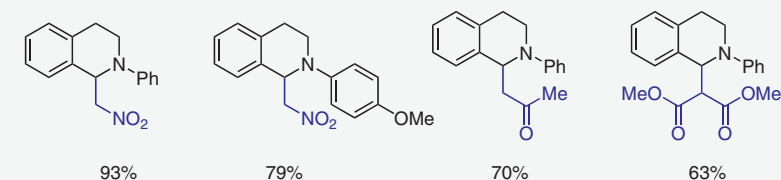
(19e) Gao, Li, *J. Org. Chem.* **2014**, *79*, 1084

## Examples of more complex reaction cascades

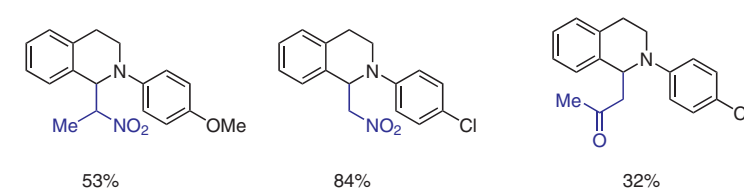


(19f) Reddy, Sridhar, *Adv. Synth. Catal.* **2012**, *354*, 2985.

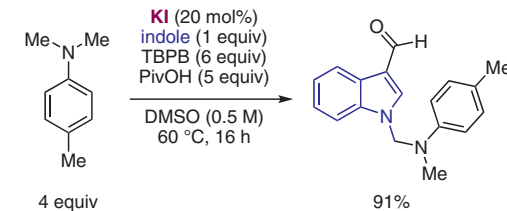
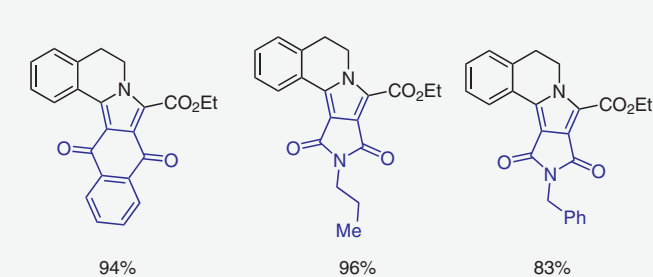
## Selected scope



## Selected scope



## Selected scope



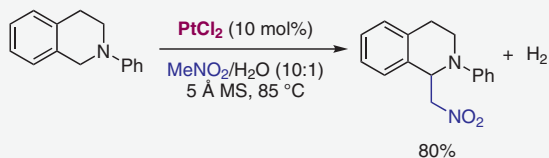
(19g) Wang, *Org. Biomol. Chem.* **2012**, *10*, 9519.

Figure 19 Iodine-catalyzed cross-dehydrogenative-coupling (CDC) reactions.<sup>19</sup>

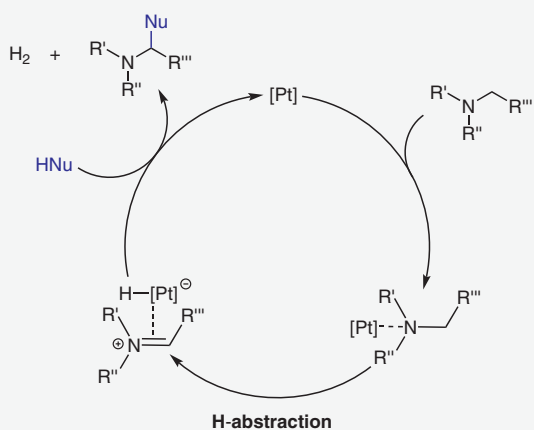
## Notable features

- Coupling with concomitant release of hydrogen gas obviates the need for a stoichiometric oxidant.
- Thermal, photochemical, and electrochemical variants have been developed.

## Seminal example



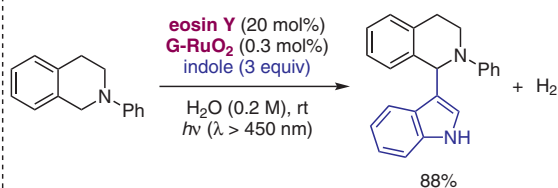
## Proposed mechanism



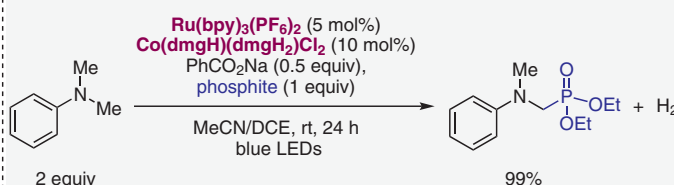
(20a) Liang, *Org. Biomol. Chem.* **2010**, *8*, 4077.

## Further reading

- (20m) Milstein, *J. Am. Chem. Soc.* **2014**, *136*, 2998.  
 (20n) Li, *ChemSusChem* **2014**, *7*, 2788.  
 (20o) Zhang, *Org. Lett.* **2017**, *19*, 3390.  
 (20p) Tung, Wu, *Acc. Chem. Res.* **2018**, *51*, 2512.  
 (20q) Lei, *J. Am. Chem. Soc.* **2018**, *140*, 13128.  
 (20r) Lei, *Chem. Rev.* **2019**, *119*, 6769.

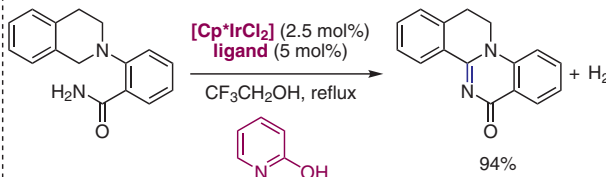
Photochemical  $\alpha$ -arylation

(20b) Wu, *J. Am. Chem. Soc.* **2013**, *135*, 19052.  
 See also: (20c) Wu, *Org. Lett.* **2014**, *16*, 1988.

Photochemical  $\alpha$ -phosphonylation

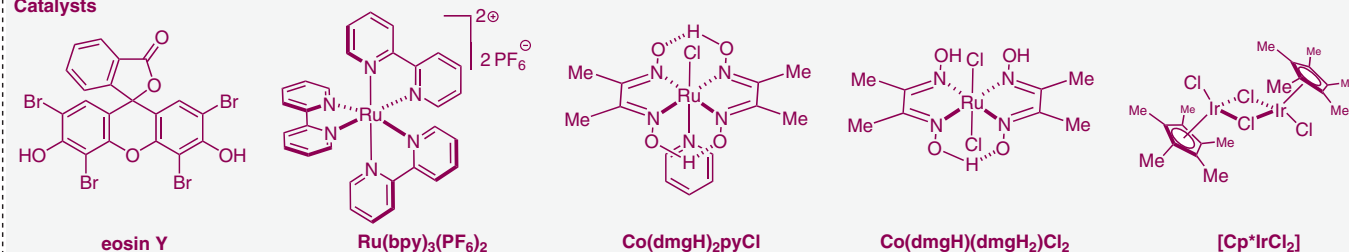
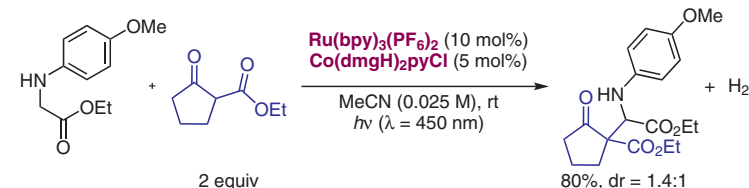
(20f) Lei, *Chem. Commun.* **2018**, *54*, 1659.  
 See also: (20g) Yang, *Chem. Commun.* **2014**, *50*, 8529.

## Intramolecular coupling



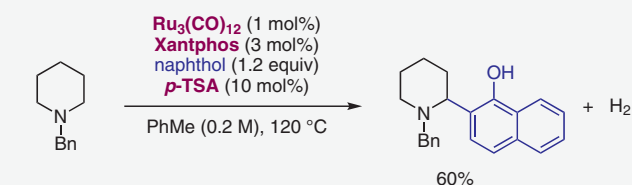
(20i) Yan, *Adv. Synth. Catal.* **2013**, *355*, 2179.  
 See also: (20j) Xiao, *Org. Lett.* **2013**, *15*, 2394.  
 (20k) Yan, *Org. Biomol. Chem.* **2015**, *13*, 7381.

## Catalysts

Photochemical  $\alpha$ -alkylation of amino acid esters

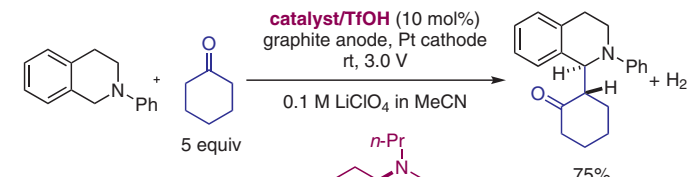
(20d) Wu, *ACS Catal.* **2015**, *5*, 2391.  
 See also: (20e) Zhang, *J. Org. Chem.* **2019**, *84*, 3559.  
 Relative stereochemistry of major diastereomer not established.

## Thermal cross-coupling



(20h) Zhang, *Org. Lett.* **2020**, *22*, 4781.

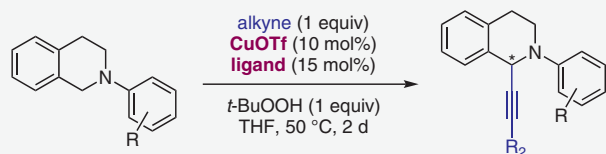
## Asymmetric electrochemical cross-coupling hydrogen evolution



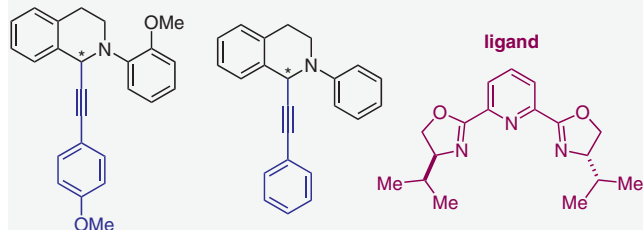
(20l) Luo, *Org. Lett.* **2017**, *19*, 2122.

Figure 20 Acceptorless cross-dehydrogenative-coupling (CDC) reactions with hydrogen evolution.<sup>20</sup>

## Seminal asymmetric example



## Selected scope

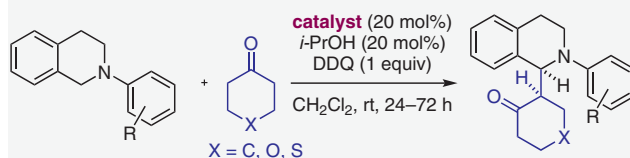


56%, 69% ee

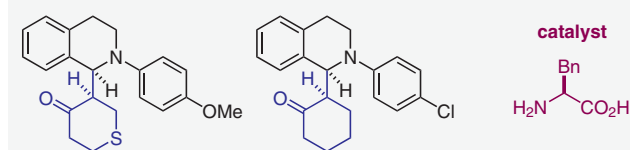
67%, 63% ee

(21a) Li, *Org. Lett.* **2004**, *6*, 4997.(21b) Li, *Tetrahedron: Asymmetry* **2006**, *17*, 590.

## Organocatalytic alkylation with ketones



## Selected scope



73%, dr = 8:1, 90% ee

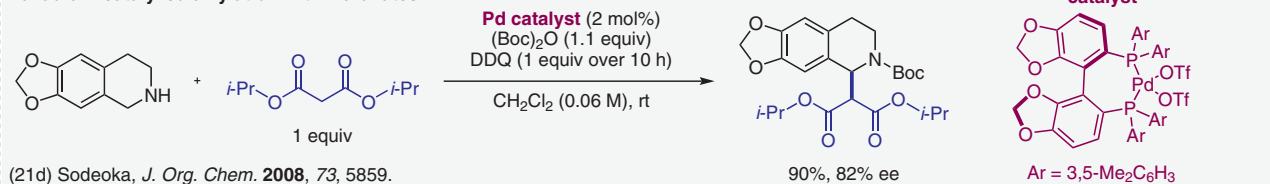
75%, dr = 3:1, 84% ee

(21c) Wang, *Chem. Sci.* **2013**, *4*, 2645.

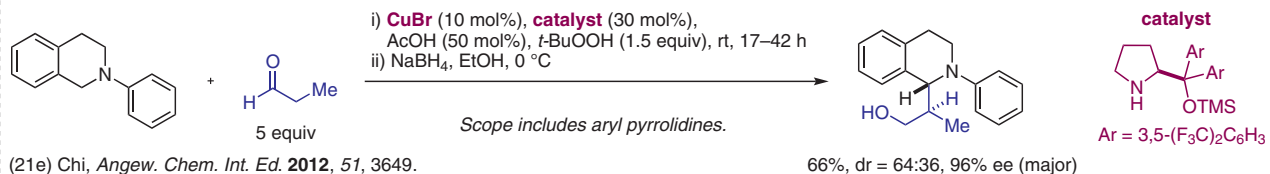
## Further reading

(21i) Xu, *Tetrahedron Lett.* **2015**, *56*, 3703.(21j) Yang, *Synlett* **2017**, *28*, 159(21k) Gandhi, *Org. Biomol. Chem.* **2019**, *17*, 9683.(21l) Pombeiro, *Catalysts* **2020**, *10*, 529.(21m) Vila, *Adv. Synth. Catal.* **2021**, *363*, 602.

## Palladium-catalyzed alkylation with malonates

(21d) Sodeoka, *J. Org. Chem.* **2008**, *73*, 5859.

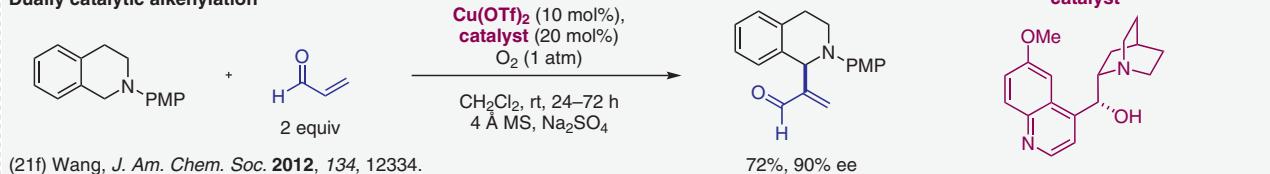
## Dually catalytic alkylation with aldehydes

(21e) Chi, *Angew. Chem. Int. Ed.* **2012**, *51*, 3649.

Scope includes aryl pyrrolidines.

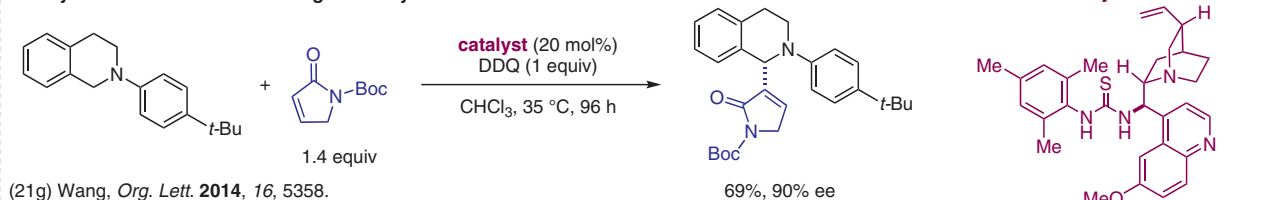
66%, dr = 64:36, 96% ee (major)

## Dually catalytic alkenylation

(21f) Wang, *J. Am. Chem. Soc.* **2012**, *134*, 12334.

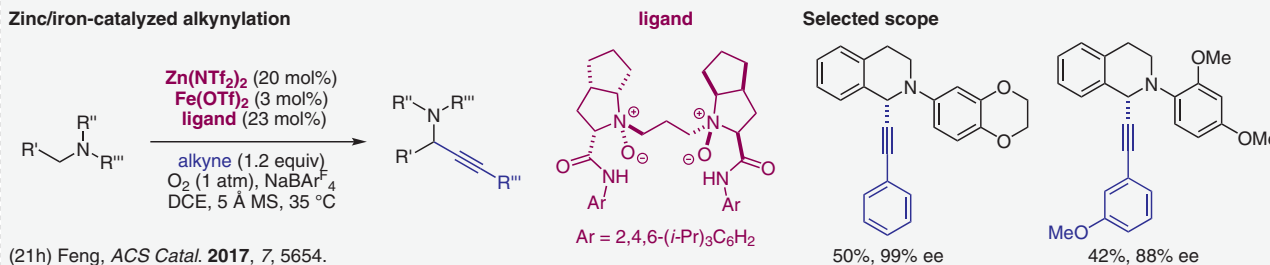
72%, 90% ee

## Alkenylation with a bifunctional organocatalyst

(21g) Wang, *Org. Lett.* **2014**, *16*, 5358.

69%, 90% ee

## Zinc/iron-catalyzed alkylation

(21h) Feng, *ACS Catal.* **2017**, *7*, 5654.

50%, 99% ee

42%, 88% ee

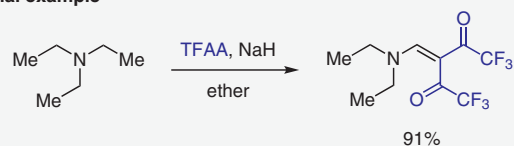
Figure 21 Catalytic enantioselective cross-dehydrogenative-coupling (CDC) reactions.<sup>21</sup>



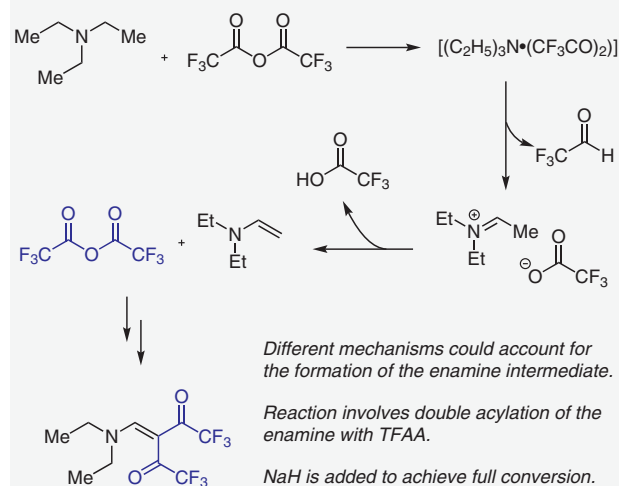
## Notable features

- Mechanistically diverse methods access enamines from amines as a platform for  $\beta$ - and multifunctionalization.
- Applicable to both linear and cyclic tertiary amines.

## Seminal example



## Proposed mechanism

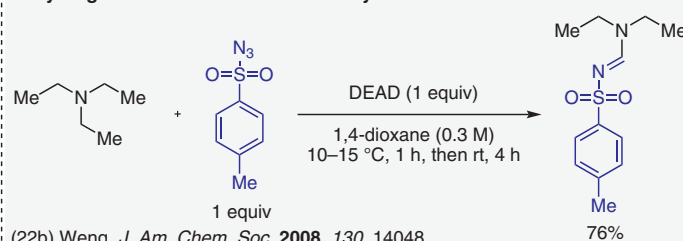


(22a) Schreiber, *Tetrahedron Lett.* **1980**, 21, 1027.

## Further reading

- (22k) Archard, *Chem. Eur. J.* **2015**, 21, 14319  
 (22l) Zhang, *Synlett* **2017**, 28, 1630.  
 (22m) Zhou, *Chem. Commun.* **2017**, 53, 8770.  
 (22n) Fan, *Chem. Commun.* **2017**, 53, 4002.  
 (22o) Opatz, *Adv. Heterocycl. Chem.* **2018**, 125, 107.  
 (22p) Fan, Zhang, *J. Org. Chem.* **2018**, 83, 6524.  
 (22q) Fan, Zhang, He, *Chem. Commun.* **2019**, 55, 12372.  
 (22r) Jia, Yuan, *Org. Lett.* **2019**, 21, 5030.

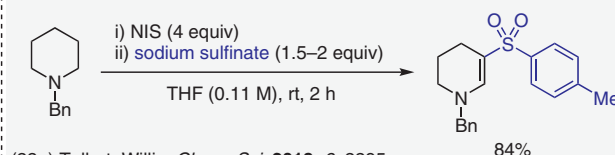
## Dehydrogenation with DEAD followed by cascade reactions with azides



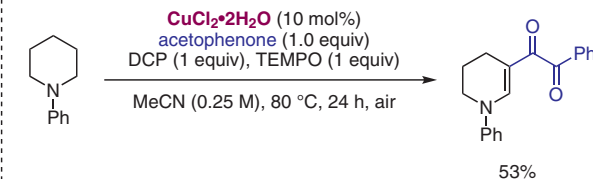
(22b) Weng, *J. Am. Chem. Soc.* **2008**, 130, 14048.  
 See also: (22c) Zheng, Wang, *Chem. Commun.* **2009**, 47, 7372.

Platinum-catalyzed  $\alpha,\beta$ -difunctionalization

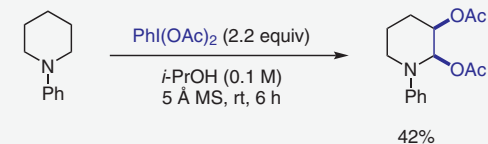
(22e) Liang, *J. Org. Chem.* **2010**, 75, 2893.

Oxidative  $\beta$ -sulfonylation with NIS

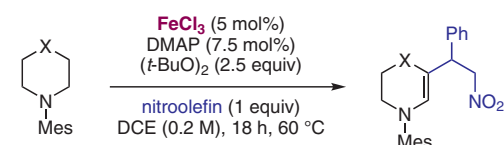
(22g) Talbot, Willis, *Chem. Sci.* **2018**, 9, 2295.  
 See also: (22h) Fan, He, *J. Org. Chem.* **2020**, 85, 15600.

Complex reaction cascade leading to  $\alpha$ -keto-enaminones

(22j) Fan, Zhang, *J. Org. Chem.* **2020**, 85, 2220.

 $\alpha,\beta$ -Dioxygenation with DIB

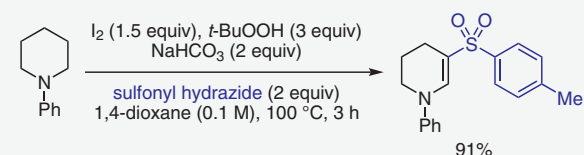
(22d) Liang, *J. Org. Chem.* **2009**, 74, 7464.

Iron-catalyzed  $\beta$ -alkylation

Applicable to linear amines.

(22f) Kanai, Oisaki, *Org. Lett.* **2013**, 15, 1918.

X = C, 70%  
 X = O, 58%  
 X = S, 44%  
 X = NBoc, 54%

Oxidative  $\beta$ -sulfonylation with iodine

(22i) Xia, Gu, *Eur. J. Org. Chem.* **2021**, 701.

## Selected scope

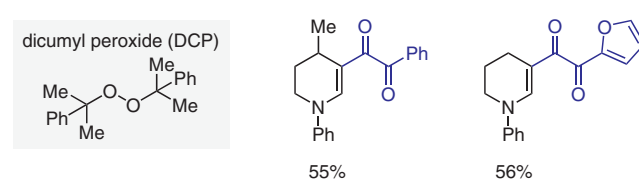
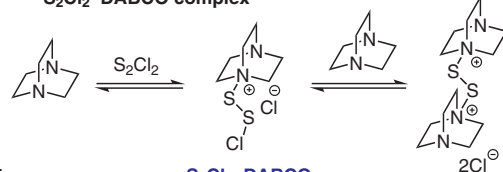


Figure 22 Oxidative  $\beta$ -functionalization.<sup>22</sup>

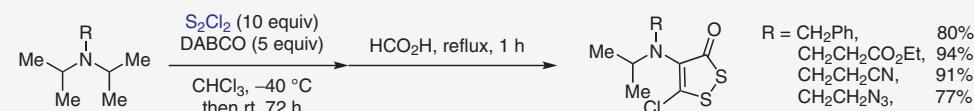
## Notable features

- $S_2Cl_2$  serves as a sulfurating, chlorinating, oxidizing, and dehydrating agent.
- Formation of sulfur-rich heterocycles.

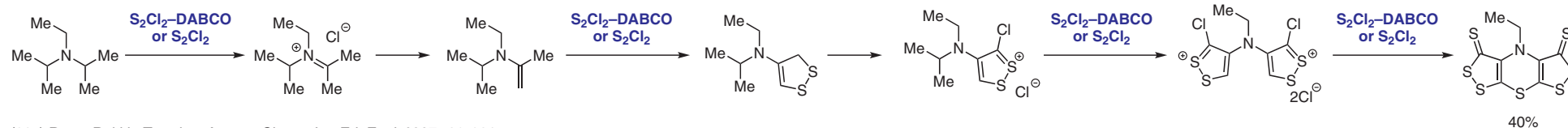
## Reviews

(23a) Rakitin, Rees, *Chem. Rev.* **2004**, 104, 2617.(23b) Rakitin, *Chem. Heterocycl. Compd. (Engl. Transl.)* **2020**, 56, 837. $S_2Cl_2$ -DABCO complex

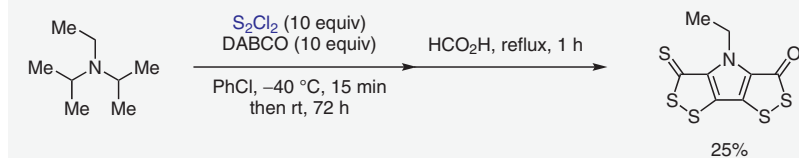
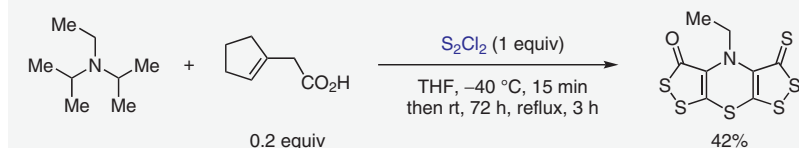
## Synthesis of 1,2-dithiol rings

(23h) Rakitin, *Russ. Chem. Bull., Int. Ed.* **2006**, 55, 147.

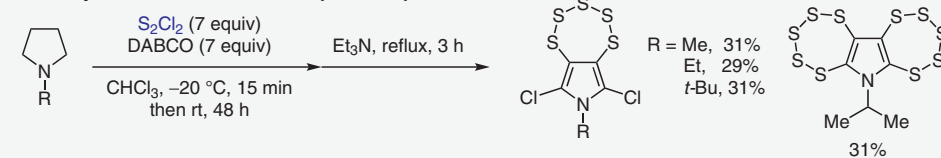
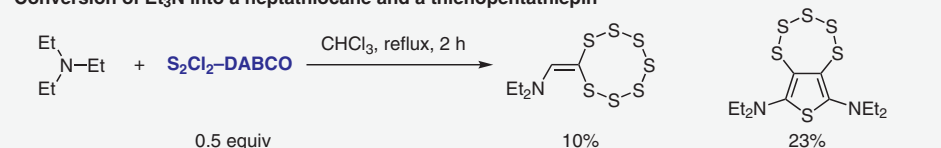
## From Hünig's base to bis[1,2]dithiolo[1,4]thiazine

(23c) Rees, Rakitin, Torroba, *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 281.

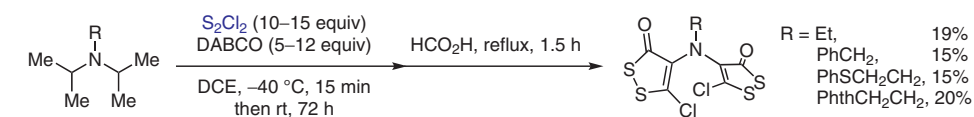
## Synthesis of bis[1,2]dithiolo[1,4]thiazines and bis[1,2]dithiopyrroles from Hünig's base

(23d) Rakitin, Rees, Torroba, *Chem. Commun.* **1997**, 879.(23e) Rees, Rakitin, Torroba, *J. Org. Chem.* **1998**, 63, 2189.See also: (23f) Rakitin, Rees, Torroba, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3421.

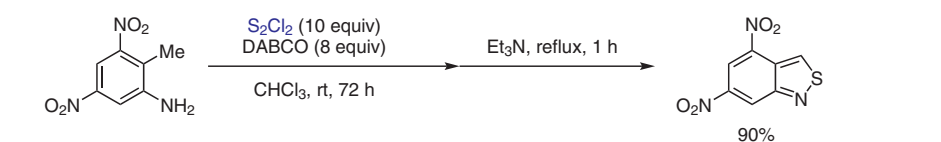
## Direct synthesis of fused 1,2,3,4,5-pentathiepins

(23i) Rakitin, Rees, *Org. Biomol. Chem.* **2005**, 3, 3496.See also: (23j) Rakitin, *Russ. Chem. Bull., Int. Ed.* **2006**, 55, 2081.Conversion of Et<sub>3</sub>N into a heptathiocane and a thienopentathiepin(23k) Rakitin, Rees, *Org. Lett.* **2003**, 5, 1939.

## Synthesis of N,N-bis(5-chloro-3-oxo[1,2]dithiol-4-yl)amines

(23g) Rees, *J. Chem. Soc., Perkin Trans. 1* **1999**, 2237.

## Synthesis of 4,6-dinitrobenzo[c]isothiazole

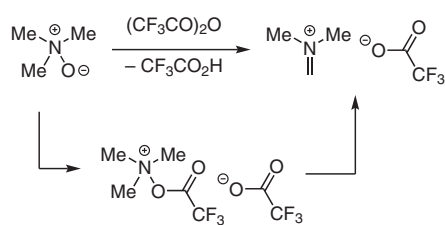
(23l) Shevelev, *Mendeleev Commun.* **2010**, 20, 353.Figure 23 Oxidative formation of sulfur-rich heterocycles.<sup>23</sup>

**Polonovski–Potier Reaction**

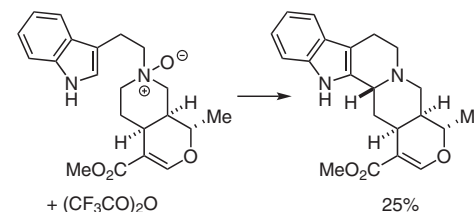
Oxidation of tertiary amines to *N*-oxides enables iminium ion formation via acylation followed by elimination.

Reviews:  
(24a) Koskinen, *Heterocycles* **1984**, *22*, 1591.  
(24b) Grierson, *Org. React.* **1990**, *39*, 85.

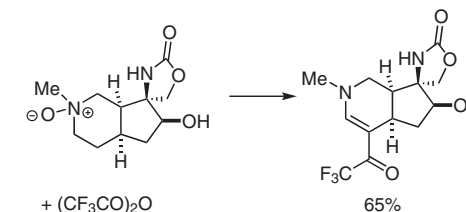
Application to complex natural product synthesis:  
(24c) Potier, *J. Am. Chem. Soc.* **1976**, *98*, 7017.  
(24d) Fukuyama, *Angew. Chem. Int. Ed.* **2011**, *50*, 4884.

**Iminium ion formation**

(24e) Potier, *J. Am. Chem. Soc.* **1968**, *90*, 5622.

**Application to the Pictet–Spengler reaction**

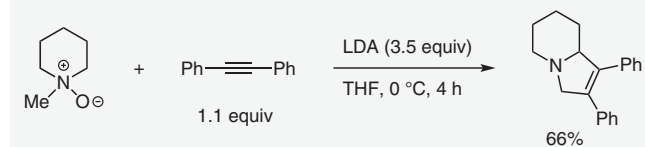
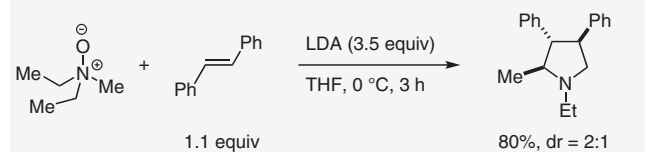
(24f) Sakai, *Tetrahedron* **1973**, *29*, 2015.

**Enamine formation**

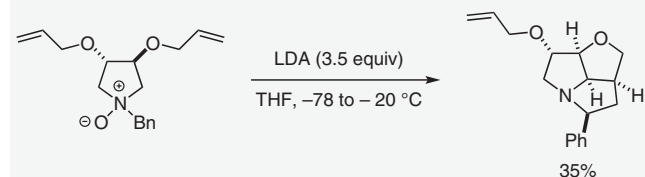
(24g) Kende, *J. Am. Chem. Soc.* **1995**, *117*, 10597.  
See also: (24h) Wenkert, *Synth. Commun.* **1973**, *3*, 73.

**Roussi reaction**

Treatment of tertiary amine *N*-oxides with LDA leads to deoxygenative formation of azomethine ylides that subsequently engage in (3+2) cycloadditions.

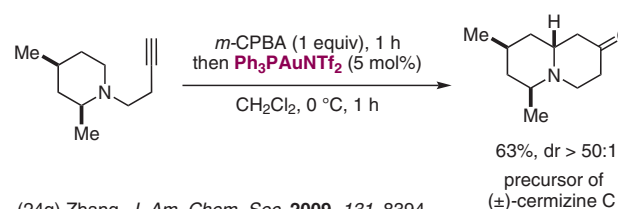


(24i) Roussi, *Chem. Commun.* **1983**, 31. (24j) Roussi, *Heterocycles* **1985**, *23*, 653. (24k) Roussi, *J. Org. Chem.* **1985**, *50*, 2910. (24l) Roussi, *J. Org. Chem.* **1988**, *53*, 3808. See also: (24m) Davoren, *Synlett* **2010**, 2490.

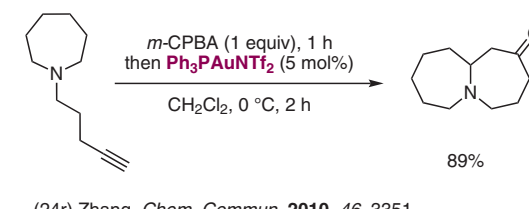


(24n) Takano, *Heterocycles* **1992**, *34*, 1519.  
Mechanistic studies: (24o) Williams, *Aust. J. Chem.* **2014**, *67*, 1309.

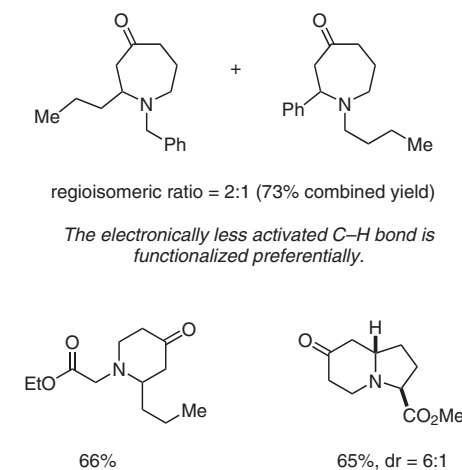
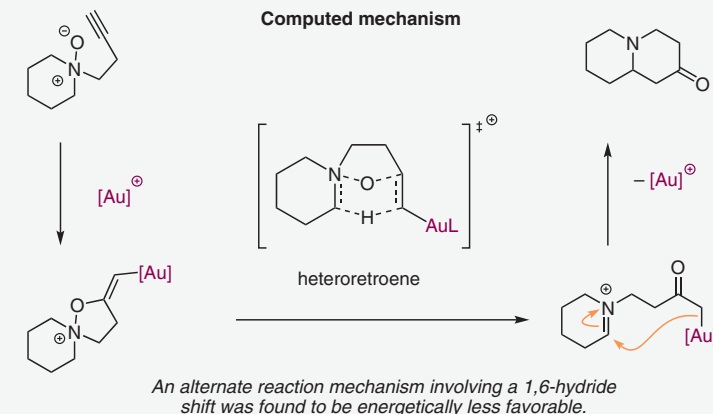
Review on amine *N*-oxides:  
(24p) Woodward, *Org. Prep. Proced. Int.* **2009**, *41*, 173.

**Gold-catalyzed C–H functionalization**

(24q) Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 8394.



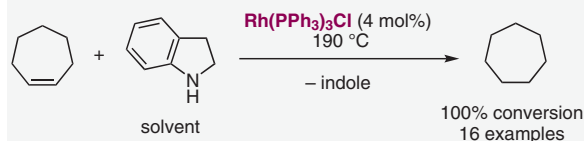
(24r) Zhang, *Chem. Commun.* **2010**, 46, 3351.

**Additional scope****Computed mechanism**

(24s) Zhang, Houk, *J. Am. Chem. Soc.* **2012**, *134*, 1078.

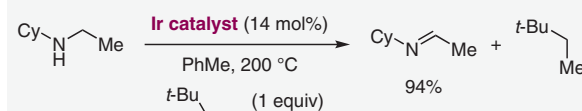
**Figure 24** Reactions involving amine *N*-oxides.<sup>24</sup>

## Historical precedent

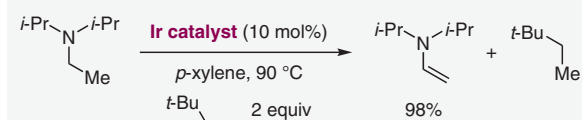


(25a) Nishiguchi, *J. Org. Chem.* **1975**, *40*, 237.  
See also: (25b) Otsuka, *J. Chem. Soc., Chem. Commun.* **1979**, 870.  
(25c) Murahashi, *J. Chem. Soc., Chem. Commun.* **1985**, 613.

## Seminal work



(25d) Jensen, *J. Mol. Catal. A: Chem.* **2002**, *189*, 119.

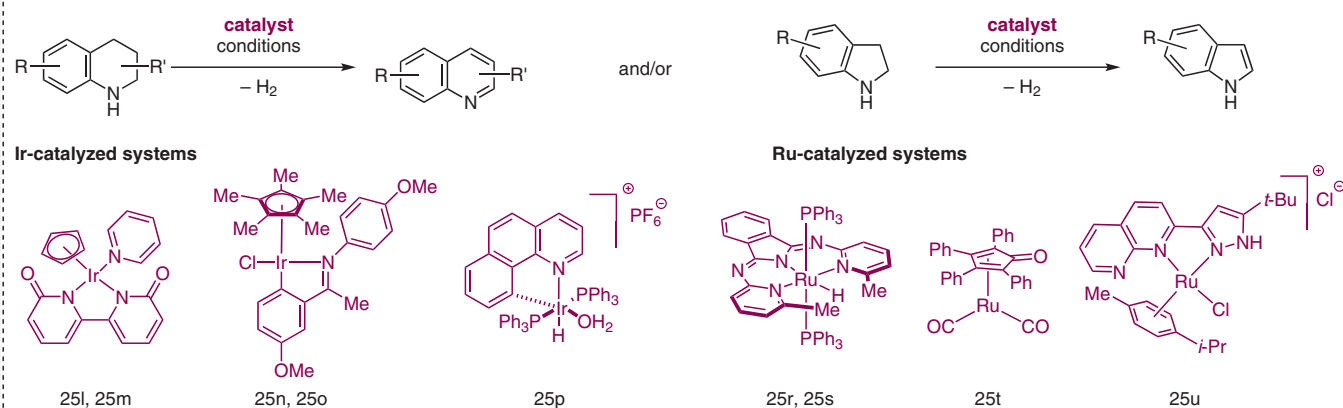


(25e) Knapp, Goldman, *Chem. Commun.* **2003**, 2060.  
See also: (25f) Chihara, *J. Catal.* **2005**, *230*, 204.  
(25g) Yi, *Organometallics* **2009**, *28*, 947.  
(25h) Jensen, *J. Organomet. Chem.* **2009**, *694*, 2854.  
(25i) Brayton, *Chem. Commun.* **2014**, *50*, 5987.  
(25j) Goldman, *J. Org. Chem.* **2020**, *85*, 3020.  
(25k) Liu, Huang, *Chin. J. Chem.* **2020**, *38*, 837.

## Further reading

(25ad) Yu, *Adv. Synth. Catal.* **2019**, *361*, 3958.  
(25ae) Kanai, *J. Am. Chem. Soc.* **2017**, *139*, 2204.  
(25af) Ihee, Hong, *Chem. Sci.* **2021**, *12*, 1915.  
(25ag) Li, *Angew. Chem. Int. Ed.* **2017**, *56*, 3080.  
(25ah) Jones, *J. Am. Chem. Soc.* **2014**, *136*, 8564.  
(25ai) Brookhart, *J. Am. Chem. Soc.* **2007**, *129*, 14544.

## Selected examples of acceptorless dehydrogenation of amines utilizing metal catalysts

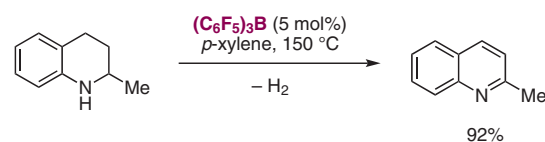


(25l) Fujita, Yamaguchi, *J. Am. Chem. Soc.* **2014**, *136*, 4829.  
(25m) Yamaguchi, Fujita, *J. Am. Chem. Soc.* **2009**, *131*, 8410.  
(25n) Xiao, *Angew. Chem. Int. Ed.* **2013**, *52*, 6983.  
(25o) Xiao, *Angew. Chem. Int. Ed.* **2015**, *54*, 5223.  
(25p) Crabtree, *J. Organomet. Chem.* **2015**, *792*, 184.  
See also: (25q) Iwai, Sawamura, *Org. Lett.* **2020**, *22*, 5240.

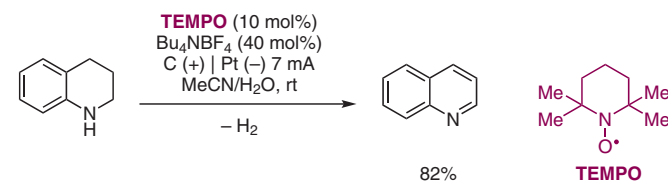
(25r) Szymczak, *J. Am. Chem. Soc.* **2013**, *135*, 16352.  
(25s) Paul, Szymczak, *ACS Catal.* **2016**, *6*, 4799.  
(25t) Hong, *Adv. Synth. Catal.* **2012**, *354*, 3045.  
(25u) Holscher, Bera, *J. Am. Chem. Soc.* **2018**, *140*, 8662.  
See also: (25v) Yu, *Organometallics* **2018**, *37*, 584.  
(25w) Blacquiere, *Organometallics* **2017**, *36*, 1692.

## Selected examples of transition-metal-free systems for the dehydrogenation of amines

## Acceptorless

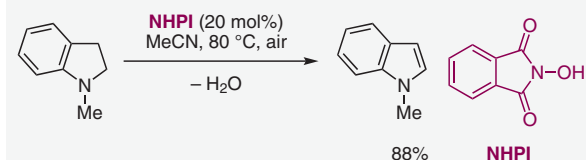


(25x) Kanai, *Angew. Chem. Int. Ed.* **2016**, *55*, 12224.  
See also: (25y) Grimme, Paradies, *Angew. Chem. Int. Ed.* **2016**, *55*, 12219.

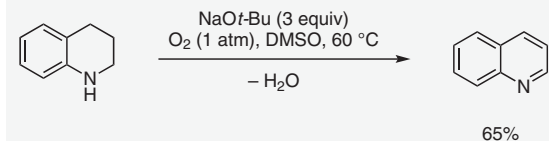


(25z) Lei, *ACS Catal.* **2018**, *8*, 1192.

## Aerobic



(25aa) Luo, *Adv. Synth. Catal.* **2020**, *362*, 3905.



(25ab) Xie, Cai, *J. Org. Chem.* **2020**, *85*, 7501.  
See also: (25ac) Song, Wang, *Chem. Eur. J.* **2018**, *24*, 2065.

Figure 25 Dehydrogenation/aromatization.<sup>25</sup>

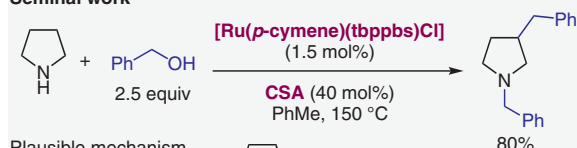
## Notable features

- Powerful tool for the formation of both C–C and C–N bonds.
- No need for prefunctionalizing the amine, alcohol, or aldehyde coupling partners.
- Typically initiates by oxidation of a substrate by the catalyst and ends with reduction of an intermediate to regenerate the catalyst.

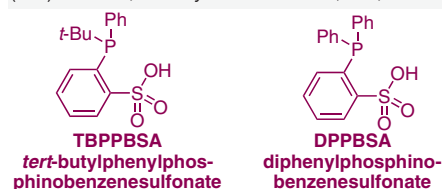
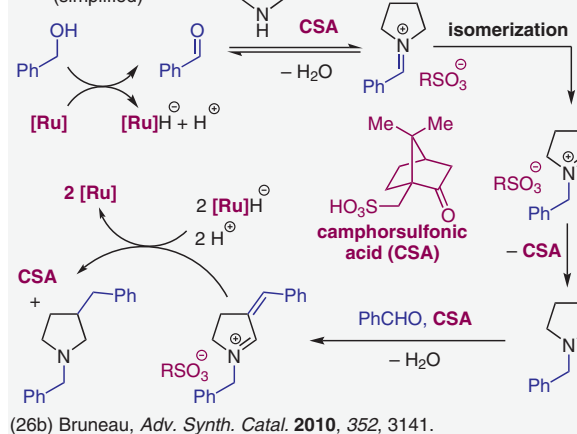
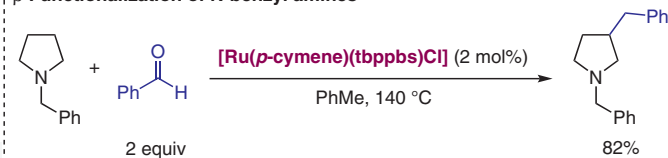
## Historical precedent



## Seminal work

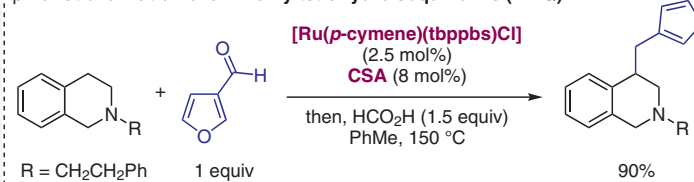


## Plausible mechanism (simplified)

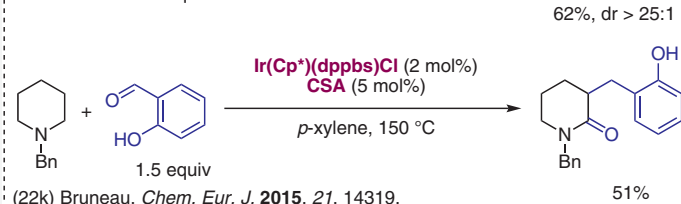
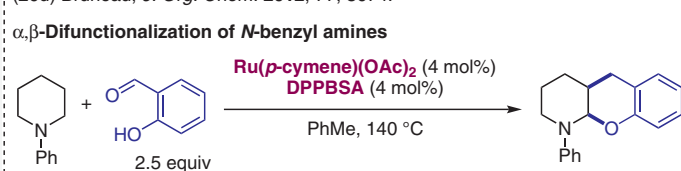
 $\beta$ -Functionalization of *N*-benzyl amines

Both electron-donating and -withdrawing groups on the aryl group are tolerated. Pyrrolidines, piperidines, azepanes, morpholine and THIQ are viable substrates.

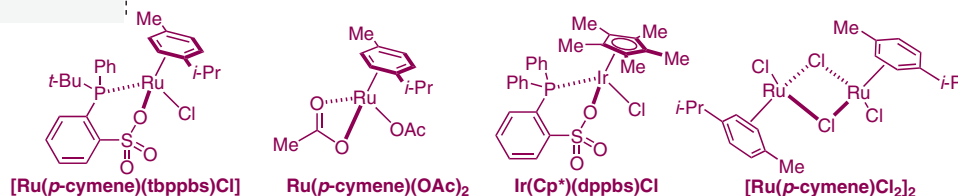
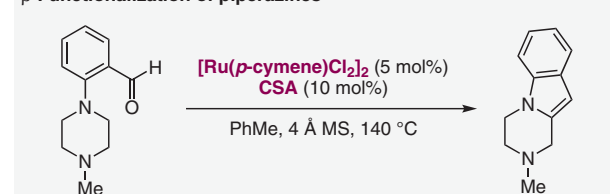
(26c) Bruneau, *J. Am. Chem. Soc.* **2011**, 133, 10340.

 $\beta$ -Functionalization of an *N*-alkyltetrahydroisoquinoline (THIQ)

Other aldehydes based on benzofurans, thiofurans, and indoles are also tolerated.

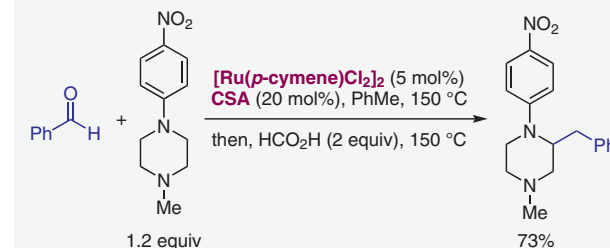
 $\alpha,\beta$ -Difunctionalization of *N*-benzyl amines

(22k) Bruneau, *Chem. Eur. J.* **2015**, 21, 14319.

 $\beta$ -Functionalization of piperazines

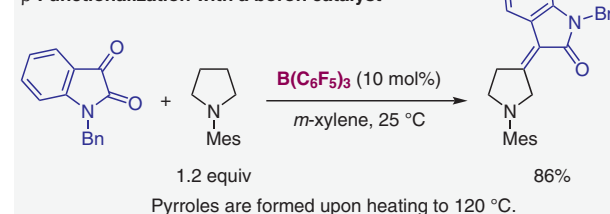
Aryl substituents tolerated: F, Cl, Br, CF<sub>3</sub>, NO<sub>2</sub>.

(26e) Suresh, *Chem. Commun.* **2017**, 53, 10448.



Electron donating and withdrawing groups on aldehyde tolerated. Alkyl aldehydes also tolerated.

(26f) Suresh, *Adv. Synth. Catal.* **2021**, 363, 453.

 $\beta$ -Functionalization with a boron catalyst

Pyrroles are formed upon heating to 120 °C.

## Further reading

- (26h) Bruneau, *Angew. Chem. Int. Ed.* **2012**, 51, 8876.
- (26i) Bruneau, *Green Chem.* **2013**, 15, 775.
- Review on ruthenium-catalyzed hydrogen autotransfer: (26j) Bruneau, *Top. Organomet. Chem.* **2014**, 48, 195.
- Review on alkylation via hydrogen autotransfer: (26k) Kempe, *Chem. Rev.* **2019**, 119, 2524.

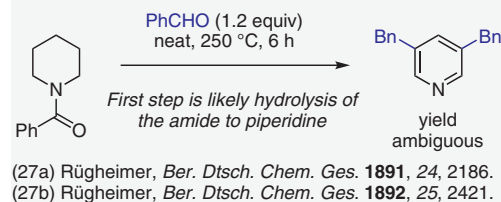
Figure 26 Hydrogen borrowing.<sup>26</sup>



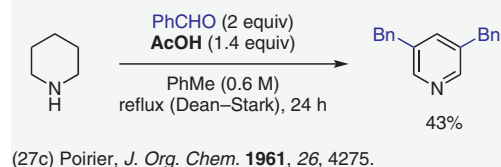
## Notable features

- Simple method for obtaining substituted aromatic heterocycles from their (partially) saturated azacycles.
- Formation of pyrroles from 3-pyrroline or pyrrolidine, and indoles from indoline, are redox-neutral. One equivalent of aldehyde serves as oxidant in the formation of pyridines from piperidine, and isoquinolines from 1,2,3,4-tetrahydroisoquinoline.
- Reactions are mostly limited to arylaldehydes.

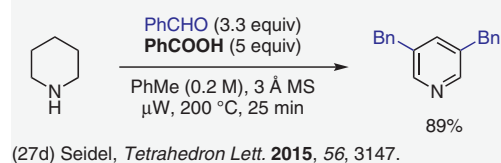
## Seminal discovery



## Improved procedure



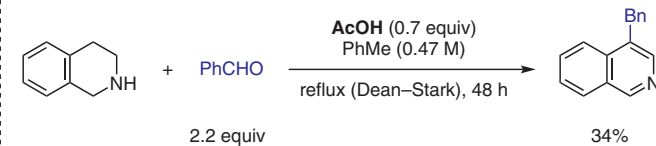
## Further optimization



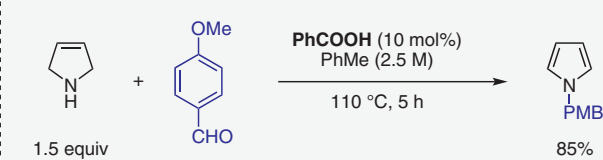
## Other selected contributions

- (27e) Burrows, *J. Org. Chem.* **1962**, 27, 316.  
 (27f) Sainsbury, *Tetrahedron* **1968**, 24, 427.  
 (27g) Dannhardt, *Arch. Pharm.* **1986**, 319, 977.  
 (27h) Cook, *Lett. Org. Chem.* **2004**, 1, 1.  
 (27i) Toma, *Synth. Commun.* **2009**, 39, 1871.  
 (27j) Yu, *Org. Lett.* **2011**, 13, 6054.  
 (27k) Lodeiro, *Chem. Eur. J.* **2014**, 20, 6684.

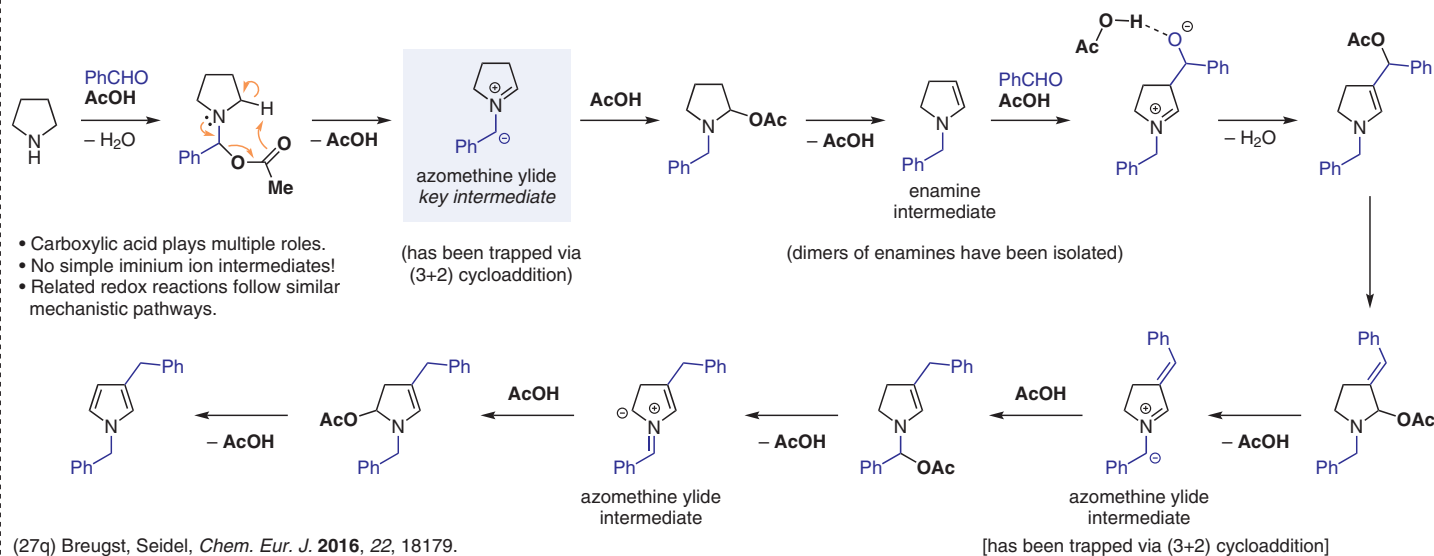
## Isoquinolines from 1,2,3,4-tetrahydroisoquinoline



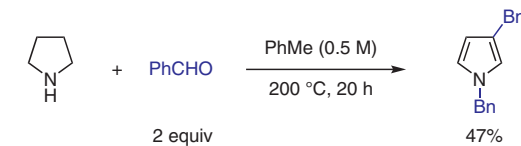
## Pyrroles from 3-pyrroline



## Computationally determined lowest-energy pathway for the acetic acid catalyzed reaction between benzaldehyde and pyrrolidine



## Pyrroles from pyrrolidine



## Indoles from indoline

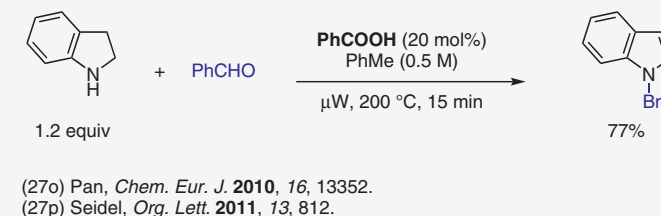
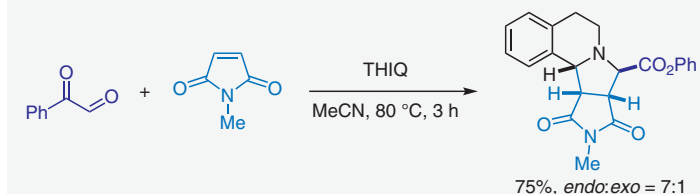
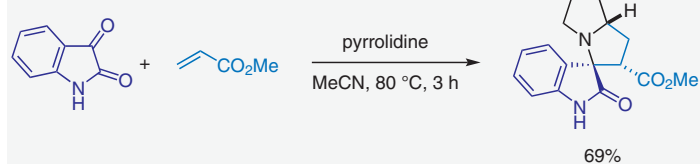


Figure 27 Condensation-based methods involving azomethine ylide intermediates, aromatization.<sup>27</sup>

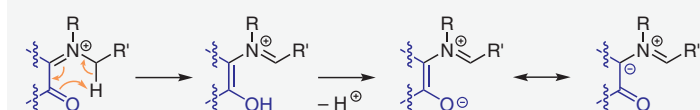
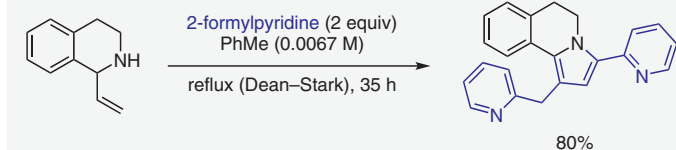
## Notable features

- Azomethine ylides resulting from condensation of a secondary amine with a carbonyl compound undergo pericyclic reactions.
- Redox-neutral method enabling rapid increase of molecular complexity.

## Seminal work: (3+2) cycloaddition



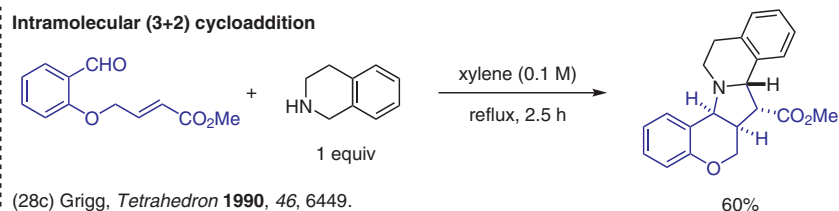
via:

(28a) Grigg, *J. Chem. Soc., Chem. Commun.* **1986**, 602.Seminal work: 6 $\pi$ -electrocyclization

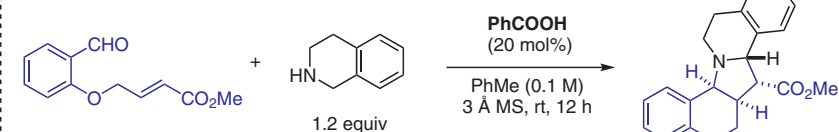
## Other selected contributions

- (28j) Risch, *Synthesis* **1996**, 367.  
 (28k) Miao, *J. Org. Chem.* **2016**, *81*, 11201.  
 (28l) Wu, *ChemistrySelect* **2017**, *2*, 10762.  
 (28m) Zanoni, Protti, *Molecules* **2019**, *24*, 1318.

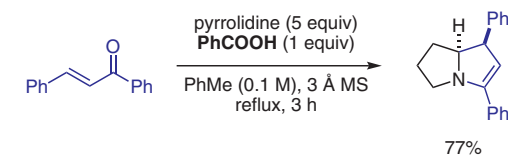
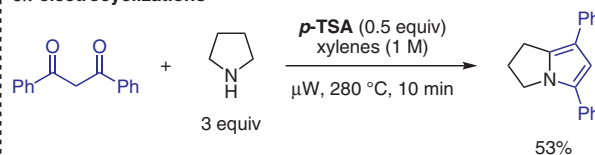
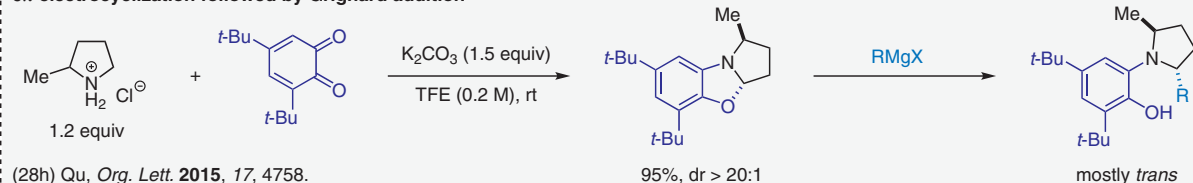
## Intramolecular (3+2) cycloaddition



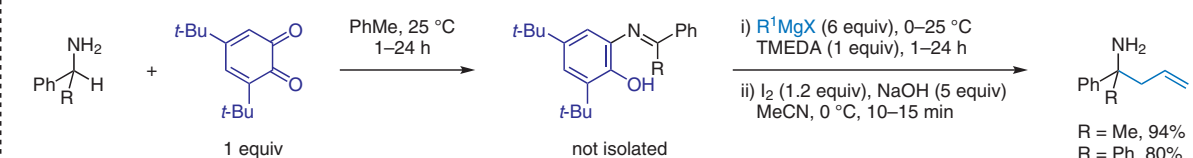
## Benzoic acid catalyzed variant operates at room temperature



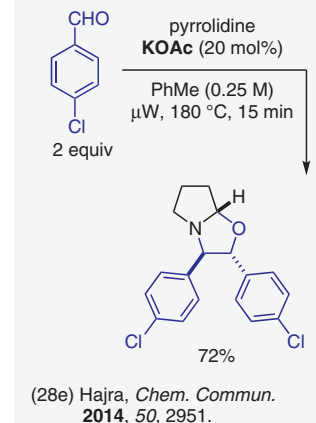
Less reactive amines (e.g., piperidine, morpholine) react at elevated temperatures.

6 $\pi$ -electrocyclizations6 $\pi$ -electrocyclization followed by Grignard addition

## Related transformation with primary amines



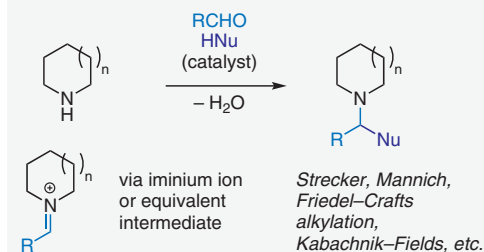
## Synthesis of bicyclic oxazolidines

Figure 28 Condensation-based methods involving azomethine ylide intermediates, pericyclic reactions.<sup>28</sup>

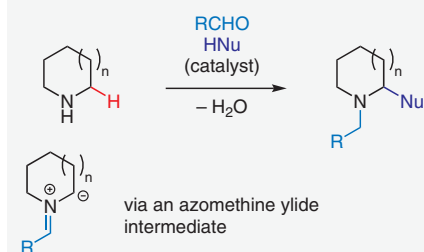
## Notable features

- Mirrors classic amine condensation reactions with incorporation of a C–H functionalization step.
- Merges reductive *N*-alkylation with oxidative  $\alpha$ -C–H bond functionalization in an overall redox-neutral sequence.
- Reactions are often catalyzed/promoted by simple carboxylic acids.
- Water is the only byproduct.

## Classic condensation-based transformations



## Complementary redox-transformations



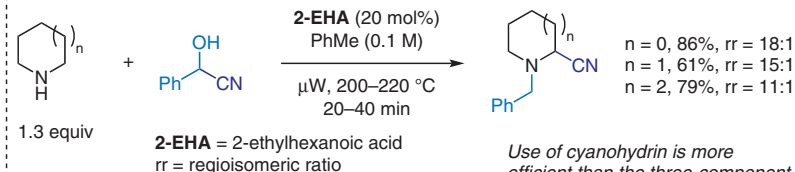
## Reviews

- (29p) Seidel, *Org. Chem. Front.* **2014**, 1, 426.  
 (29q) Seidel, *Acc. Chem. Res.* **2015**, 48, 317.  
 (29r) Jana, *Chem. Rec.* **2016**, 16, 1477.

## Other selected contributions

- (29s) Seidel, *Org. Lett.* **2013**, 15, 4358.  
 (29t) Jana, *Org. Lett.*, **2015**, 17, 3762.  
 (29u) Tong, *Chem. Eur. J.* **2016**, 22, 7084.  
 (29v) Zhou, *Asian J. Org. Chem.* **2016**, 5, 1204.  
 (29w) Meng, *Chem. Commun.* **2017**, 53, 1684.  
 (29x) Qu, *Org. Lett.* **2018**, 20, 668.  
 (29y) Jana, *Org. Biomol. Chem.* **2019**, 17, 1800.  
 (29z) Deb, Baruah, *Org. Biomol. Chem.* **2020**, 18, 6514.

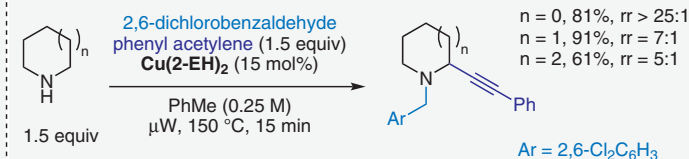
## Redox-Strecker reaction



(29a) Seidel, *J. Am. Chem. Soc.* **2012**, 134, 15305.

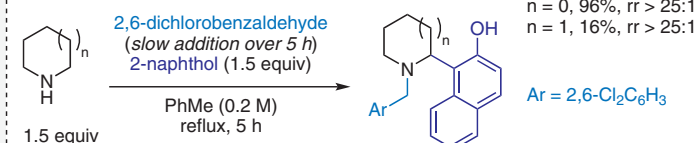
Use of cyanohydrin is more efficient than the three-component variant using PhCHO + TMSCN.

## Redox-A3 reaction



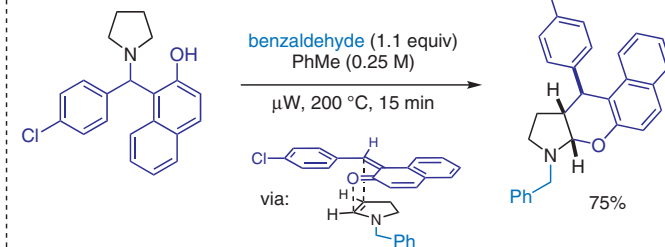
(29b) Seidel, *Angew. Chem. Int. Ed.* **2013**, 52, 3765.  
 See also: (29c) Yu, *Org. Lett.* **2013**, 15, 5928.

## Redox-Friedel–Crafts alkylation



(29f) Seidel, *Org. Lett.* **2014**, 16, 730.  
 See also: (29g) Jana, *Asian J. Org. Chem.* **2014**, 3, 44.

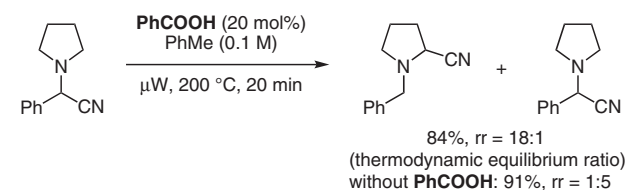
Other viable nucleophiles: indoles, pyrroles, phenols

 $\beta$ -C–H Functionalization via enamine intermediates

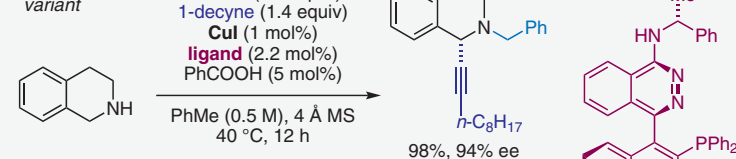
(29h) Seidel, *Angew. Chem. Int. Ed.* **2014**, 53, 5179. See also:  
 (29i) Wu, *Org. Lett.* **2016**, 18, 3526. (29j) Jana, *J. Org. Chem.* **2018**, 83, 8874.

## Initial observation:

Regioisomers undergo equilibration in the presence of benzoic acid.

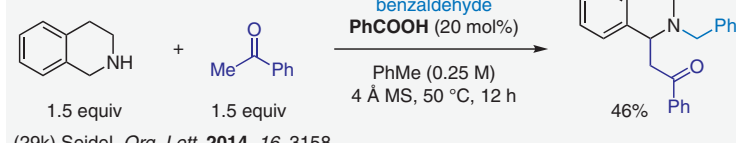


## Asymmetric variant



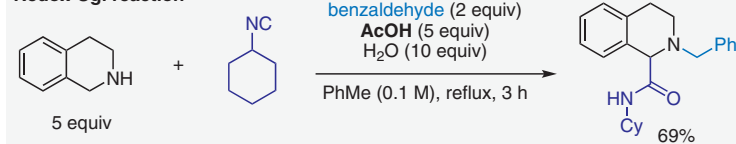
(29d) Ma, *Angew. Chem. Int. Ed.* **2014**, 53, 277.  
 See also: (29e) Ma, *Org. Chem. Front.* **2014**, 1, 338.

## Redox-Mannich reaction



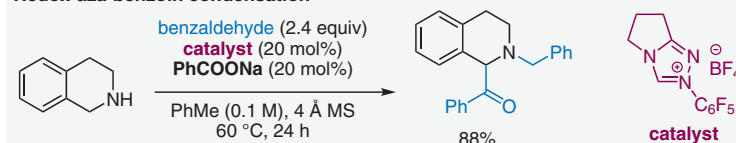
(29k) Seidel, *Org. Lett.* **2014**, 16, 3158.

## Redox-Ugi reaction



(29l) Seidel, *Org. Lett.* **2016**, 18, 631. See also:  
 (29m) Feng, *Synthesis*, **2016**, 48, 3730. (29n) Jana, *Green Chem.* **2018**, 20, 3463.

## Redox-aza-benzoin condensation



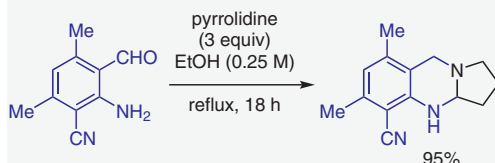
(29o) Wang, *Chin. J. Chem.* **2020**, 38, 135.

Figure 29 Condensation-based methods involving azomethine ylide intermediates, redox-neutral 3-component coupling reactions.<sup>29</sup>

## Notable features

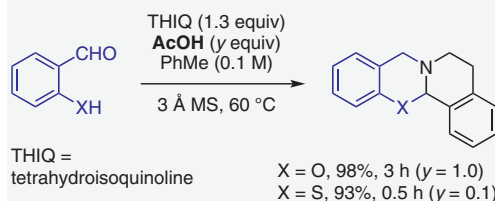
- Powerful method for generating polycyclic amines via redox-neutral ring-annulation of alicyclic amines.
- Azomethine ylides are key intermediates.
- Reactions are often catalyzed/promoted by simple carboxylic acids.
- Water is the only byproduct.

## First example



(30a) Seidel, *J. Am. Chem. Soc.* **2008**, *130*, 416.  
 (30b) Seidel, Houk, *J. Org. Chem.* **2013**, *78*, 4132.  
 (30c) Seidel, *Synthesis* **2013**, *45*, 1730.  
 See also: (30d) Dang, Bai, *Org. Lett.* **2008**, *10*, 889.

## Variants with (thio)salicylaldehydes



(30e) Houk, Seidel, *J. Am. Chem. Soc.* **2014**, *136*, 6123.  
 (30f) Houk, Seidel, *Org. Lett.* **2014**, *16*, 3556.  
 See also: (30g) Jana, *RSC Adv.* **2014**, *4*, 46214.  
 (30h) Roberts, *Chem. Commun.* **2020**, *56*, 9118.

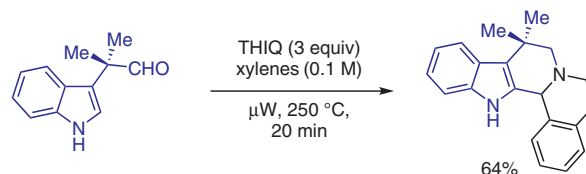
## Reviews

(29q) Seidel, *Acc. Chem. Res.* **2015**, *48*, 317.  
 (29r) Jana, *Chem. Rec.* **2016**, *16*, 1477.

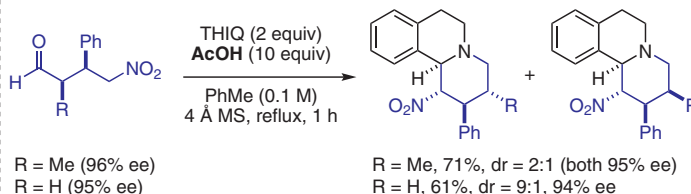
## Other selected contributions

(30s) Seidel, *Org. Lett.* **2017**, *19*, 6424.  
 (30t) Wu, *Synlett* **2018**, *29*, 1061.  
 (30u) Chusov, *J. Org. Chem.* **2020**, *85*, 9347.

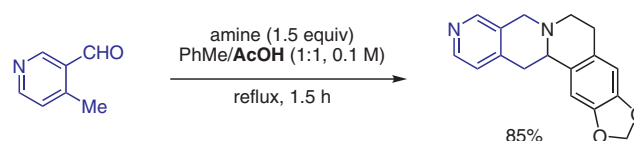
## Redox-Pictet–Spengler reaction



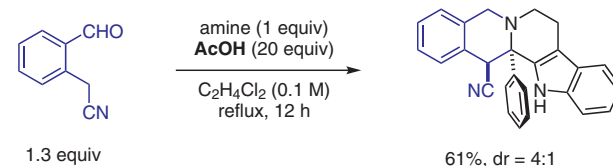
(30i) Seidel, *Chem. Sci.* **2011**, *2*, 233.

Asymmetric redox-annulations of  $\gamma$ -nitroaldehydes

(30k) Breugst, Seidel, *J. Org. Chem.* **2015**, *80*, 9628.

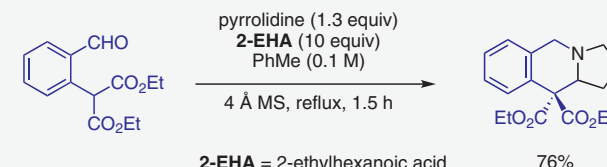
Redox-annulations of heteroaromatic  $\alpha$ -alkyl aldehydes

(30m) Seidel, *Org. Lett.* **2017**, *19*, 2841.  
 See also (30n) Wang, *Adv. Synth. Catal.* **2017**, *359*, 2191.  
 Catalytic enantioselective variant: (30o) Wang, *Org. Biomol. Chem.* **2017**, *15*, 6474.

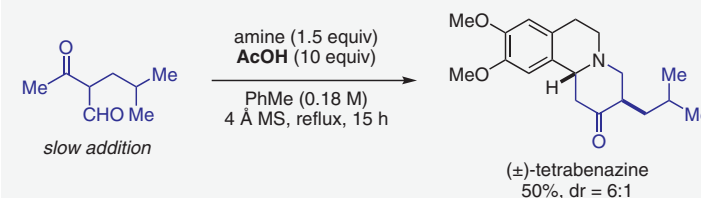
Redox-annulations of  $\alpha$ -cyanomethyl benzaldehydes

(30q) Seidel, *Org. Lett.* **2020**, *22*, 976.

## Redox-annulations of 2-formylaryl malonates

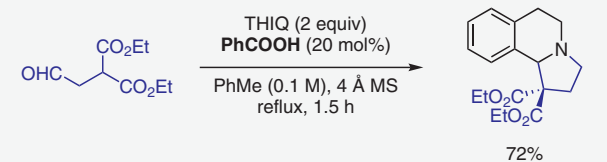


(30j) Seidel, *Chem. Eur. J.* **2015**, *21*, 12908.

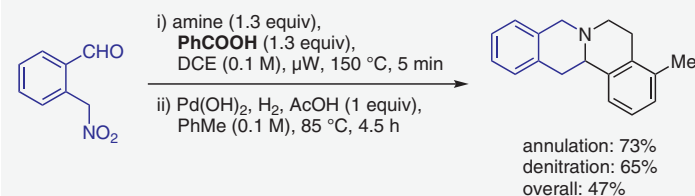
Redox-annulations of  $\beta$ -ketoaldehydes

(30l) Seidel, *Org. Lett.* **2016**, *18*, 1024.

## Redox-annulations of 2-(2-oxoethyl)malonates



(30p) Seidel, *Org. Lett.* **2018**, *20*, 4090.

Traceless redox-annulations of  $\alpha$ -nitromethyl benzaldehyde

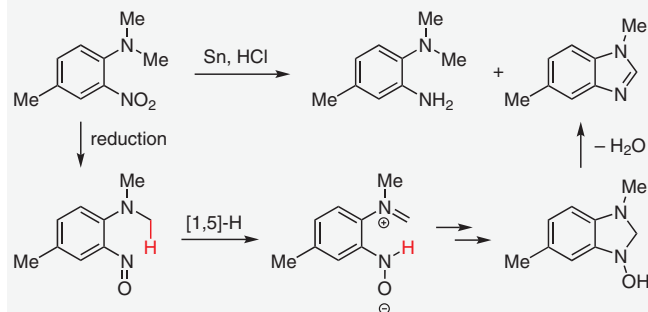
(30r) Seidel, *SynOpen* **2020**, *4*, 123.

Figure 30 Condensation-based methods involving azomethine ylide intermediates, redox-annulations.<sup>30</sup>

### Notable features

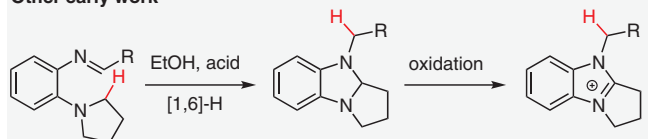
- Redox-neutral method for amine  $\alpha$ -C–H bond functionalization involving intramolecular H-transfer followed by cyclization. Can involve oxidation state changes prior to or after the key step.
- Historically categorized under the term “*Tert*-Amino Effect”: originally defined as cyclizations of tertiary anilines containing unsaturated bonds at the *ortho*-position.
- “*Tert*-Amino Effect” reactions are not mechanistically uniform. Distinction between 1,*n*-hydride transfer vs 1,*n*-proton abstraction (*n* most commonly = 5, 6) is not always clear. May also involve pericyclic steps such as 1,5-sigmatropic rearrangements and electrocyclic ring closures.

### Seminal discovery



(31a) Pinnow, *Ber. Dtsch. Chem. Ges.* **1895**, 28, 3039.  
See also: (31b) Vasella, *Helv. Chim. Acta* **2011**, 94, 785.

### Other early work

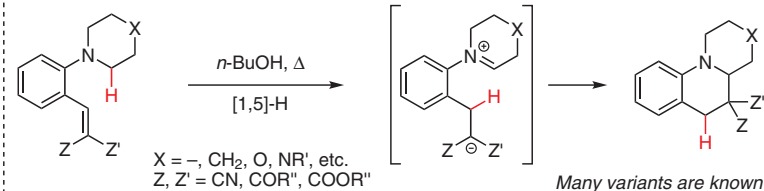


(31c) Meth-Cohn, *Chem. Commun.* **1967**, 1157.  
See also: (31d) Volochnyuk, *J. Org. Chem.* **2007**, 72, 7417.

### Reviews

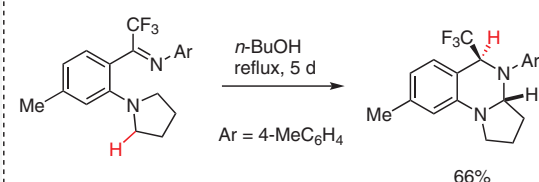
(31q) Meth-Cohn, *Adv. Heterocycl. Chem.* **1972**, 14, 211.  
(31r) Meth-Cohn, *Adv. Heterocycl. Chem.* **1996**, 65, 1.  
(31s) Matyus, *Synthesis* **2006**, 2625.  
(31t) Morzherin, *Chem. Heterocycl. Compd. (Engl. Transl.)* **2013**, 49, 357.

### Key contribution



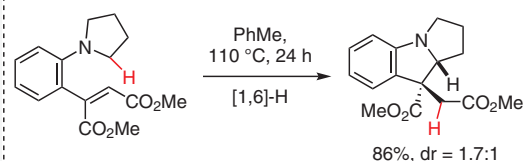
(31e) Reinhoudt, *J. Org. Chem.* **1984**, 49, 269.  
See also: (31f) Reinhoudt, *J. Org. Chem.* **1989**, 54, 199.

### C–N bond formation



(31h) Reinhoudt, *Tetrahedron Lett.* **1984**, 25, 4309.

### Formation of a 5-membered ring



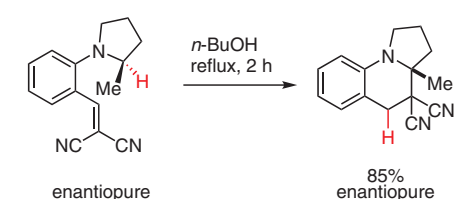
(31e) Reinhoudt, *J. Org. Chem.* **1984**, 49, 269.  
See also: (31j) Reinhoudt, *J. Am. Chem. Soc.* **1983**, 105, 4775.

### Example of higher order H-transfer



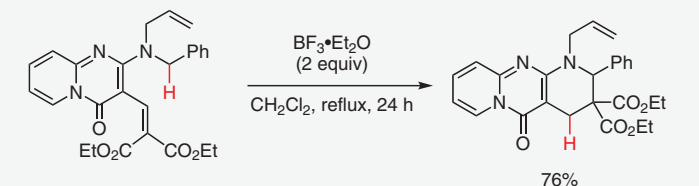
(31n) Matyus, *Synlett* **2008**, 2846.  
See also: (31o) Matyus, *Synlett* **2010**, 2109.

### Memory of chirality



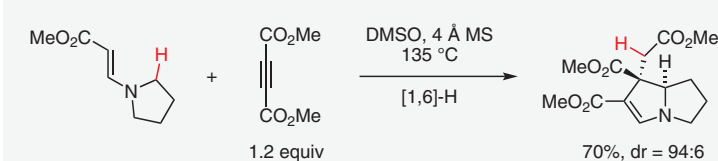
(31g) Reinhoudt, *J. Org. Chem.* **1989**, 54, 209.

### Example of a Lewis acid promoted process



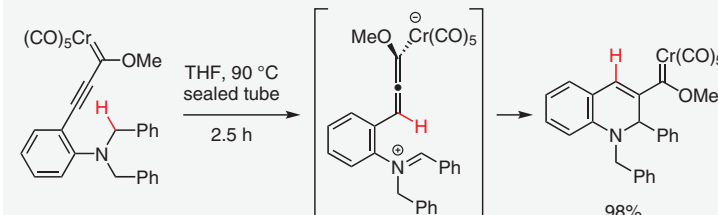
(31i) Noguchi, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3327.

### In situ formation of a dienamine



(31k) Viehe, *Tetrahedron Lett.* **1994**, 35, 1185. See also: (31l) Viehe, *Bull. Soc. Chim. Belg.* **1993**, 102, 663. (31m) Viehe, *Tetrahedron* **1995**, 51, 13239.

### An alkynyl Fischer carbene as an H-acceptor



(31p) Barluenga, *Angew. Chem. Int. Ed.* **2008**, 47, 6594.

**Figure 31** Internal redox transformations involving [1,*n*]-H transfers, the ‘*tert*-amino effect’.<sup>31</sup>

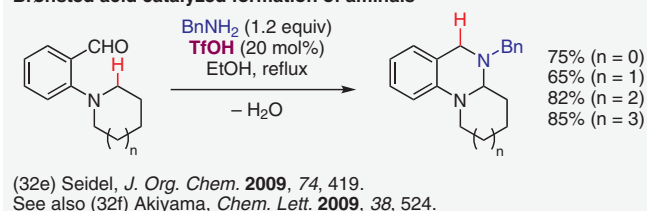
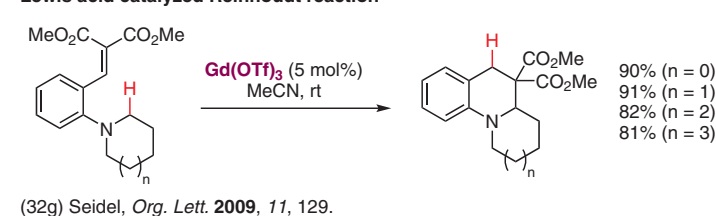
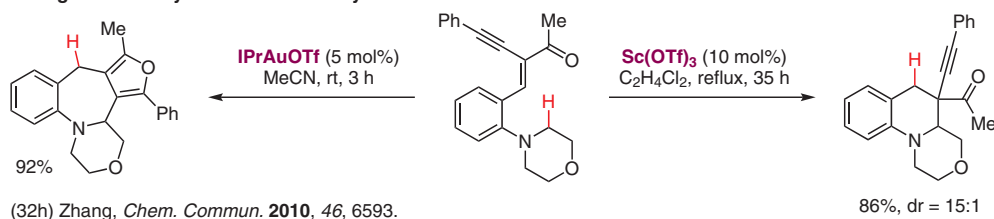
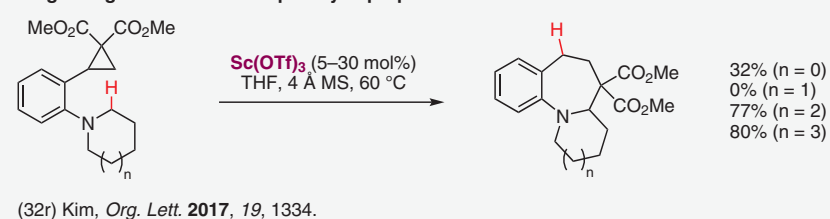
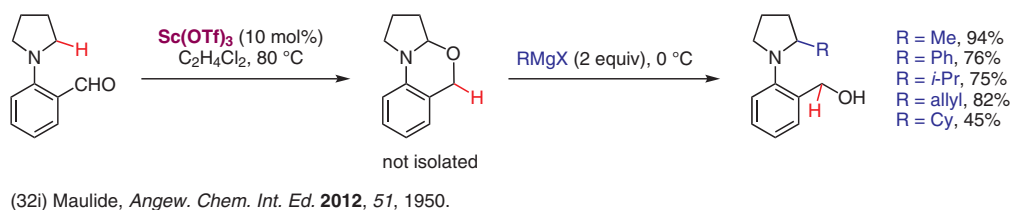
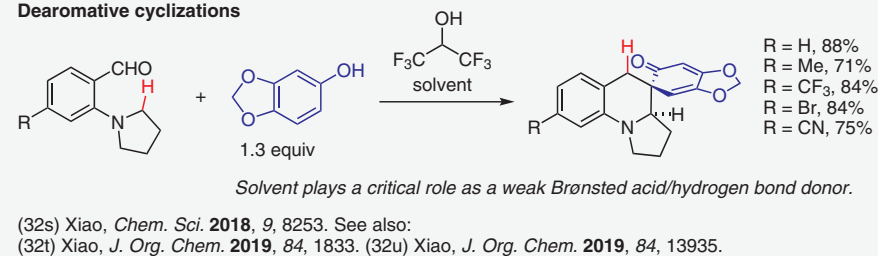
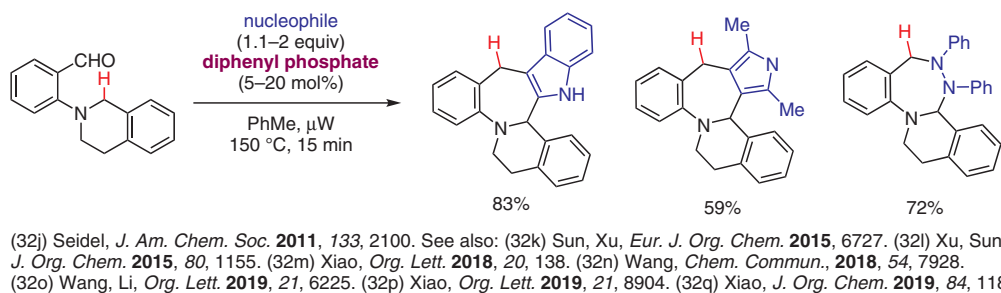
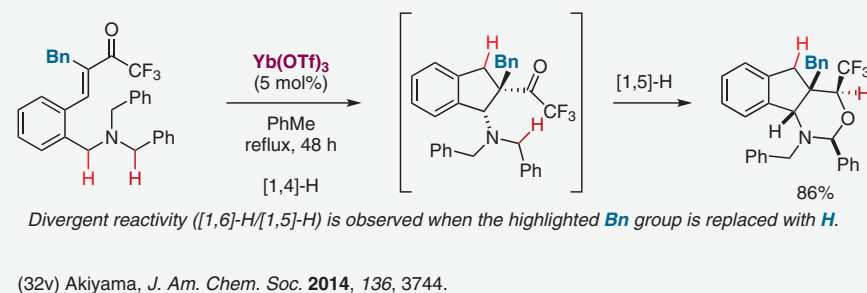


**Notable features**

- Redox neutral [1,*n*]-hydride transfer/ring-closure reactions that fall within the broader category of the “*Tert*-Amino Effect.”
- Application of Lewis and Brønsted acid catalysis has significantly increased the scope of these transformations.

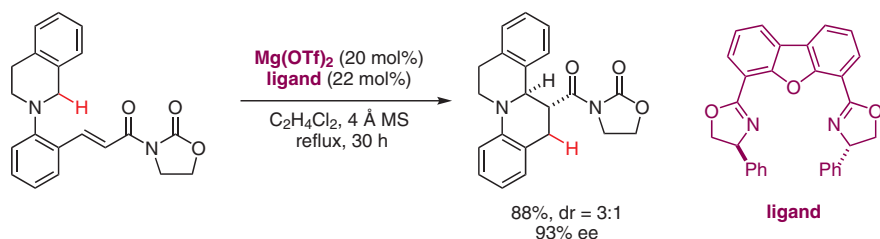
**Reviews**

- (32a) Maulide, *Chem. Eur. J.* **2013**, *19*, 13274.  
 (32b) Seidel, *Angew. Chem. Int. Ed.* **2014**, *53*, 5010.  
 (32c) Kim, *Chem. Rec.* **2016**, *16*, 1191.  
 (32d) Xiao, *Org. Chem. Front.* **2021**, *8*, 1364.

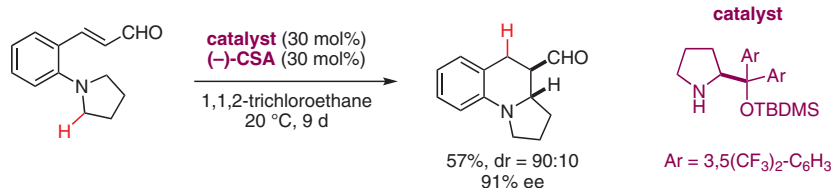
**Brønsted acid catalyzed formation of animalins****Lewis acid catalyzed Reinholdt reaction****Divergent reactivity based on the catalyst****Larger rings from donor/acceptor cyclopropanes****Redox-isomerization/Grignard addition****Dearomative cyclizations****Annulation with doubly nucleophilic species to access larger rings****Cascades with two consecutive hydride transfers**

**Figure 32** Lewis and Brønsted acid catalyzed internal redox transformations involving [1,*n*]-H transfers.<sup>32</sup>

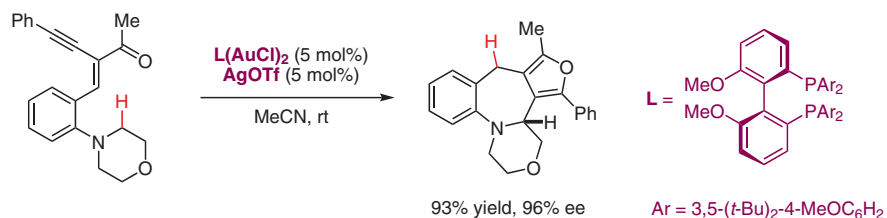
## First highly enantioselective catalytic variant

(33a) Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 13226.

## First organocatalytic enantioselective variant

(33b) Kim, *J. Am. Chem. Soc.* **2010**, *132*, 11847. See also:(33c) Kim, *Adv. Synth. Catal.* **2013**, *355*, 3131. (33d) Kim, *Chem. Commun.* **2014**, *50*, 222.(33e) Kim, *Org. Lett.* **2014**, *16*, 5374.

## Enantioselective gold-catalyzed cascade reaction

(33f) Zhang, *Chem. Eur. J.* **2011**, *17*, 3101.

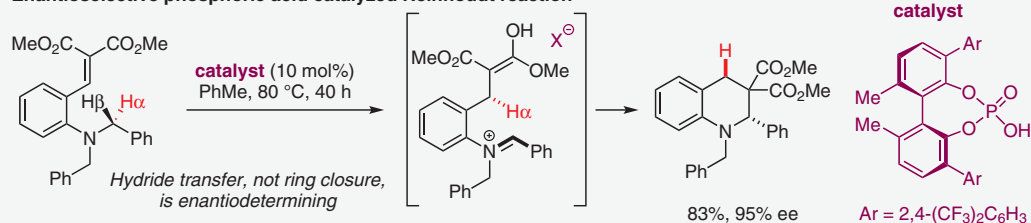
## Reviews

(33l) Wang, *ChemCatChem* **2013**, *5*, 1291.  
(33m) Wang, Xiao, *Chin. J. Org. Chem.* **2018**, *38*, 328.

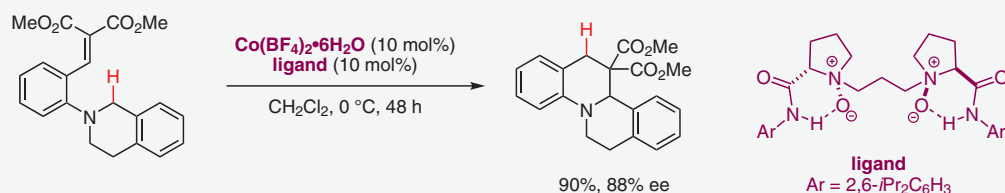
## Additional examples

(33n) Feng, *Chem. Eur. J.* **2015**, *21*, 1632.  
(33o) Gong, *Chem. Eur. J.* **2013**, *19*, 5232.  
(33p) Lin, *Synlett* **2016**, *27*, 546.  
(33q) Wen, Xu, *Tetrahedron* **2018**, *74*, 7480.

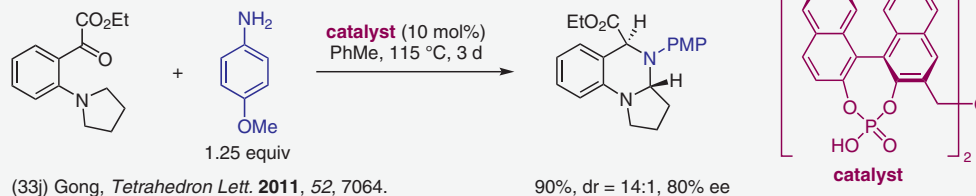
## Enantioselective phosphoric acid catalyzed Reinholdt reaction

(33g) Akiyama, *J. Am. Chem. Soc.* **2011**, *133*, 6166.

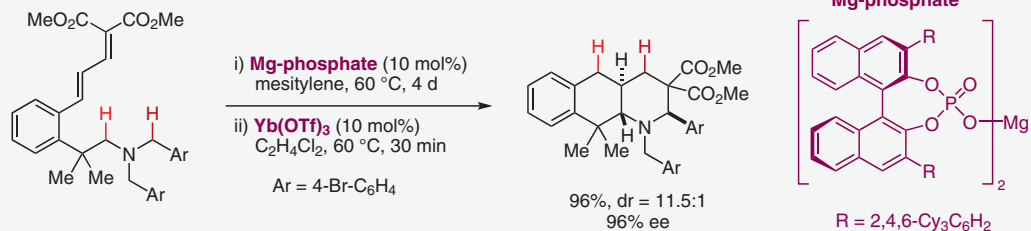
## Enantioselective cobalt-catalyzed Reinholdt reaction

(33h) Feng, *Org. Lett.* **2011**, *13*, 600. See also: (33i) Luo, *Chem. Commun.* **2013**, *49*, 847.

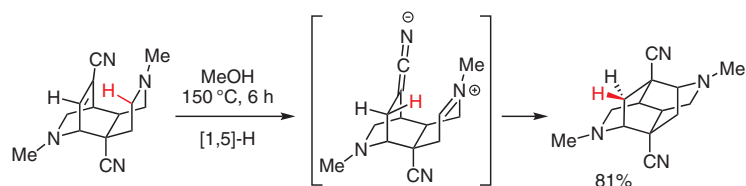
## Enantioselective amination formation

(33j) Gong, *Tetrahedron Lett.* **2011**, *52*, 7064.

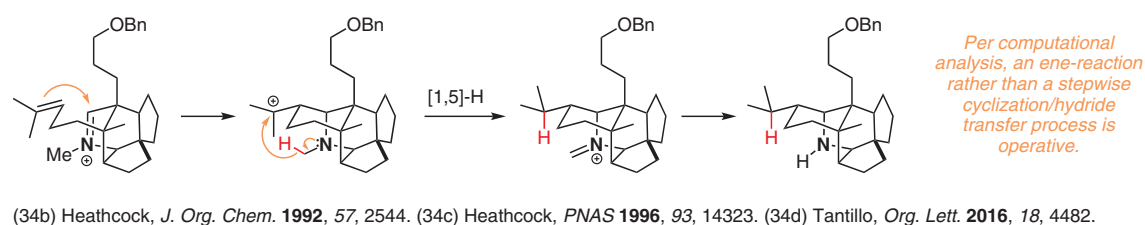
## Enantioselective cascades with two consecutive [1,5]-hydride transfers

(33k) Mori, Akiyama, *J. Am. Chem. Soc.* **2018**, *140*, 6203.Figure 33 Catalytic enantioselective internal redox transformations involving [1,*n*]-H transfers.<sup>33</sup>

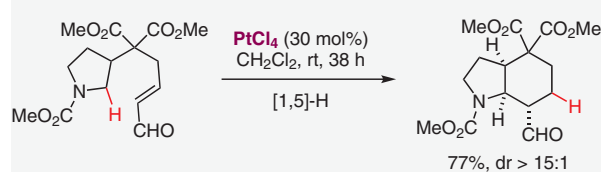
## Seminal discovery, formation of a symmetrical diazaditwistane



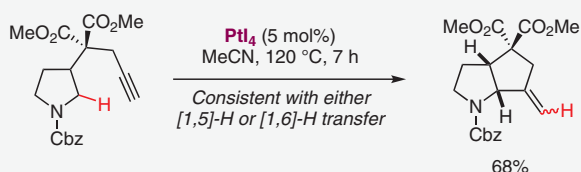
## Biomimetic total synthesis of methyl homosecodaphniphyllate, serendipitous discovery and originally proposed mechanism



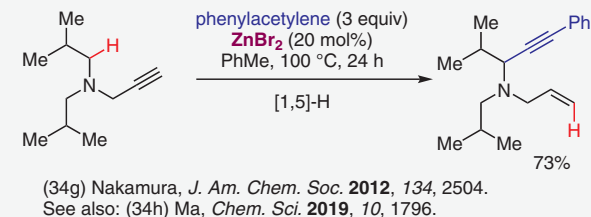
## Seminal catalytic example



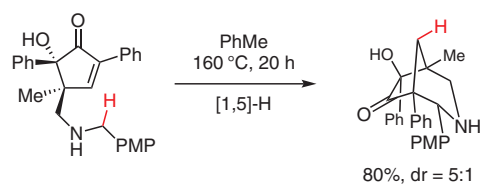
## An alkyne as a hydride acceptor



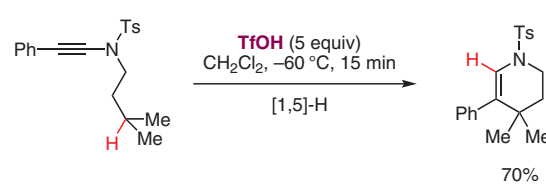
## Intramolecular hydride transfer/external nucleophile



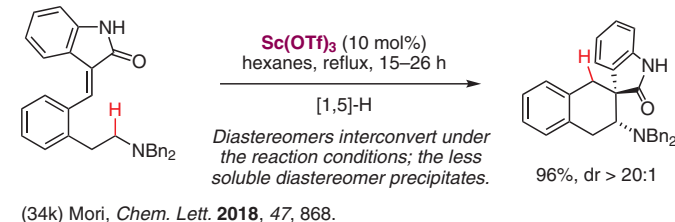
## Synthesis of bridged bicyclic amines



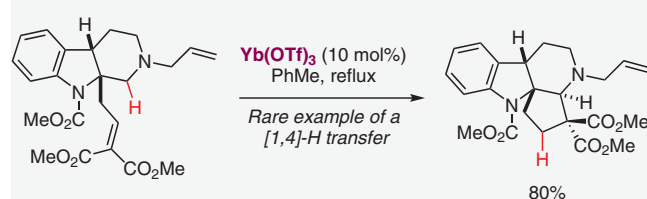
## Hydride transfer initiating from a remote C–H bond



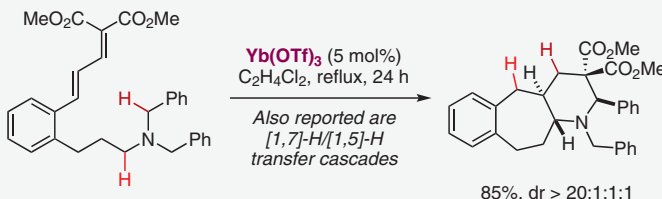
## Synthesis of carbacycles



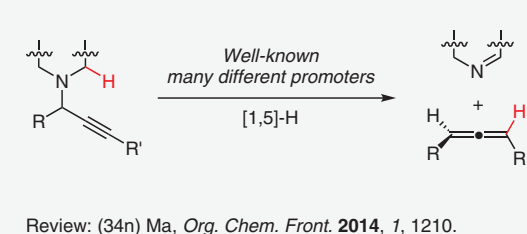
## Alkaloid synthesis



## Cascades with consecutive [1,6]-H/[1,5]-H transfers



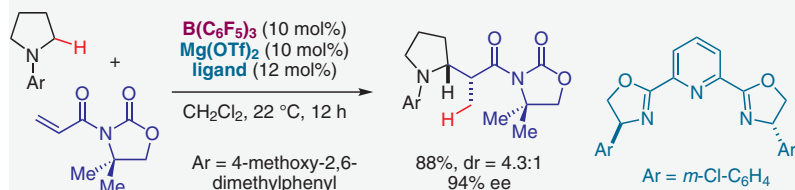
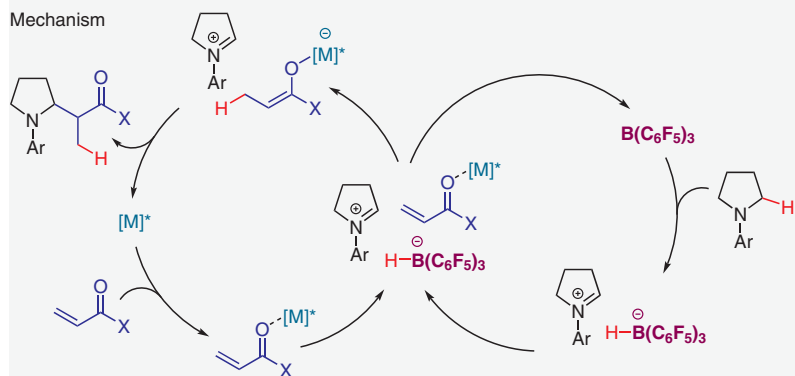
## Synthesis of allenes



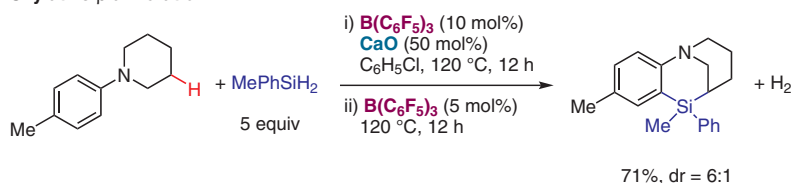
**Figure 34** Internal redox transformations involving [1,*n*]-H transfers in non-conjugated systems.<sup>34</sup>

**Notable features**

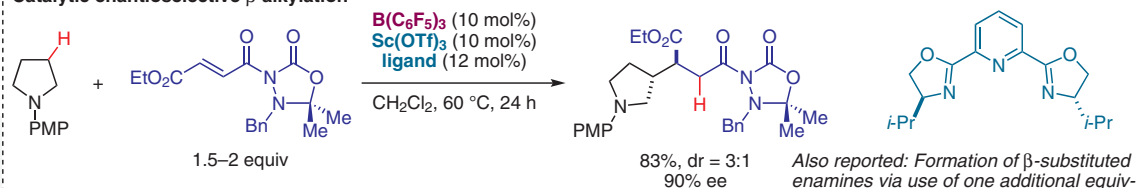
- Intermolecular hydride transfer from amine to  $B(C_6F_5)_3$  generates an iminium ion and a  $H-B(C_6F_5)_3$  anion. The iminium ion is alkylated directly or undergoes deprotonation to form an enamine which typically reacts further. The  $H-B(C_6F_5)_3$  anion reacts with a pronucleophile or reduces the immediate product of enamine alkylation.
- Some reactions are intermolecular variants of transformations shown in **Figures 31–34**.

**Landmark study: Catalytic enantioselective  $\alpha$ -alkylation****Mechanism**

(35a) Wasa, *J. Am. Chem. Soc.* **2018**, *140*, 10593. Seminal work [stoichiometric  $B(C_6F_5)_3$ ]:  
 (35b) Santini, *Eur. J. Inorg. Chem.* **2002**, 3328. (35c) Erker, *Chem. Eur. J.* **2017**, *23*, 4723.

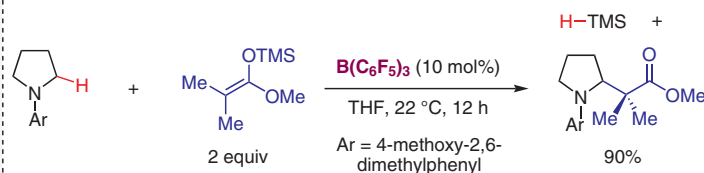
**Silylative  $\beta$ -annulation**

(35d) Chang, *J. Am. Chem. Soc.* **2018**, *140*, 13209.  
 See also: (35e) Park, Dang, *Org. Chem. Front.* **2020**, *7*, 944.

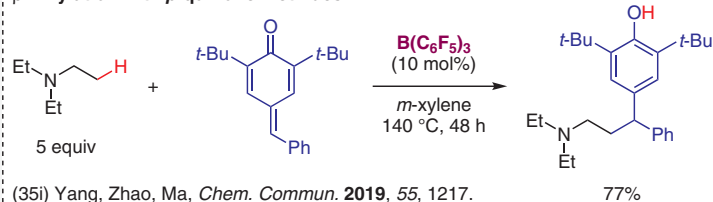
**Catalytic enantioselective  $\beta$ -alkylation**

(35f) Wasa, *J. Am. Chem. Soc.* **2021**, *143*, 2441.

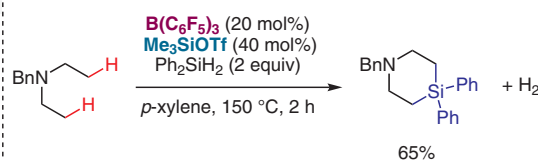
Catalytic enantioselective  $\alpha$ -alkynylation with alkynylsilanes: (35g) Wasa, *J. Am. Chem. Soc.* **2020**, *142*, 16493.

 **$\alpha$ -Alkylation with silyl ketene acetals**

(35h) Wasa, *Org. Lett.* **2019**, *21*, 984.

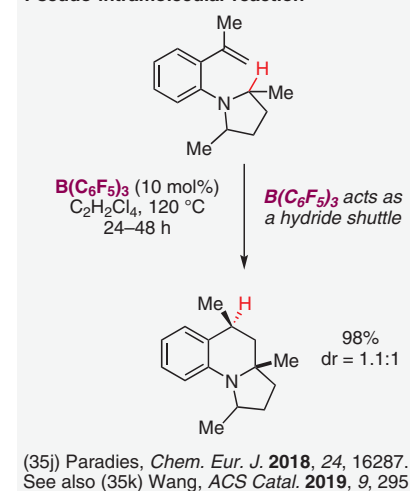
 **$\beta$ -Alkylation with *p*-quinone methides**

(35i) Yang, Zhao, Ma, *Chem. Commun.* **2019**, 55, 1217.

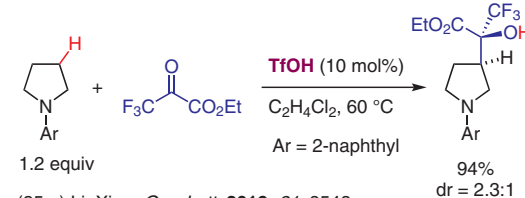
**Silylative ring closure**

(35l) Oestreich, *Angew. Chem. Int. Ed.* **2021**, *60*, 8542.

**Additional examples:** (35n) Wasa, *J. Am. Chem. Soc.* **2019**, *141*, 14570. (35o) Shao, Xiao, *Org. Lett.* **2020**, *22*, 776. (26h) Yang, Ma, *Org. Lett.* **2020**, *22*, 7797. **Reviews:** (35p) Ma, Hou, *Chem. Soc. Rev.* **2021**, *50*, 1945. (35q) Pulis, *Chem. Soc. Rev.* **2021**, *50*, 3720.

**Pseudo-intramolecular reaction**

(35j) Paradies, *Chem. Eur. J.* **2018**, *24*, 16287.  
 See also (35k) Wang, *ACS Catal.* **2019**, *9*, 295.

**Bronsted acid catalyzed  $\beta$ -alkylation**

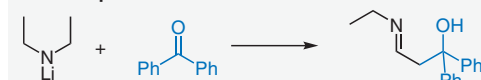
(35m) Li, Xiao, *Org. Lett.* **2019**, *21*, 8543.

**Figure 35** (Redox-neutral) methods involving intermolecular hydride transfer.<sup>35</sup>

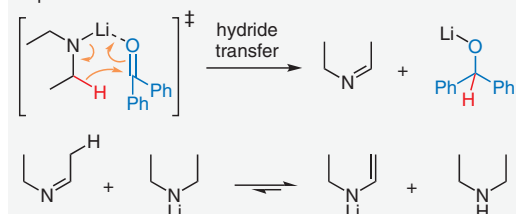
## Notable features

- Rapid access to imines from unprotected alicyclic amines via their in situ generated Li-amides.
  - Oxidation of Li-amide is fast at  $-78\text{ }^{\circ}\text{C}$ , generating cyclic imines under mild conditions.
  - Method prevents imine decomposition and formation of undesirable, and typically unreactive, imine trimers.
- [see: (36a) Fandrick, *Org. Lett.* **2016**, *18*, 6192.]

## Historical precedent



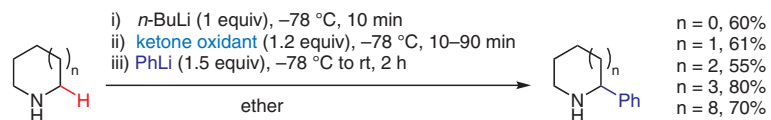
## Proposed mechanism



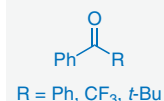
(36b) Wittig, *Chem. Ber.* **1962**, *95*, 2377. See also:  
(36c) Wittig, *Liebigs Ann. Chem.* **1971**, *746*, 174.  
(36d) Wittig, *Liebigs Ann. Chem.* **1971**, *746*, 185.

## Further reading

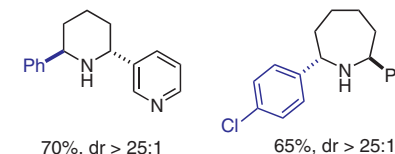
Review on Li-amides as reductants:  
(36g) Majewski, *J. Organomet. Chem.* **1994**, *470*, 1.  
Precedent for adding organolithiums to cyclic imines:  
(36h) Scully, *J. Org. Chem.* **1980**, *45*, 1515.  
Addition of TMSOTf or  $\text{BF}_3$  etherate enables expansion of scope to Grignard reagents, Li-acetylides, and others:  
(36i) Seidel, *J. Am. Chem. Soc.* **2019**, *141*, 8778.  
(36j) Seidel, *Org. Lett.* **2021**, *23*, 797.  
Annulation:  
(36k) Seidel, *Org. Lett.* **2021**, *23*, 3729.  
Decarboxylative alkylation of imines:  
(36l) Seidel, *Angew. Chem. Int. Ed.* **2021**, *60*, 1625.  
See also: (36m) Ellman, *J. Am. Chem. Soc.* **2021**, *143*, 126.

Application to amine  $\alpha$ -functionalization (36e) Seidel, *Nat. Chem.* **2018**, *10*, 165.

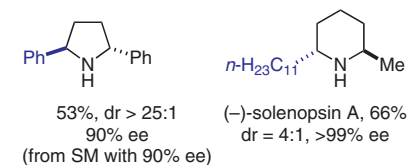
## Ketone oxidants:



Reactions of  $\alpha$ -substituted amines are regioselective for the  $\alpha'$ -position:

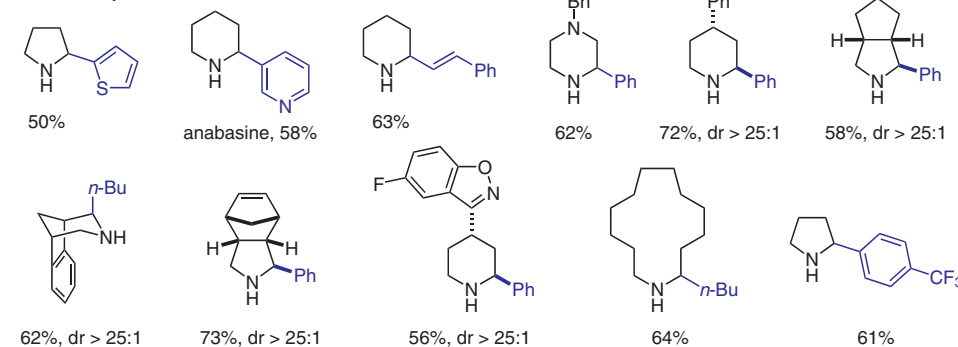
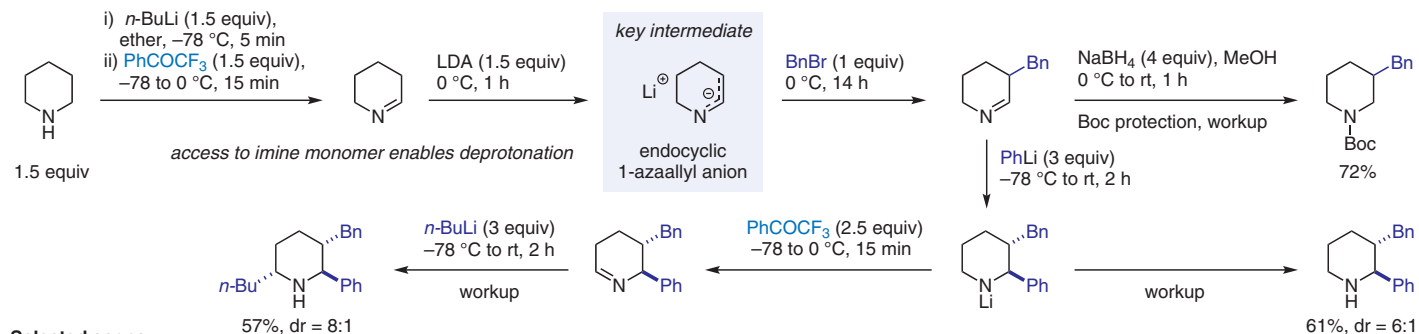


ee of starting material (SM) is maintained:



Other functional groups tolerated:  
ArF, ArCl, ArBr, ArOMe, alkyl-OSiR<sub>3</sub>

## Selected scope

Extension of concept to  $\beta$ - and multi-functionalization (36f) Seidel, *Nat. Chem.* **2020**, *12*, 545.

## Selected scope

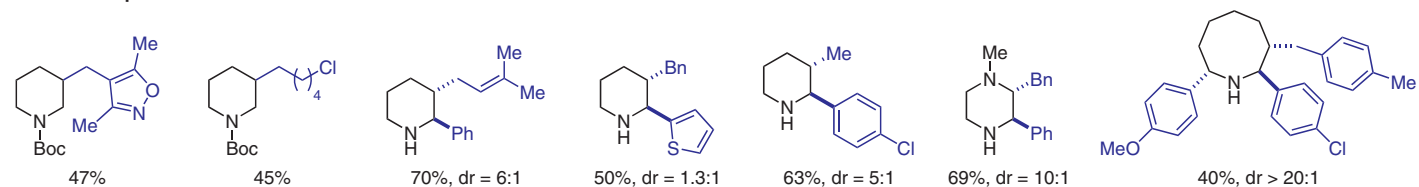
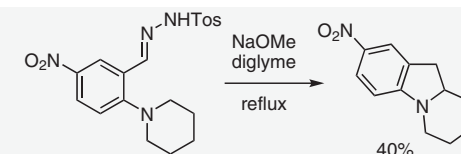
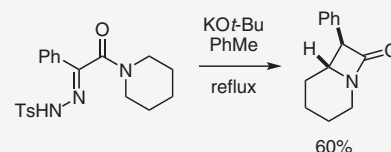
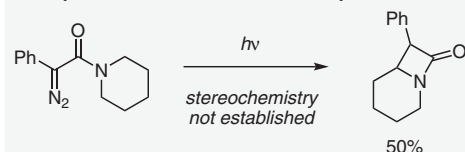


Figure 36 Li-amide-based imine and 1-azaallyl anion generation from unprotected azacycles.<sup>36</sup>

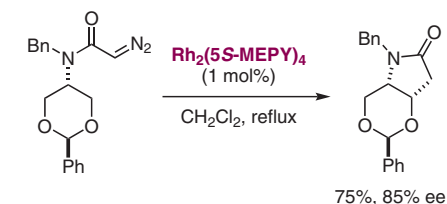
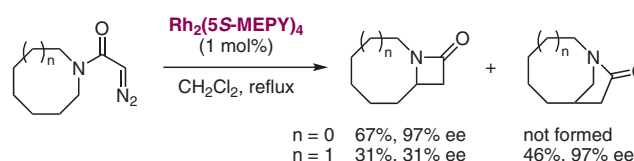
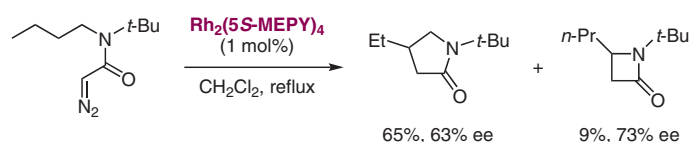
## Notable features

- Powerful method for C–H bond functionalization involving carbene or metal carbenoid intermediates.
- Typically proposed mechanistic pathway involves insertion into C–H bond. Alternatively, an ion pair is generated by intermolecular hydride transfer to the carbene, followed by recombination.
- Most common starting materials are diazo compounds and tosyl hydrazones.

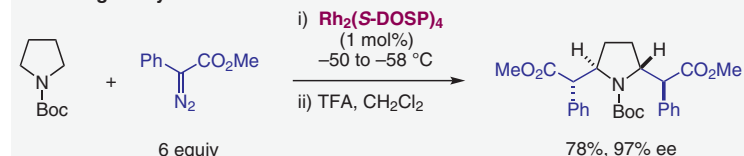
## Examples of metal-free, thermal and photochemical reactions



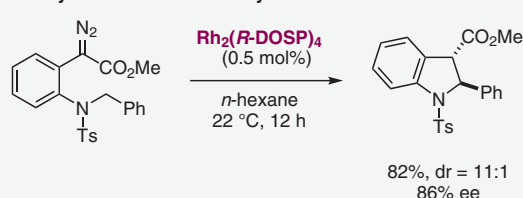
## Pioneering catalytic enantioselective intramolecular variants



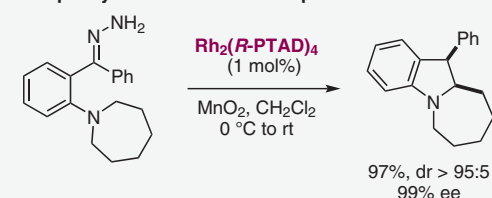
## Pioneering catalytic enantioselective intermolecular variants



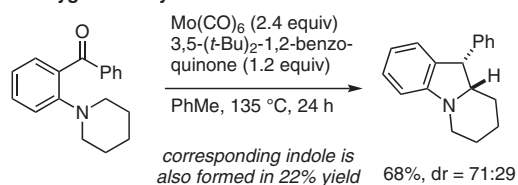
## Catalytic enantioselective synthesis of indolines



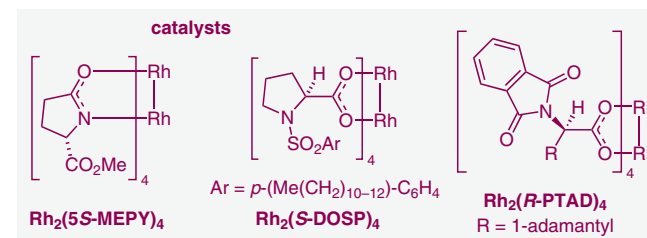
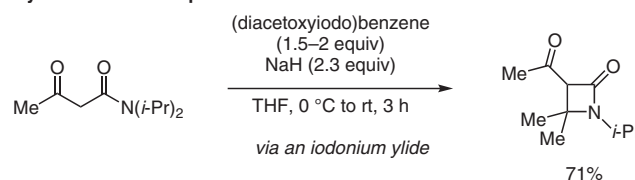
## Simple hydrazones as carbene precursors



## Deoxygenative cyclization



## Cyclization without pre-functionalization



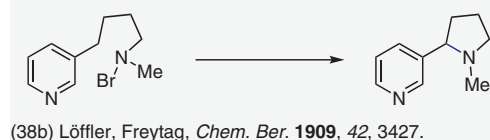
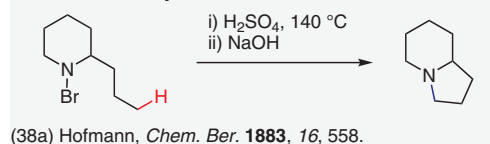
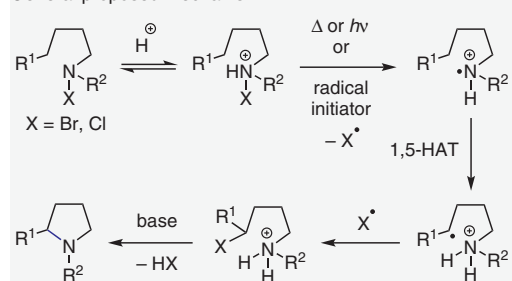
**Additional examples:** (37u) Doyle, *Tetrahedron Lett.* **1996**, *37*, 1371. (37v) Sulikowski, *Tetrahedron* **1997**, *53*, 16521. (37w) Sulikowski, *Tetrahedron Lett.* **1999**, *40*, 8035. (37x) Compain, *Org. Lett.* **2006**, *8*, 4493. (37y) Compain, *Tetrahedron Lett.* **2007**, *48*, 8531. (37z) Davies, *Nat. Commun.* **2015**, *6*, 5943. (37aa) Chen, Arnold, *ACS Catal.* **2020**, *10*, 5393. **Reviews:** (37ab) Davies, *Chem. Rev.* **2003**, *103*, 2861. (37ac) Davies, *Nature* **2008**, *451*, 417. (37ad) Doyle, *Chem. Rev.* **2010**, *110*, 704. (37ae) Davies, *Chem. Soc. Rev.* **2011**, *40*, 1857. (37af) Sultanova, *Chem. Heterocycl. Compd. (Engl. Transl.)* **2015**, *51*, 775.

**Figure 37** Reactions involving carbenes or metal carbenoids.<sup>37</sup>



**Notable features**

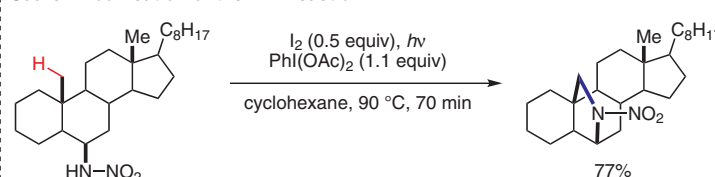
- Involves an intramolecular Hydrogen Atom Transfer (HAT) process with a chair-like TS.
- Typically selective for  $\delta$  C–H bonds.
- Reactivity can be modulated by varying the substituents on the N-atom.

**Seminal discovery****General proposed mechanism****Further reading**

- Reviews on HLF and related reactions:  
 (38i) Wolff, *Chem. Rev.* **1963**, 63, 55.  
 (38j) Stella, *Angew. Chem., Int. Ed. Engl.* **1983**, 22, 337.  
 (38k) Sarpong, *Chem. Sci.* **2013**, 4, 4092.  
 (38l) Nagib, *Synthesis* **2018**, 50, 1569.

**Other selected contributions:**

- (38m) Wawzonek, *J. Am. Chem. Soc.* **1950**, 72, 2118.  
 (38n) Corey, *J. Am. Chem. Soc.* **1960**, 82, 1657.  
 (38o) Fan, *J. Org. Chem.* **2007**, 72, 8994.  
 (38p) Yu, *Org. Lett.* **2015**, 17, 1894.  
 (38q) Herrera, *Org. Lett.* **2015**, 17, 2370.  
 (38r) Nagib, *Angew. Chem. Int. Ed.* **2016**, 55, 9974.  
 (38s) Roizen, *Chem. Sci.* **2020**, 11, 217.

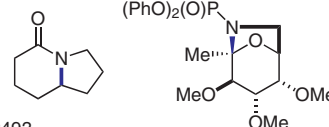
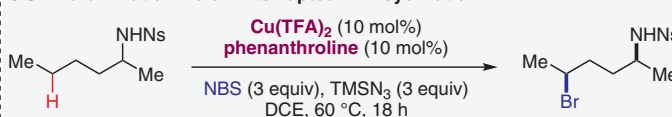
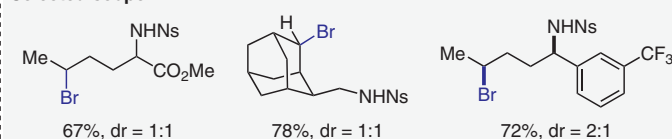
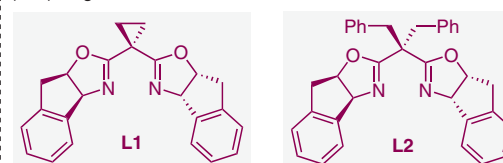
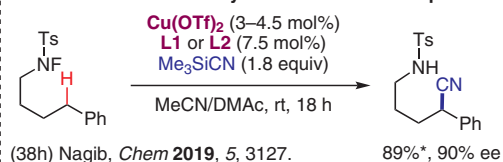
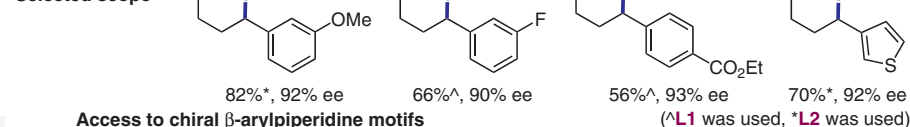
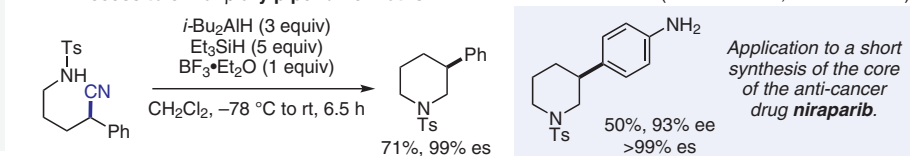
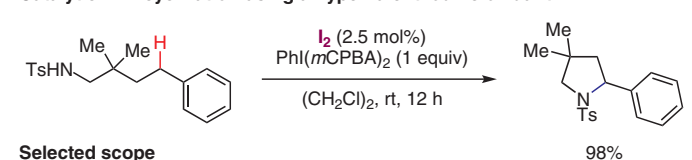
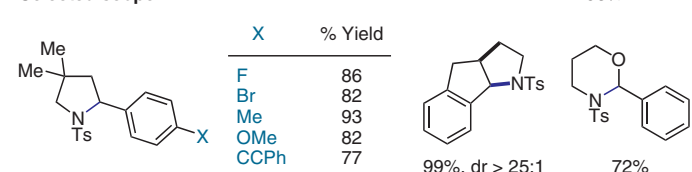
**Suárez modification of the HLF reaction****Key features**

No preformed N-haloamine required as N–I bond is generated in situ.

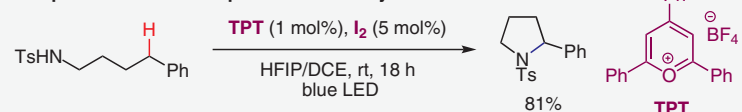
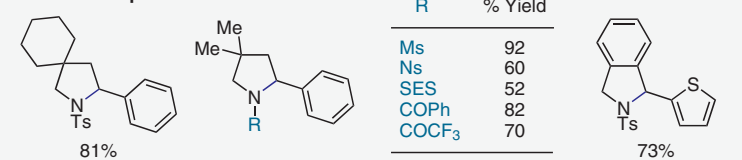
Circumventing harsh reaction conditions by employing electron-deficient protecting groups [e.g., CN, NO<sub>2</sub> and P(O)(OEt)<sub>2</sub>].

(38c) Suárez, *Tetrahedron Lett.* **1985**, 26, 2493.

(38d) Suárez, *J. Org. Chem.* **2003**, 68, 1012.

**Extension to other systems** **$\delta$  C–H bromination via an interrupted HLF cyclization****Selected scope****Enantioselective  $\delta$  C–H cyanation via an interrupted HLF cyclization****Selected scope****Access to chiral  $\beta$ -arylpiperidine motifs****Catalytic HLF cyclization using a hypervalent iodine oxidant****Selected scope**

(38e) Muñiz, *Angew. Chem. Int. Ed.* **2015**, 54, 8287.

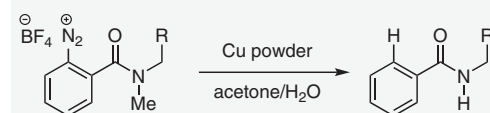
**Cooperative-iodine and photoredox catalysis in the HLF reaction****Selected scope**

**Figure 38** Hofmann–Löffler–Freytag (HLF) reaction.<sup>38</sup>

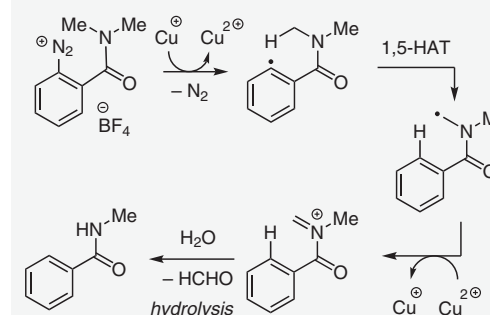
## Notable features

- HAT reactivity dependent on BDE and bond strength.
- Energy difference between C(sp<sup>2</sup>) and C(sp<sup>3</sup>) radicals favor HAT from an alkyl C–H to an aryl/vinyl C–H.
- HAT mediated by C-centered radicals are rarer than their heteroatom counterparts.

## Seminal discovery

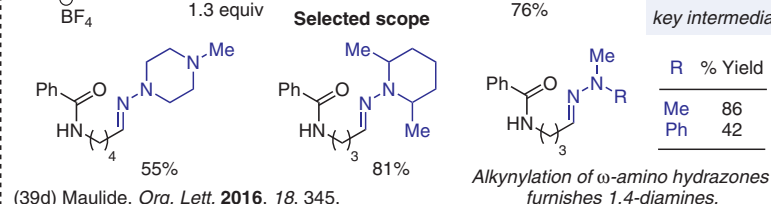
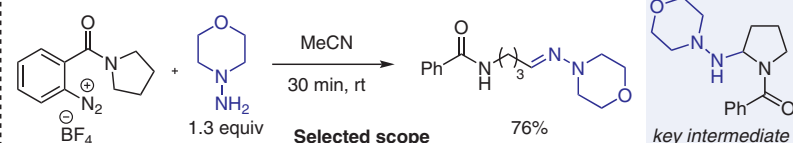
(39a) Hey, Turpin, *J. Chem. Soc.* **1954**, 2471.

## Proposed mechanism of the Cu(I)-catalyzed process

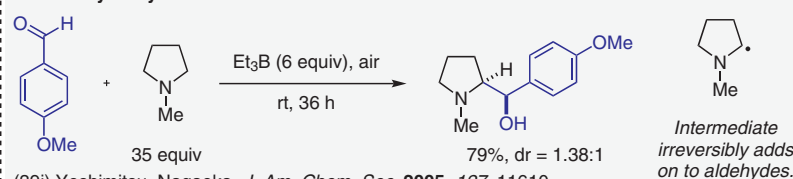
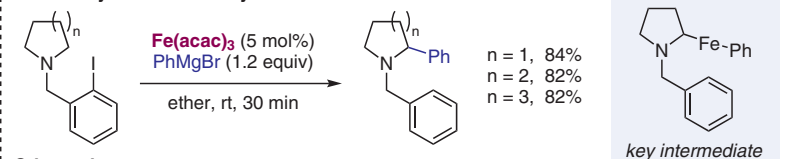
(39b) Cohen, *Tetrahedron* **1966**, 22, 1527.  
See also: (39c) Cohen, *J. Am. Chem. Soc.* **1968**, 90, 6866.

## Further reading

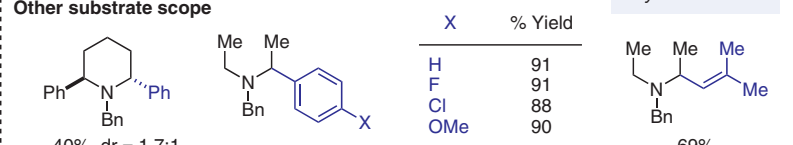
- Reviews on HAT chemistry:
- (38l) Nagib, *Synthesis* **2018**, 50, 1569.
- (39l) Gevorgyan, *Chem. Sci.* **2020**, 11, 12974.
- Other selected contributions:
- (39m) Robertson, *Tetrahedron Lett.* **1996**, 37, 5825.
- (39n) Murphy, *Org. Lett.* **2003**, 5, 2971.
- (39o) Storey, *Angew. Chem. Int. Ed.* **2004**, 43, 95.
- (39p) Renaud, *Org. Lett.* **2007**, 9, 4375.
- (39q) Yoshimitsu, Tanaka, *Org. Lett.* **2007**, 9, 5115.
- (39r) Tanaka, *Tetrahedron Lett.* **2008**, 49, 4473.
- (39s) Kalyani, *Org. Lett.* **2013**, 15, 5986.
- (39t) Ragains, *Angew. Chem. Int. Ed.* **2015**, 54, 7837.
- (39u) Xu, *Chem. Commun.* **2016**, 52, 6455.
- (39v) Zeng, *Org. Lett.* **2016**, 18, 5536.
- (39w) Qi, Zhang, *Tetrahedron Lett.* **2016**, 57, 1600.

Redox-Neutral  $\alpha$ -C–H amination(39d) Maulide, *Org. Lett.* **2016**, 18, 345.

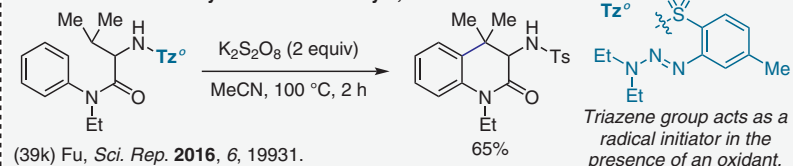
## Radical hydroxylation of C–H bonds

(39i) Yoshimitsu, Nagaoka, *J. Am. Chem. Soc.* **2005**, 127, 11610.Iron-catalyzed  $\alpha$ -amino arylation

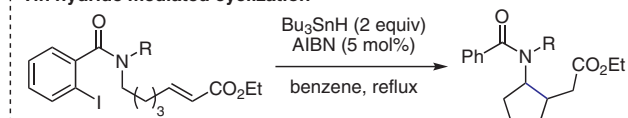
## Other substrate scope

(39j) Nakamura, *J. Am. Chem. Soc.* **2010**, 132, 5568.

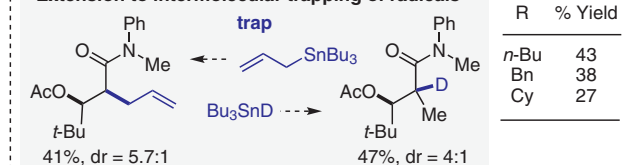
## Intramolecular C–H arylation mediated by 1,6-HAT

(39k) Fu, *Sci. Rep.* **2016**, 6, 19931.

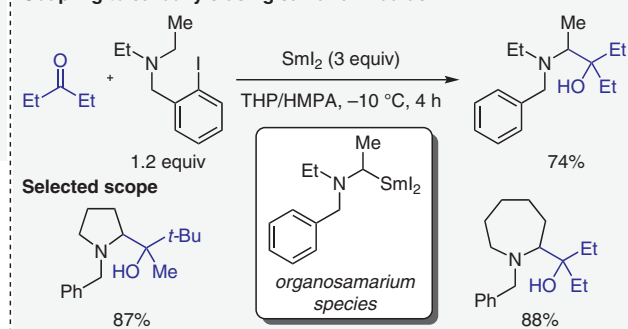
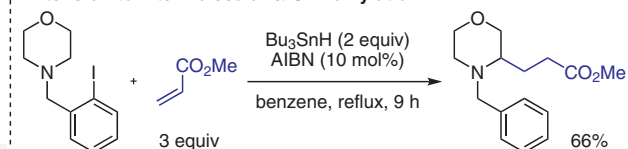
## Tin hydride mediated cyclization



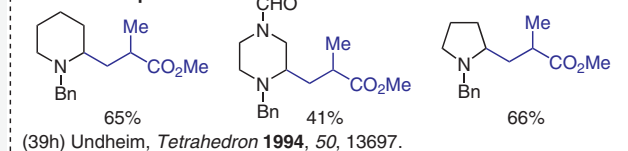
## Extension to intermolecular trapping of radicals

(39e) Snieckus, Curran, *J. Am. Chem. Soc.* **1990**, 112, 896.  
(39f) Curran, *Tetrahedron* **1993**, 49, 4821.

## Coupling to carbonyls using samarium iodide

(39g) Ito, *J. Org. Chem.* **1992**, 57, 793.Extension to intermolecular  $\alpha$ -C–H alkylation

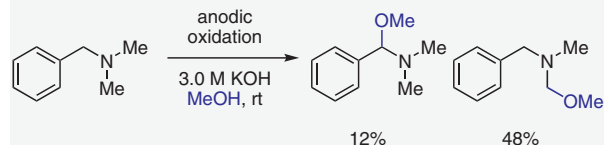
## Selected scope

(39h) Undheim, *Tetrahedron* **1994**, 50, 13697.Figure 39 Miscellaneous radical-based methods.<sup>39</sup>

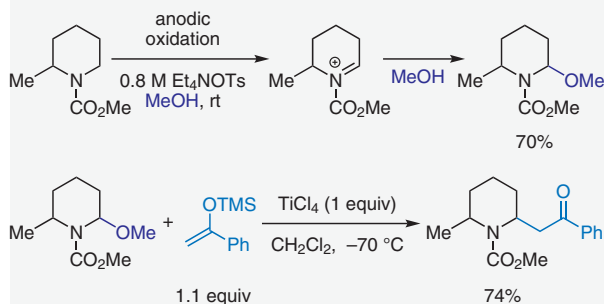
## Notable features

- Obviates the need for chemical oxidants.
- Shono oxidation involves a formal hydride transfer occurring through an electron transfer/proton transfer/electron transfer sequence.
- Electroauxiliaries can be used to direct regioselectivity and lower the oxidation potential, broadening the scope.

## Early work

(40a) Weinberg, *J. Org. Chem.* **1966**, *31*, 4058.

## Landmark study: Shono oxidation

(40b) Shono, *J. Am. Chem. Soc.* **1981**, *103*, 1172.

## Further reading

'Indirect' cation pool method:

(40h) Yoshida, *J. Am. Chem. Soc.* **2006**, *128*, 7710.

Use of electroauxiliaries to lower potentials and direct oxidation:

(40i) Yoshida, *Tetrahedron Lett.* **1987**, *28*, 6621.(40j) Yoshida, *Electrochim. Acta* **1997**, *42*, 1995.Application of electroauxiliaries for amine  $\alpha$ -functionalization of C–Si and C–S bonds:(40k) Yoshida, *Electrochemistry* **2006**, *74*, 672.(40l) Jones, Banks, *Beilstein J. Org. Chem.* **2018**, *14*, 1192.

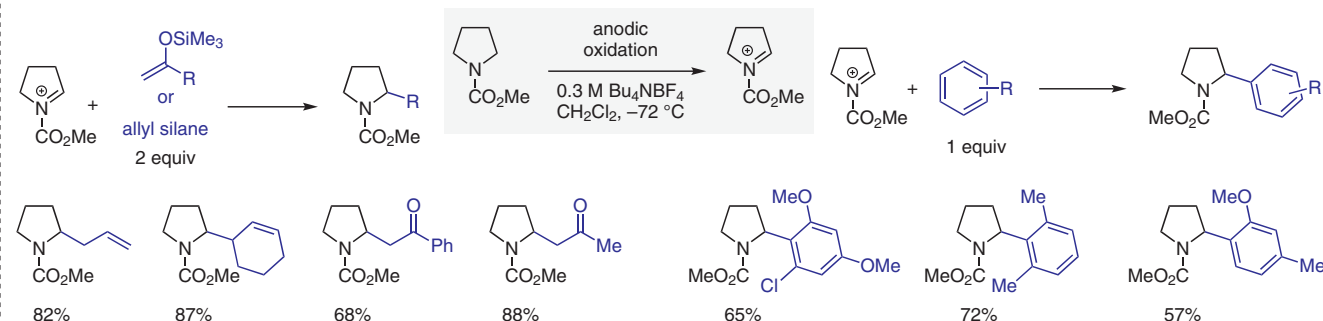
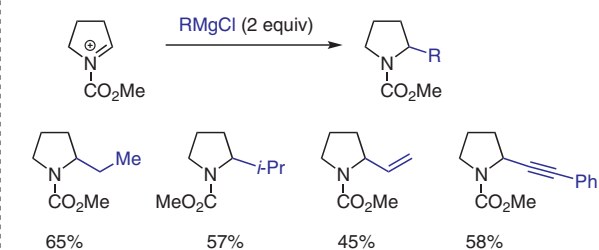
Review on Cation Pool and Cation Flow:

(40m) Yoshida, *J. Synth. Org. Chem. Jpn.* **2013**, *71*, 1136.

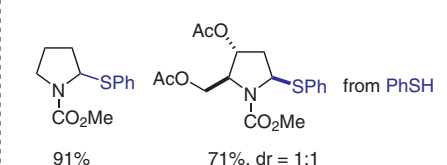
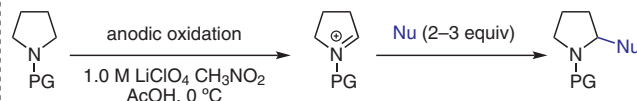
Applications of Shono-type oxidations:

(40n) Jones, Banks, *Beilstein J. Org. Chem.* **2014**, *10*, 3056.

Comprehensive review on electroorganic synthesis:

(40o) Yoshida, *Chem. Rev.* **2008**, *108*, 2265.Cation pool method and application to amine  $\alpha$ -functionalization(40c) Yoshida, *J. Am. Chem. Soc.* **1999**, *121*, 9546.(40d) Yoshida, *Tetrahedron Lett.* **2001**, *42*, 2173.

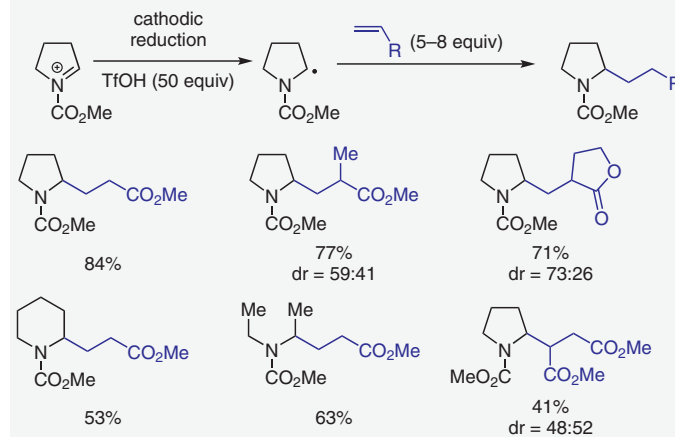
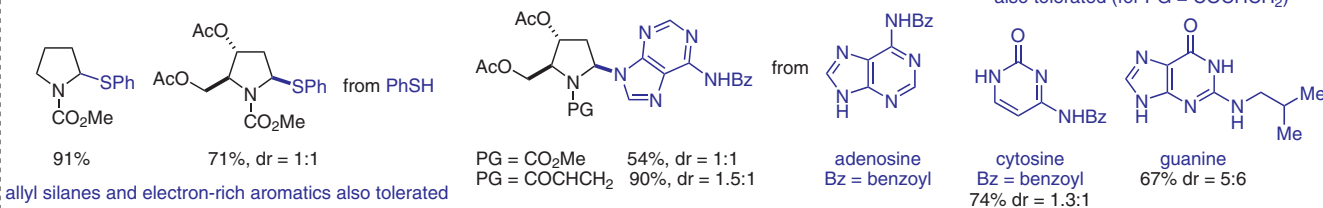
## Azanucleoside derivative synthesis



allyl silanes and electron-rich aromatics also tolerated

(40f) Chiba, *Chem. Commun.* **2013**, *49*, 6525.

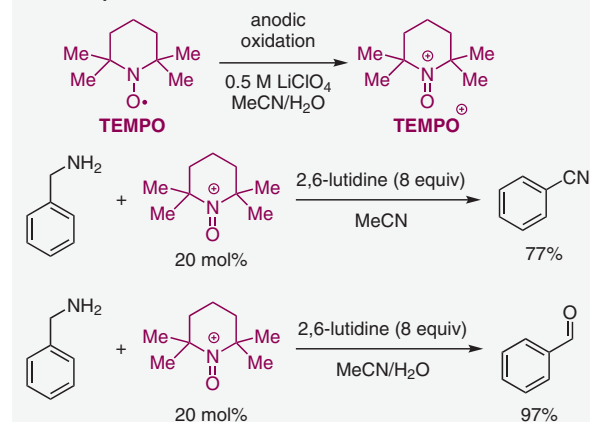
## Reduction of a Cation Pool

(40e) Yoshida, *J. Am. Chem. Soc.* **2002**, *124*, 30.(40g) Chiba, *Angew. Chem. Int. Ed.* **2017**, *56*, 4011Figure 40 Electrochemical approaches, cation pool method.<sup>40</sup>

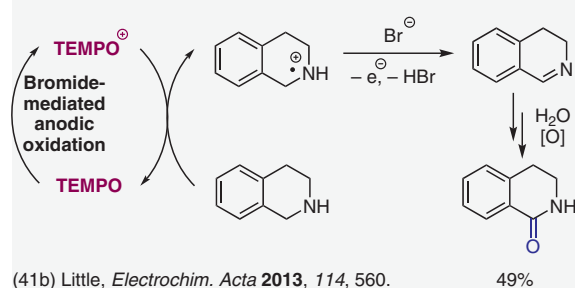
## Notable features

- Aminoxyl mediators enable a concerted hydride transfer, bypassing the traditional Shono oxidation sequence.
- Low oxidation potential of aminoxyl compounds allows for broad functional group tolerance.

## Historical precedent

(41a) Semmelhack, *J. Am. Chem. Soc.* **1983**, *105*, 6732.

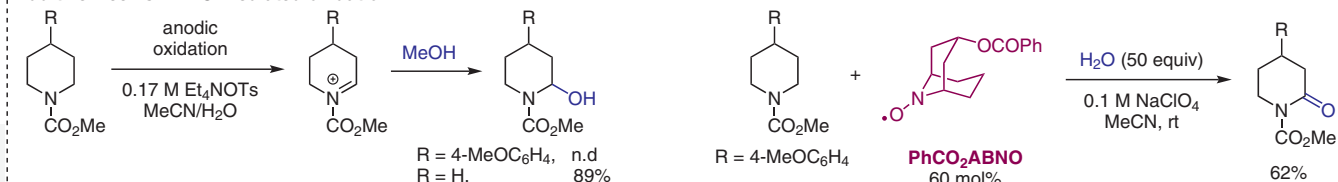
## TEMPO-mediated electrooxidation of THIQ

(41b) Little, *Electrochim. Acta* **2013**, *114*, 560.

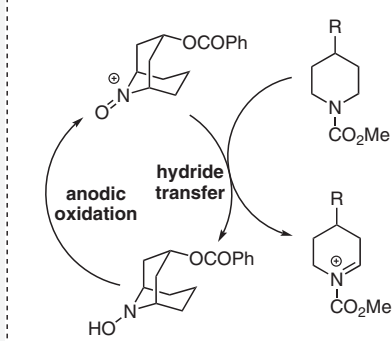
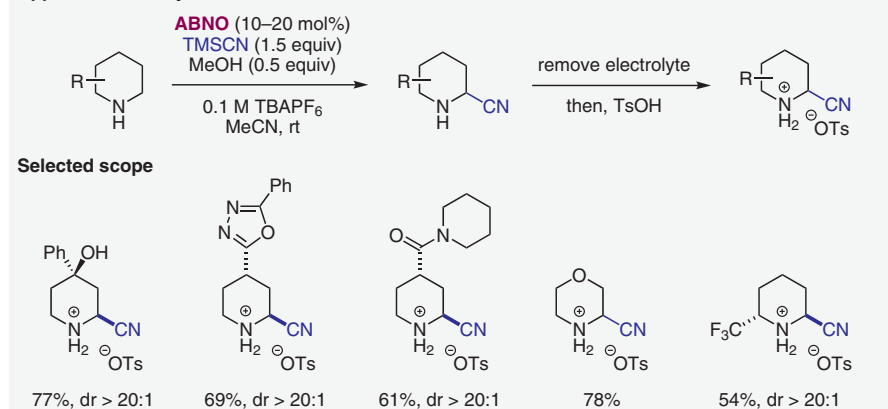
## Further reading

- (41f) Kashiwagi, *Chem. Commun.* **1999**, 1983.  
 (41g) Kashiwagi, *Chem. Pharm. Bull.* **2001**, *49*, 324.  
 Review on the use of *N*-oxyl species in electrocatalytic reactions:  
 (41h) Stahl, *Chem. Rev.* **2018**, *118*, 4834.  
 Review on electron-proton transfer mediators in electrosynthesis:  
 (41i) Stahl, *Acc. Chem. Res.* **2020**, *53*, 561.

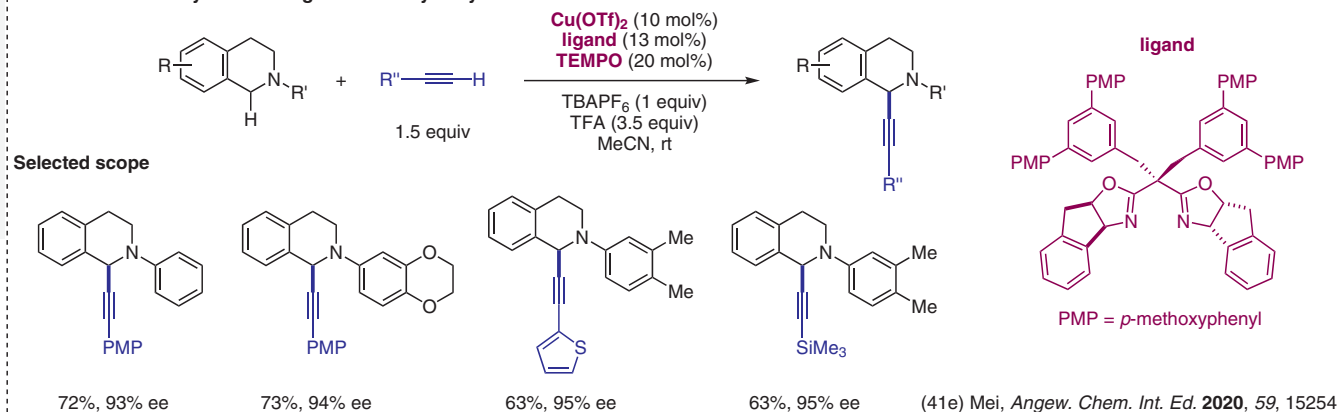
## Additive-free vs ABNO-mediated oxidation



## Mechanism

(41c) Stahl, *Angew. Chem. Int. Ed.* **2018**, *57*, 6686.Application to  $\alpha$ -cyanation(41d) Stahl, *J. Am. Chem. Soc.* **2018**, *140*, 11227.

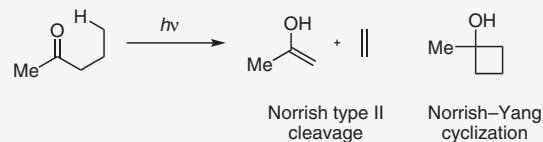
## Enantioselective alkylation using a dual catalytic system

(41e) Mei, *Angew. Chem. Int. Ed.* **2020**, *59*, 15254.Figure 41 Electrochemical approaches, 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO) catalysis.<sup>41</sup>

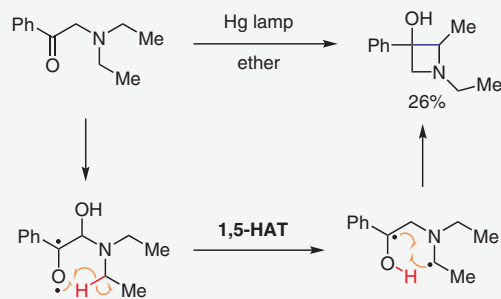
## Notable features

- Intramolecular Hydrogen Atom Transfer (HAT) represents a key step in many photochemical C–H bond functionalizations of amine derivatives.
- Initial products are useful starting materials for further transformations.

## Historical precedent: Norrish–Yang cyclization

(42a) Norrish, *Nature* **1937**, *140*, 195.(42b) Yang, *J. Am. Chem. Soc.* **1958**, *80*, 2913.

## Seminal work



## Further reading

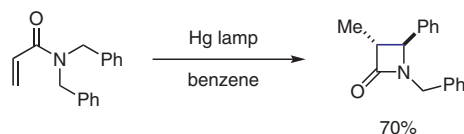
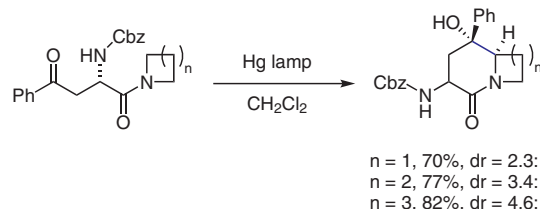
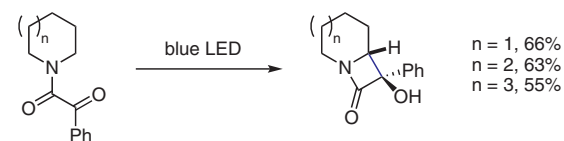
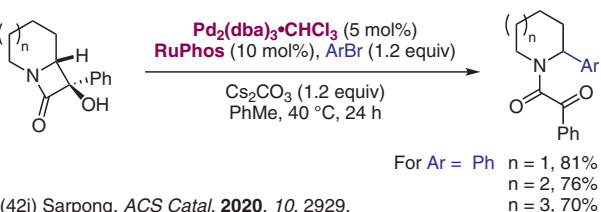
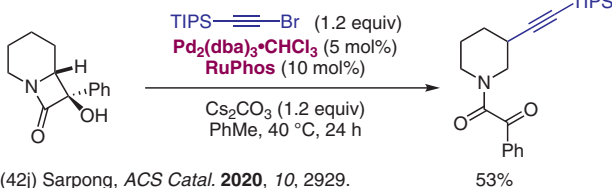
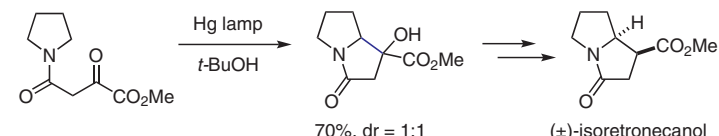
Other 1,6-HAT reactions:

(42i) Griesbeck, *Tetrahedron Lett.* **1999**, *40*, 3137.(42m) Peññory, *J. Org. Chem.* **2009**, *74*, 1223.

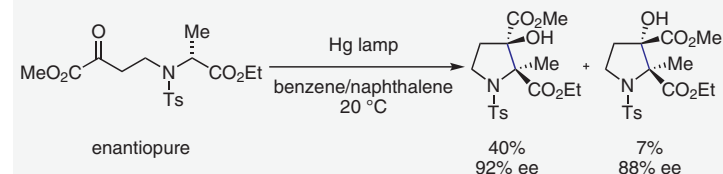
1,8-HAT reactions:

(42n) Nishio, *Helv. Chim. Acta* **2005**, *88*, 78.(42o) Nishio, *Helv. Chim. Acta* **2005**, *88*, 996.(42p) Nishio, *Helv. Chim. Acta* **2005**, *88*, 2603.

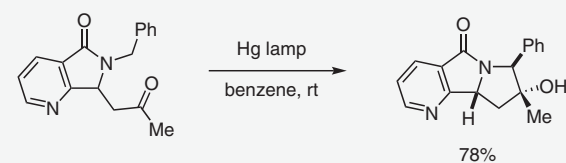
Reviews:

(42q) Nechab, Bertrand, *Chem. Eur. J.* **2014**, *20*, 16034.(39l) Gevorgyan, *Chem. Sci.* **2020**, *11*, 12974.Synthesis of  $\beta$ -,  $\gamma$ -, and  $\delta$ -lactams(42e) Aoyama, *Tetrahedron Lett.* **1975**, *16*, 1901.(42f) Wessig, *Tetrahedron: Asymmetry* **1998**, *9*, 4459.Cyclization of  $\alpha$ -ketoamides and subsequent applications $\alpha$ -Arylation(42j) Sarpong, *ACS Catal.* **2020**, *10*, 2929. $\beta$ -Alkynylation(42j) Sarpong, *ACS Catal.* **2020**, *10*, 2929.(42g) Gramain, *J. Org. Chem.* **1985**, *50*, 710.

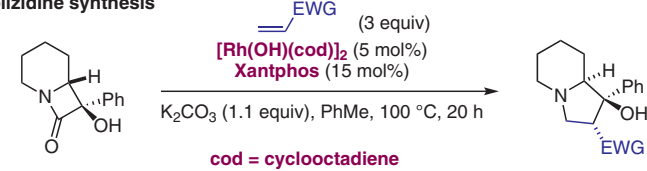
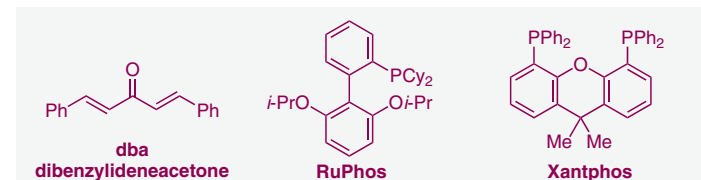
## Synthesis of pyrrolidines

(42h) Giese, *Angew. Chem. Int. Ed.* **1999**, *38*, 2586.

## Synthesis of benzopyrrolidinones

(42i) Zhang, *Synthesis* **2009**, 1821.

## Indolizidine synthesis

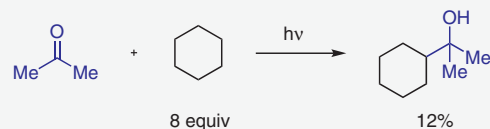
(42k) Sarpong, *J. Am. Chem. Soc.* **2020**, *142*, 13041.Figure 42 Intramolecular hydrogen atom transfer (HAT).<sup>42</sup>



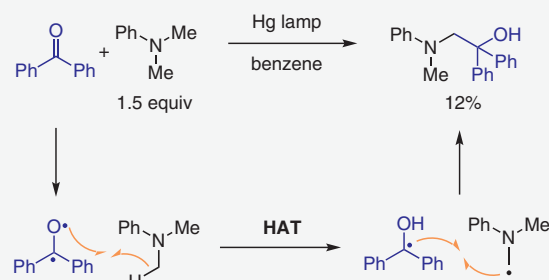
## Notable features

- High redox potentials of certain amine derivatives prevent them from undergoing single-electron transfer (SET) with typical photoredox catalysts. Direct hydrogen atom transfer (HAT) avoids this issue by using a photocatalyst to abstract a hydrogen atom from the substrate, generating the reactive  $\alpha$ -amino radicals.
- Direct HAT photocatalysis can be combined with other forms of catalysis to achieve previously elusive transformations.

## Historical precedent: Intermolecular Yang C–H Functionalization

(42b) Yang, *J. Am. Chem. Soc.* **1958**, *80*, 2913.

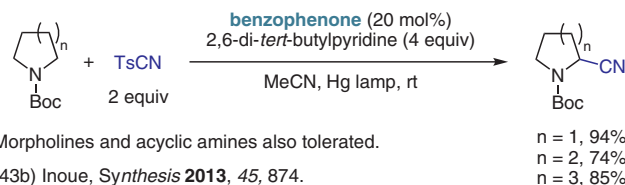
## Seminal work

(43a) Davidson, *Chem. Commun.* **1966**, 575.

## Further reading

- Early review on photoreduction by amines:  
 (42d) Cohen, *Chem. Rev.* **1973**, *73*, 141.  
 A uranyl cation and eosin Y as HAT photocatalysts:  
 (43i) Mei, Shi, *Chem. Eur. J.* **2020**, *26*, 16521.  
 (43j) Singh, *Tetrahedron Lett.* **2019**, *60*, 1333.  
 Polarity matching effect, and its application in HAT catalysis:  
 (43k) Roberts, *Chem. Soc. Rev.* **1999**, *28*, 25.  
 Benzophenone-mediated enantioselective alkylation:  
 (43l) Inoue, *Chem. Asian. J.* **2015**, *10*, 120.  
 Selected general reviews on HAT:  
 (43m) Ravelli, *Eur. J. Org. Chem.* **2017**, 2056.  
 (43n) Ravelli, *Green Chem.* **2020**, *22*, 3376.

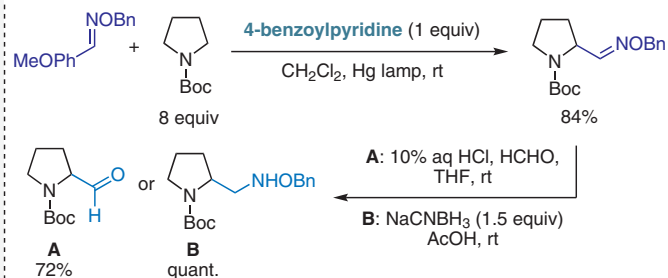
## Cyanation



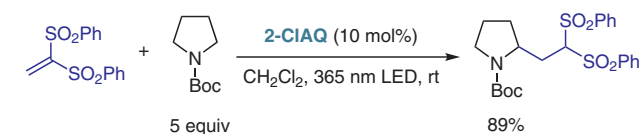
Morpholines and acyclic amines also tolerated.

(43b) Inoue, *Synthesis* **2013**, *45*, 874.

## Aldoximation and further functionalization

(43c) Kamijo, *Angew. Chem. Int. Ed.* **2016**, *55*, 9695.

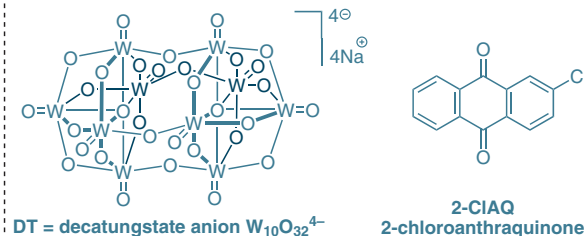
## Alkylation



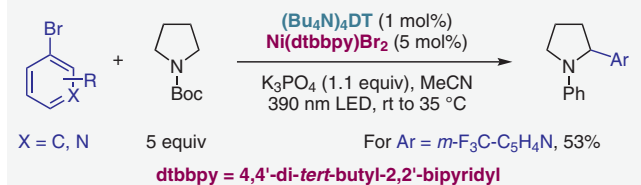
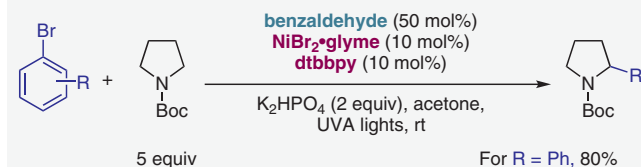
Morpholines and proline esters also tolerated.

(43d) Kamijo, *Org. Lett.* **2016**, *18*, 4912.

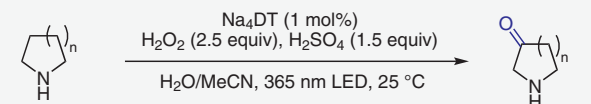
## Direct Hydrogen Atom Transfer agents



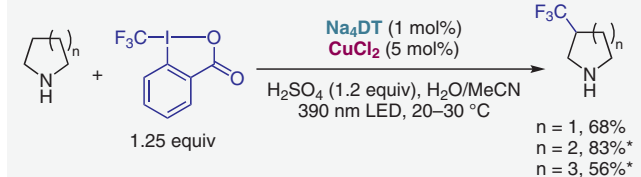
## Arylation

(43e) MacMillan, *Nature* **2018**, *560*, 70.Functional groups on aryl group tolerated: F, CF<sub>3</sub>, Me, OMe, CN, CF<sub>3</sub>.  
Alkyl bromides also tolerated as coupling partners.(43f) Hashmi, *Org. Lett.* **2019**, *21*, 6329.

## Oxidation

Protonation of the amine deactivates the  $\alpha$  C–H bond, allowing HAT to occur at the  $\beta$ - or  $\gamma$ -positions. Selective hydroxylations and iminations also possible.(43g) Schultz, *Angew. Chem. Int. Ed.* **2017**, *56*, 15274.

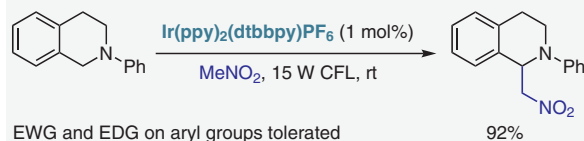
## Trifluoromethylation at distal positions

(43h) MacMillan, *Nat. Chem.* **2020** *12*, 459.Figure 43 Direct hydrogen atom transfer (HAT).<sup>43</sup>

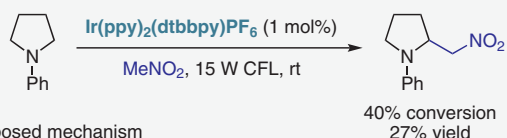


**Notable features**

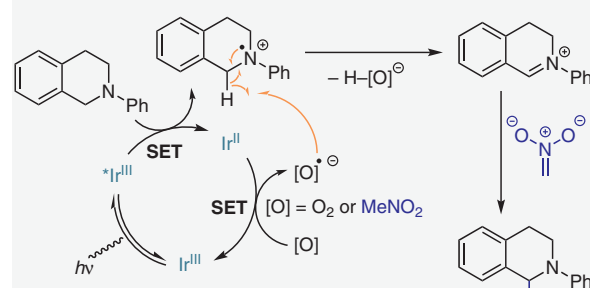
- High redox potentials of photoexcited catalysts allow for either oxidative or reductive single-electron transfer (SET) to a wide variety of substrates.
- Redox potentials of the photocatalysts can be tuned via aromatic substitution of bipyridine ligands
- Photoredox catalysis can be combined with other forms of catalysis to achieve previously elusive transformations.

**Seminal work**

EWG and EDG on aryl groups tolerated



Proposed mechanism

(44a) Stephenson, *J. Am. Chem. Soc.* **2010**, *132*, 1464.**Further reading**

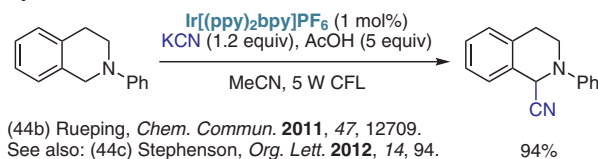
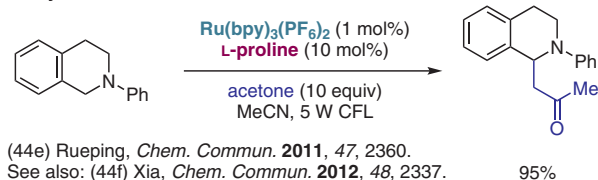
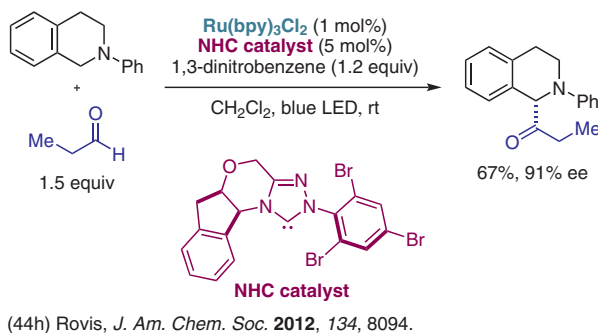
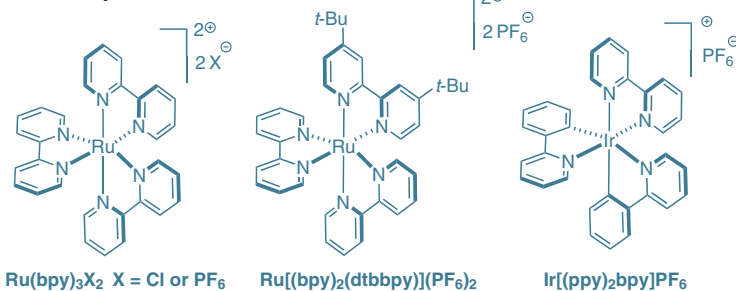
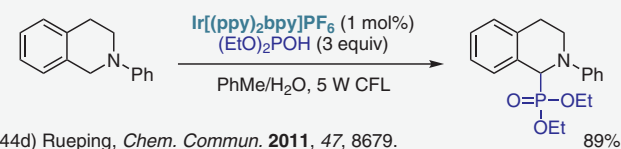
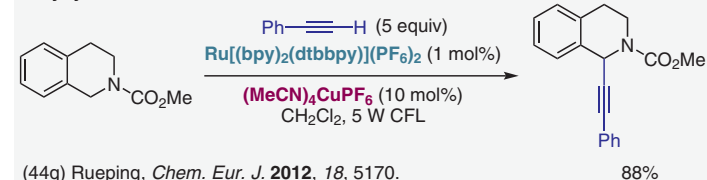
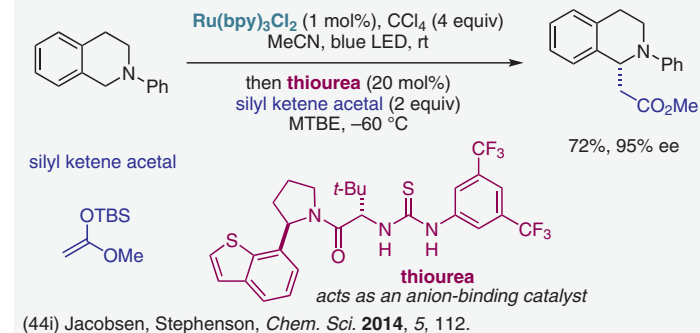
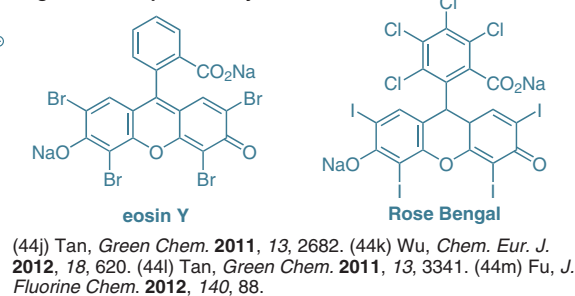
Other enantioselective strategies:

(44n) Kang, *Chem. Commun.* **2017**, *53*, 7665.(44o) Zhang, *Chem. Commun.* **2017**, *53*, 12536.

Selected examples of redox neutral C–H functionalization of THIQ:

(44p) Pandey, Reiser, *Org. Lett.* **2012**, *14*, 672.(44q) Nishibayashi, *Chem. Eur. J.* **2012**, *18*, 16473.(44r) Yoon, *J. Org. Chem.* **2013**, *78*, 4107.

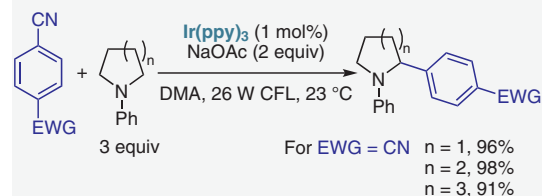
Selected reviews on organic dyes as photocatalysts:

(44s) Sharma, *Org. Biomol. Chem.* **2019**, *17*, 4384.(44t) Nicewicz, *Chem. Rev.* **2016**, *116*, 10075.**Cyanation****Acetylation****Enantioselective acylation****Photocatalysts****Phosphonylation****Alkynylation****Enantioselective synthesis of β-amino esters****Organic-based photocatalysts****Figure 44** Photoredox approaches, part I.<sup>44</sup>

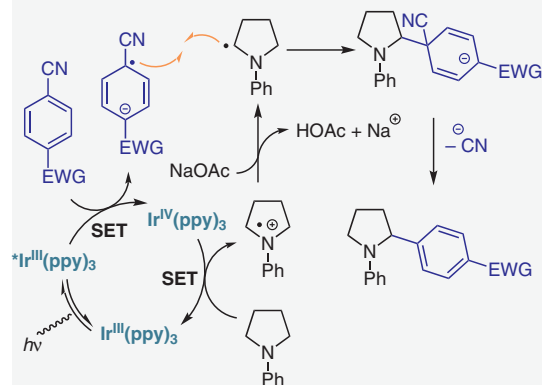
## Notable features

- Wide functional group tolerance on both coupling partners.
- Low catalyst loadings and mild conditions can be combined with flow chemistry to prepare grams of material.

## Landmark study



## Proposed mechanism

(45a) MacMillan, *Science* **2011**, 334, 1114.

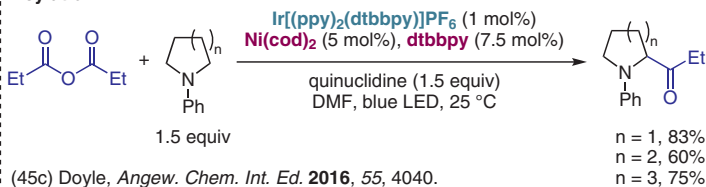
## Further reading

- Seminal work implicating SET:  
(45j) Cohen, *J. Am. Chem. Soc.* **1968**, 90, 165.  
(45k) Lewis, *J. Org. Chem.* **1981**, 46, 1077.  
Dehydrative allylation with allylic alcohols:  
(45l) Murakami, *Org. Lett.* **2020**, 22, 4467.  
Hydroaminoalkylation with conjugated dienes:  
(45m) Rovis, *J. Am. Chem. Soc.* **2017**, 139, 15504.  
Selected reviews:  
(45n) MacMillan, *J. Org. Chem.* **2016**, 81, 6898.  
(45o) Wencel-Delord, *Beilstein J. Org. Chem.* **2020**, 16, 1754.  
(10j) Gaunt, *Chem. Rev.* **2020**, 120, 2613.

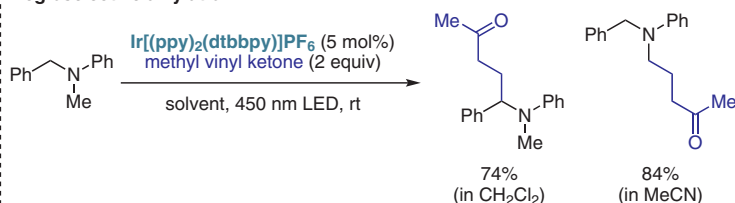
## Vinylation

Functional groups on Ar tolerated: Me, F, CO<sub>2</sub>Me, CF<sub>3</sub>, OMe.(45b) MacMillan, *J. Am. Chem. Soc.* **2014**, 136, 11602.

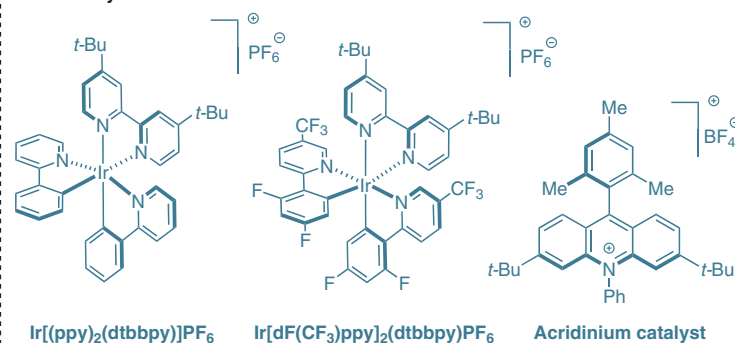
## Acylation

(45c) Doyle, *Angew. Chem. Int. Ed.* **2016**, 55, 4040.

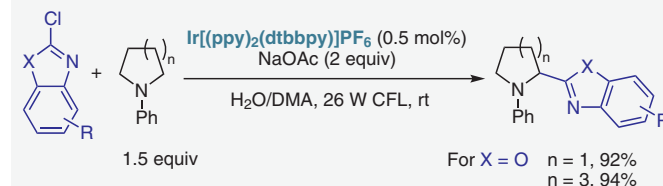
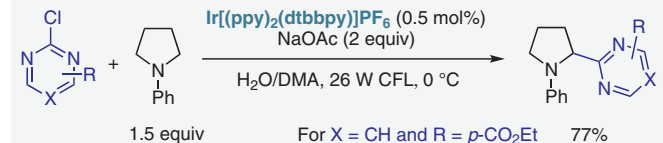
## Regioselective alkylation

(45d) Liu, Ready, *J. Am. Chem. Soc.* **2020**, 142, 11972.

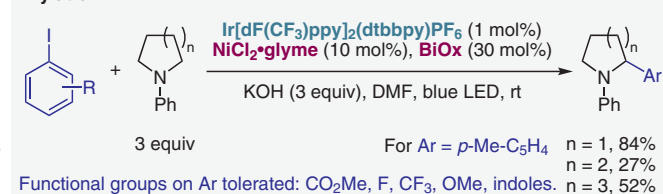
## Photocatalysts



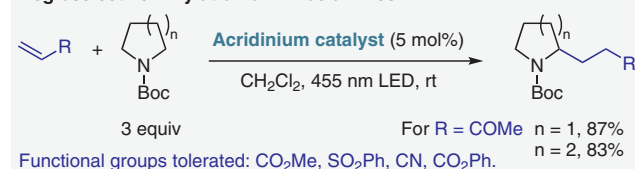
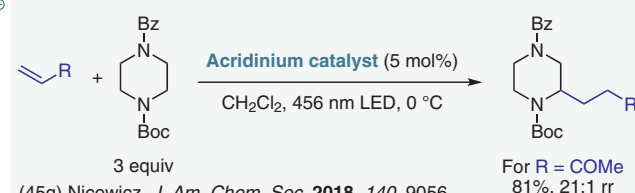
## Heteroarylation

Functional groups on Ar tolerated: Me, F, CO<sub>2</sub>Et, CF<sub>3</sub>, OMe.(45e) MacMillan, *Chem. Sci.* **2014**, 5, 4173.

## Arylation

Functional groups on Ar tolerated: CO<sub>2</sub>Me, F, CF<sub>3</sub>, OMe, indoles.(45f) Doyle, *Chem. Sci.* **2016**, 7, 7002.

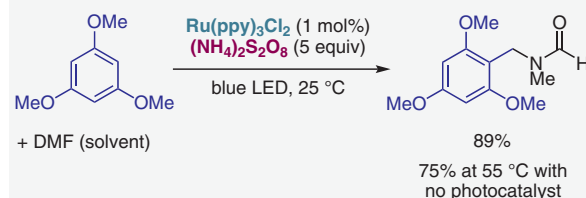
## Regioselective Alkylation of N-Boc amines

Functional groups tolerated: CO<sub>2</sub>Me, SO<sub>2</sub>Ph, CN, CO<sub>2</sub>Ph.(45g) Nicewicz, *J. Am. Chem. Soc.* **2018**, 140, 9056.(45h) Nicewicz, *Org. Lett.* **2020**, 22, 679.See also: (45i) Nicewicz, *ACS Catal.* **2021**, 11, 3153.Figure 45 Photoredox approaches, part II.<sup>45</sup>

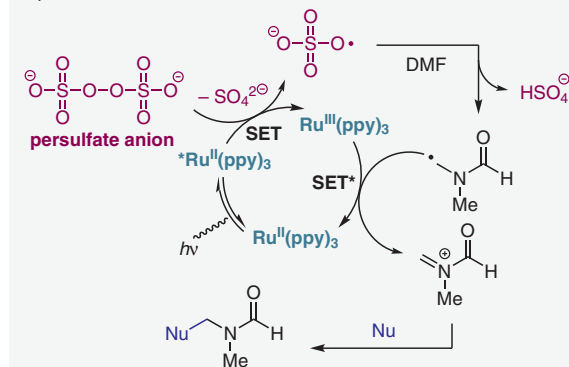
## Notable features

- High redox potentials of amides and protected amines prevent them from undergoing SET with typical photoredox catalysts. Indirect hydrogen atom transfer (HAT) circumvents this issue by using photoredox catalysts to oxidize or reduce a secondary catalyst or reagent, which then undergoes HAT with the substrate, generating the reactive  $\alpha$ -carbonyl radicals.

## Seminal work



## Proposed mechanism



## \* Oxidation with persulfate also possible

(46a) Stephenson, *J. Org. Chem.* **2012**, *77*, 4425.

## Further reading

Applications on acyclic amines:

(46i) Zhu, *Chem. Commun.* **2016**, *52*, 7596.

(46j) Miller, Knowles, *Nature* **2016**, *539*, 268.

(46k) Rovis, *Nat. Chem.* **2018**, *10*, 1037.

(46l) Rovis, *Angew. Chem. Int. Ed.* **2019**, *58*, 4002.

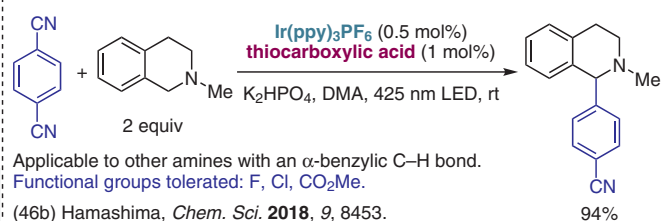
Other indirect HAT catalytic systems:

(46m) Cresswell, *Angew. Chem. Int. Ed.* **2020**, *59*, 14986.

(46n) Rovis, *J. Am. Chem. Soc.* **2021**, *143*, 2729.

(46o) Xu, *Angew. Chem. Int. Ed.* **2020**, *59*, 14275.

## Benzylic arylation

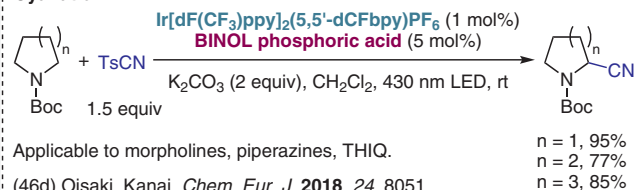


Applicable to other amines with an  $\alpha$ -benzylic C–H bond.  
Functional groups tolerated: F, Cl, CO<sub>2</sub>Me.

(46b) Hamashima, *Chem. Sci.* **2018**, *9*, 8453.

See also: (46c) Hamashima, *ACS Catal.* **2021**, *11*, 82.

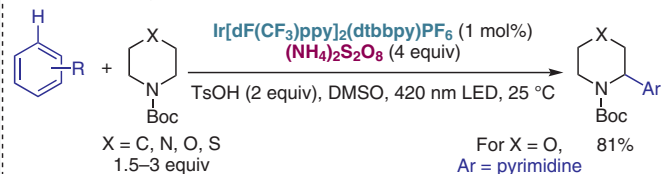
## Cyanation



Applicable to morpholines, piperazines, THIQ.

(46d) Oisaki, Kanai, *Chem. Eur. J.* **2018**, *24*, 8051.

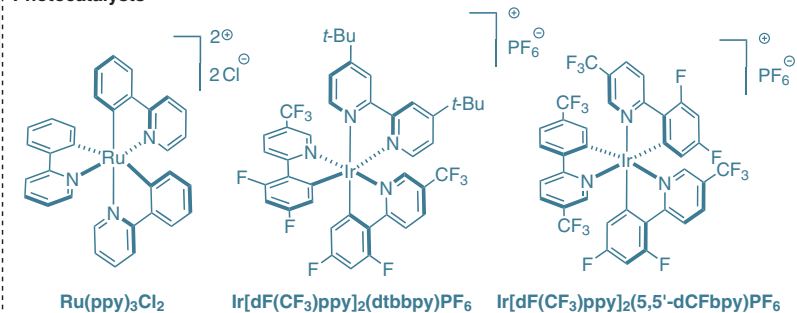
## Cross-dehydrogenative heteroarylation



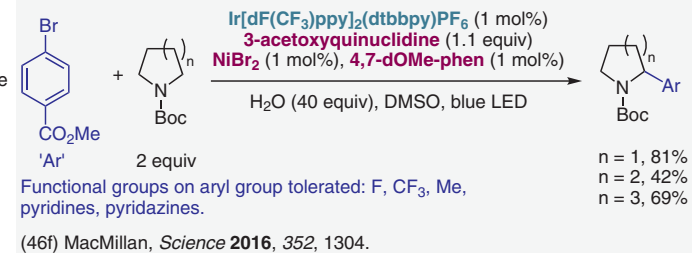
Aryl groups tolerated: pyridines, pyrimidines, pyrazines, pyridazines, quinolines.

(46e) Grainger, Johnson, *Chem. Sci.* **2019**, *10*, 2264.

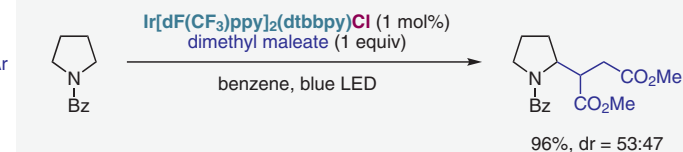
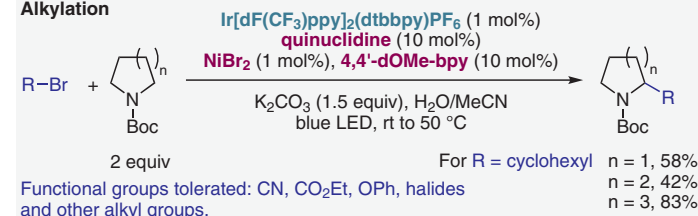
## Photocatalysts



## Arylation



## Alkylation



Chloride is used as the HAT catalyst.

(46h) Barriault, *Angew. Chem. Int. Ed.* **2018**, *57*, 15664.

## Hydrogen Atom Transfer (HAT) catalysts

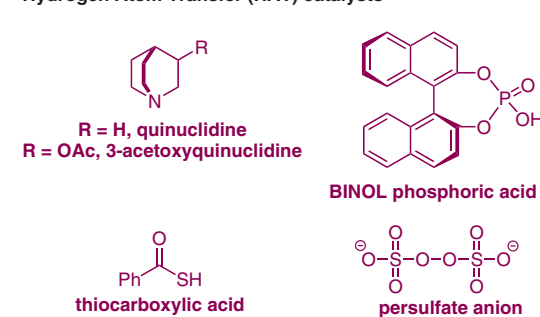
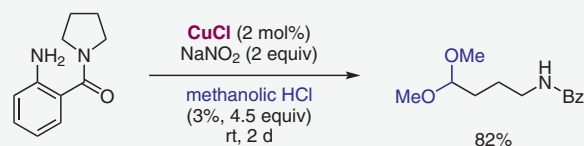


Figure 46 Indirect hydrogen atom transfer (HAT).<sup>46</sup>

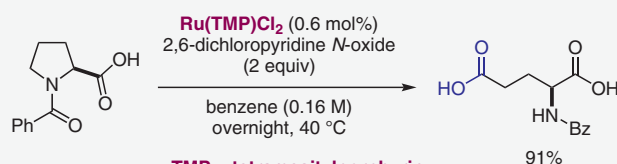
## Notable features

- Different approaches facilitate the ring cleavage of cyclic amines.
- Allows for the rapid formation of highly functionalized linear amines.
- Enables the late-stage modification of peptides.

## Early work

(47a) Weinreb, *Tetrahedron Lett.* **1994**, 35, 5813.

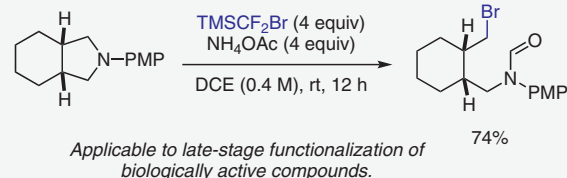
## Ruthenium-catalyzed oxidative cleavage of amides



TMP = tetramesitylporphyrin

(47b) Higuchi, *J. Am. Chem. Soc.* **2005**, 127, 834.

## Ring opening with difluorocarbenes



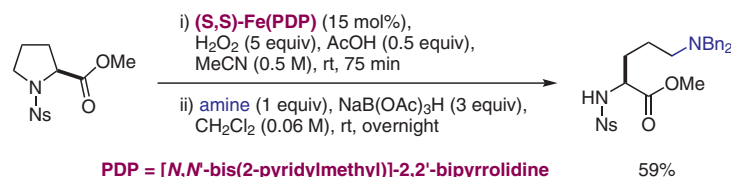
Applicable to late-stage functionalization of biologically active compounds.

(47c) Seo, Chang, *Nat. Commun.* **2020**, 11, 4761.

## Further Reading

- (47h) Sashida, *Tetrahedron Lett.* **2008**, 49, 2786.
- (47i) Liang, *J. Org. Chem.* **2011**, 76, 342.
- (39d) Maulide, *Org. Lett.* **2016**, 18, 345.
- (47j) Huigens, *Chem. Eur. J.* **2017**, 23, 4327.
- (47k) Morcillo, *Angew. Chem. Int. Ed.* **2019**, 58, 4044.
- (47l) Shi, Su, *Org. Biomol. Chem.* **2019**, 17, 4970.
- (47m) Smolobochkin, *Russ. Chem. Rev.* **2019**, 88, 1104.
- (47n) Song, *ACS Cent. Sci.* **2020**, 6, 1819.

## Deconstructive amination

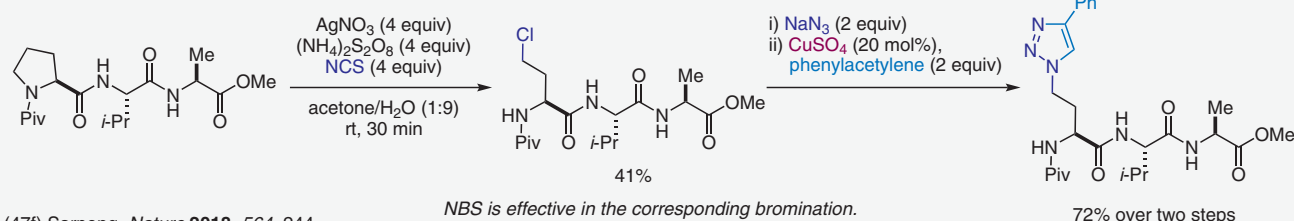


PDP = [N,N'-bis(2-pyridylmethyl)]-2,2'-bipyrrolidine

Aldehyde intermediates can also be modified otherwise (e.g., reduction and olefination).

(47d) White, *Nature* **2016**, 537, 214.

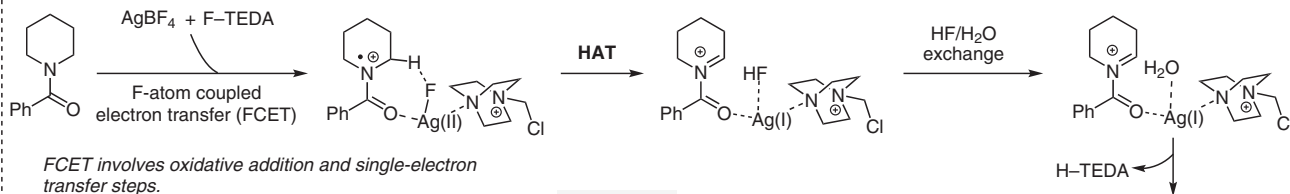
## Deconstructive chlorination



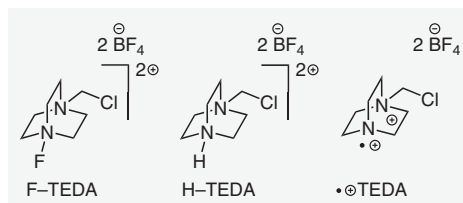
NBS is effective in the corresponding bromination.

(47f) Sarpong, *Nature* **2018**, 564, 244.

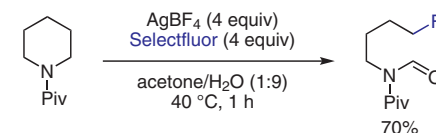
## Proposed mechanism using silver (I)



The overall HAT process involves lower-lying singlet and triplet electronic states and is characterized as a two-state reactivity event.

(47g) Sarpong, Musaev, *J. Am. Chem. Soc.* **2021**, 143, 3889.

## Deconstructive fluorination



Products obtained can arise from C–C or C–N bond cleavage with substrate-dependent mechanisms.

(47e) Sarpong, *Science* **2018**, 361, 171.Figure 47 Deconstructive functionalization.<sup>47</sup>



## Conflict of Interest

The authors declare no conflict of interest.

## Funding Information

Financial support from the NIH-NIGMS (grant no. R01GM101389) is gratefully acknowledged.

## Acknowledgment

We are grateful to the current and former members of the Seidel research group who have contributed to the development of this field.

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