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

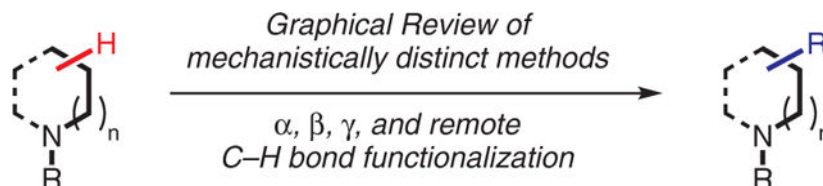
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Abstract

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.

Graphical Abstract



Keywords

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 worth-while unsolved challenges remain to be addressed.

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Conflict of Interest

The authors declare no conflict of interest.

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).

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Biographies



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).

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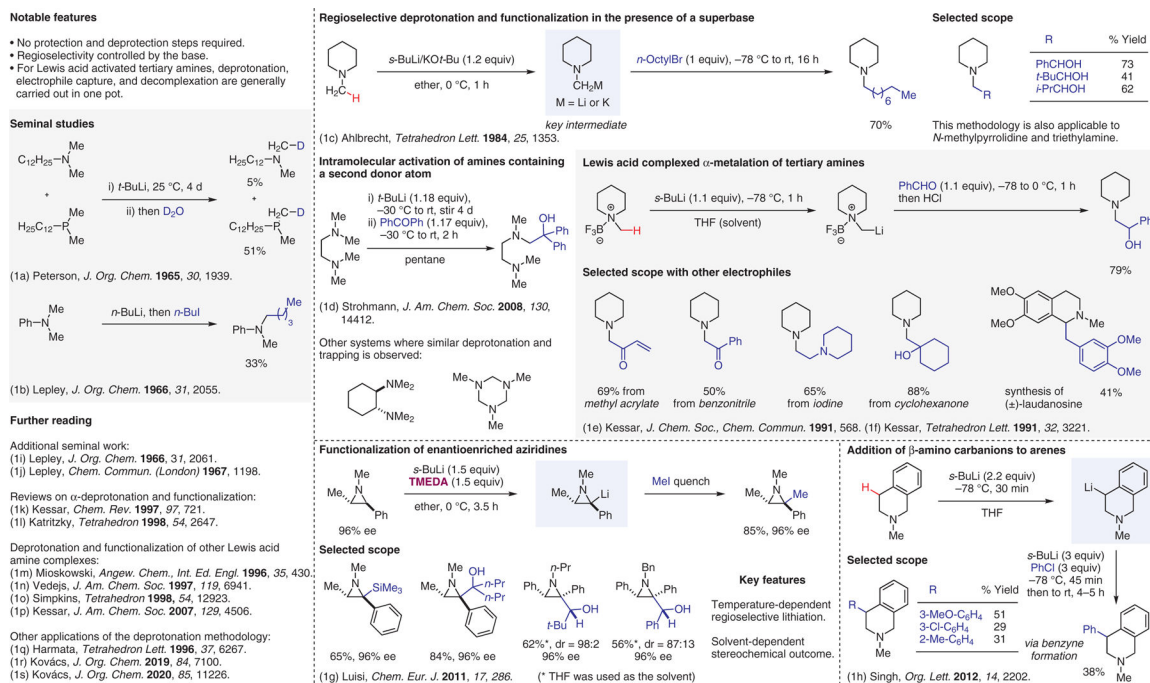


Figure 1.
 Deprotonation of tertiary amines.¹

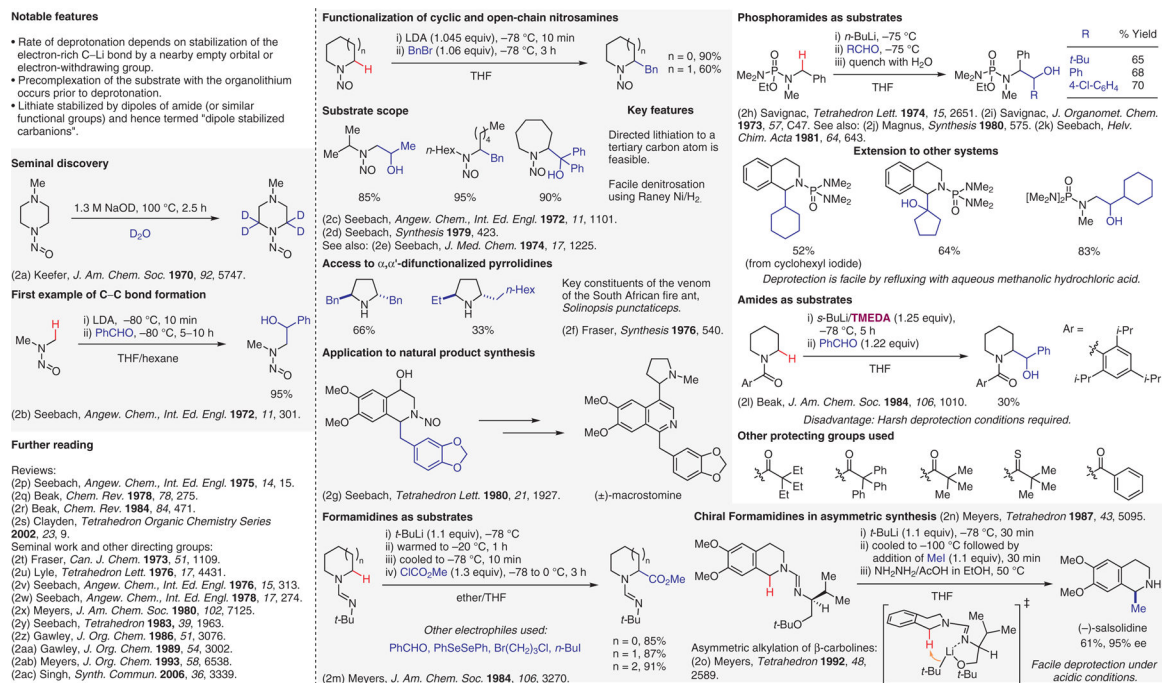
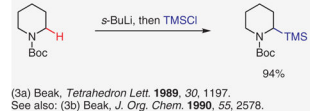
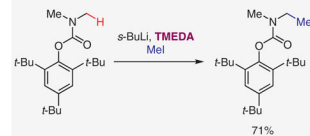


Figure 2.
 Deprotonation of protected amines, part I.²

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



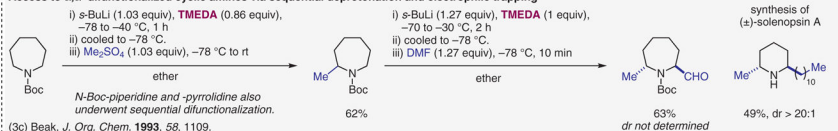
Further reading

- 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.

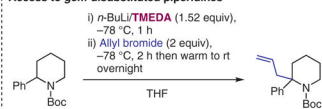
Application to natural product synthesis:
(3r) Feringa, *Org. Biomol. Chem.* **2008**, *6*, 3464.
(3s) Stoltz, *J. Am. Chem. Soc.* **2008**, *130*, 13745.

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

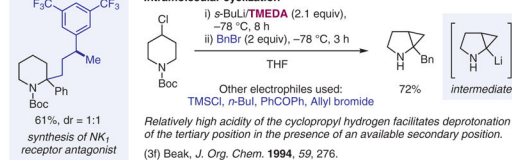
Transmetalation to organozinc species:
(3v) Coldham, *Org. Lett.* **2008**, *10*, 3923.

Access to α,α' -difunctionalized cyclic amines via sequential deprotonation and electrophile trapping

Access to gem-disubstituted piperidines



Intramolecular cyclization



Copper cyanide/palladium-catalyzed coupling with aryl iodides

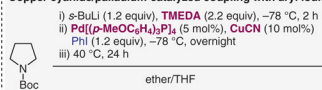
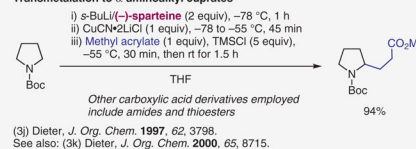
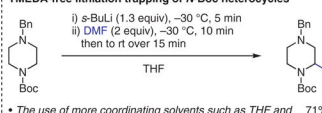
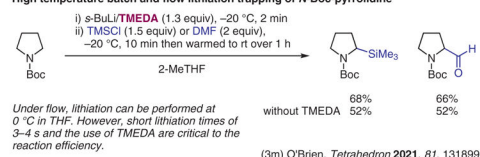
Transmetalation to α -aminoalkyl cupratesTMEDA-free lithiation trapping of *N*-Boc heterocyclesHigh temperature batch and flow lithiation trapping of *N*-Boc-pyrrolidine

Figure 3.
Deprotonation of protected amines, part II.³

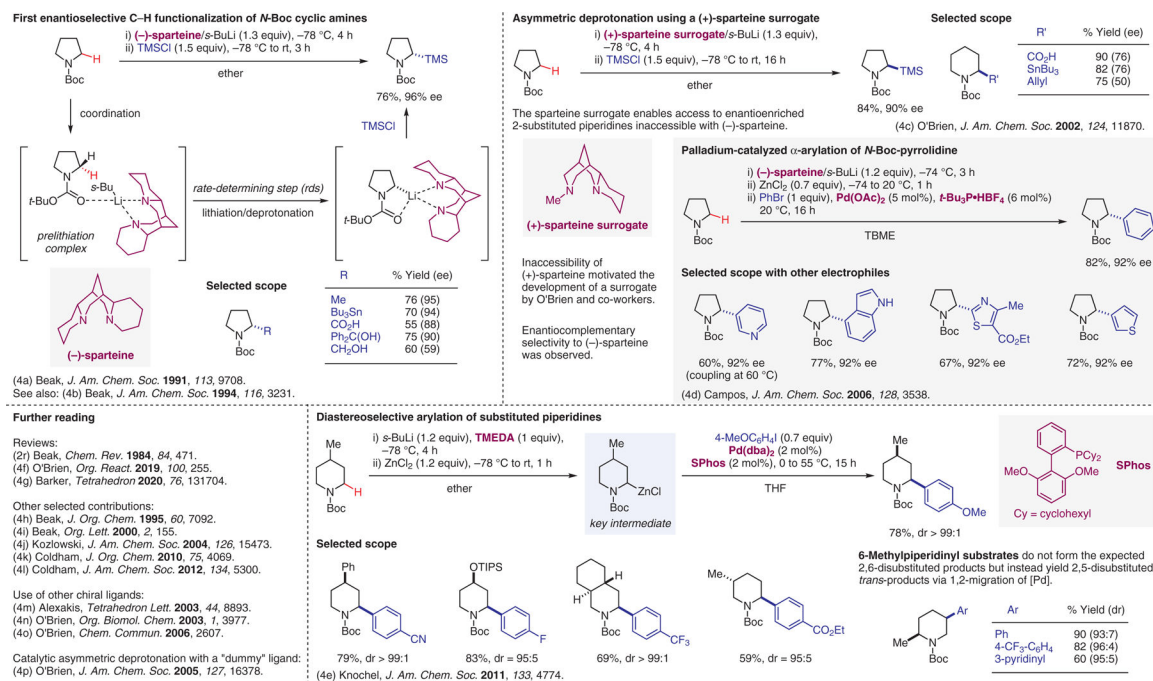
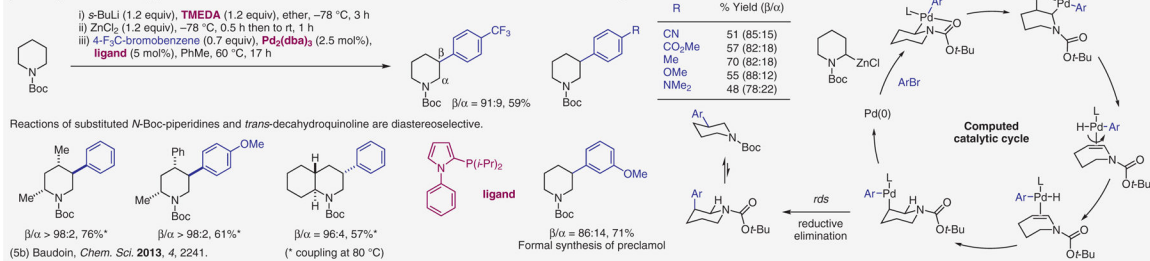


Figure 4.
Deprotonation of protected amines, part III.⁴

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

(5a) Coldham, *Chem. Eur. J.* **2010**, *16*, 4082. β -C-H Arylation of *N*-Boc-piperidines(5b) Baudoin, *Chem. Sci.* **2013**, *4*, 2241.

Enantioconvergent Negishi cross-coupling with unactivated secondary alkyl electrophiles

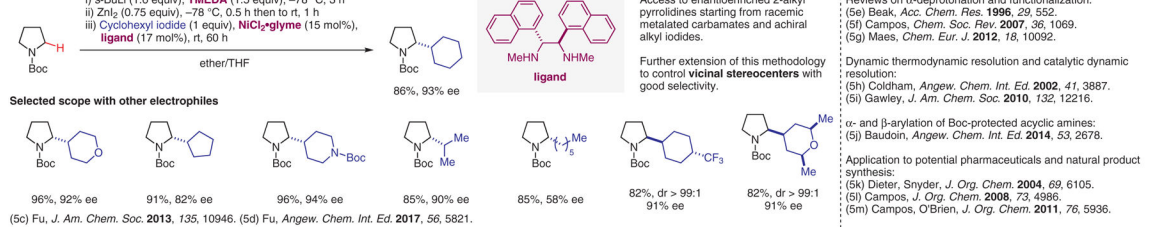


Figure 5.
Deprotonation of protected amines, part IV.⁵

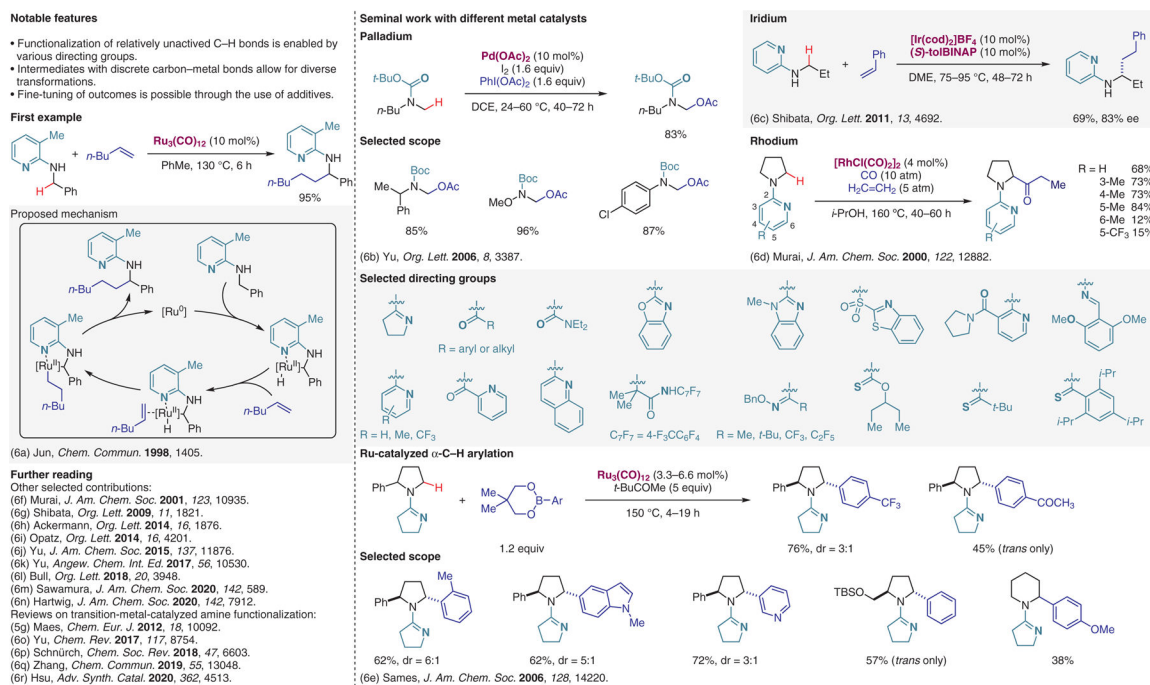


Figure 6. Transition-metal-catalyzed reactions with substrates containing directing groups, part I.⁶

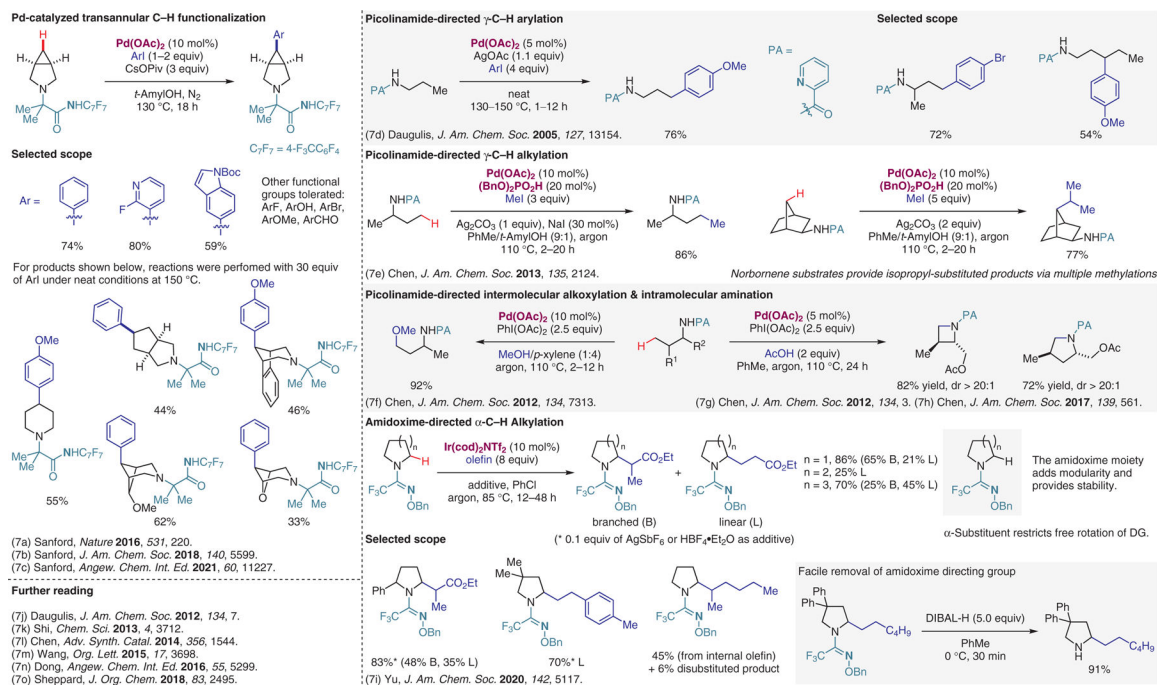


Figure 7. Transition-metal-catalyzed reactions with substrates containing directing groups, part II.⁷

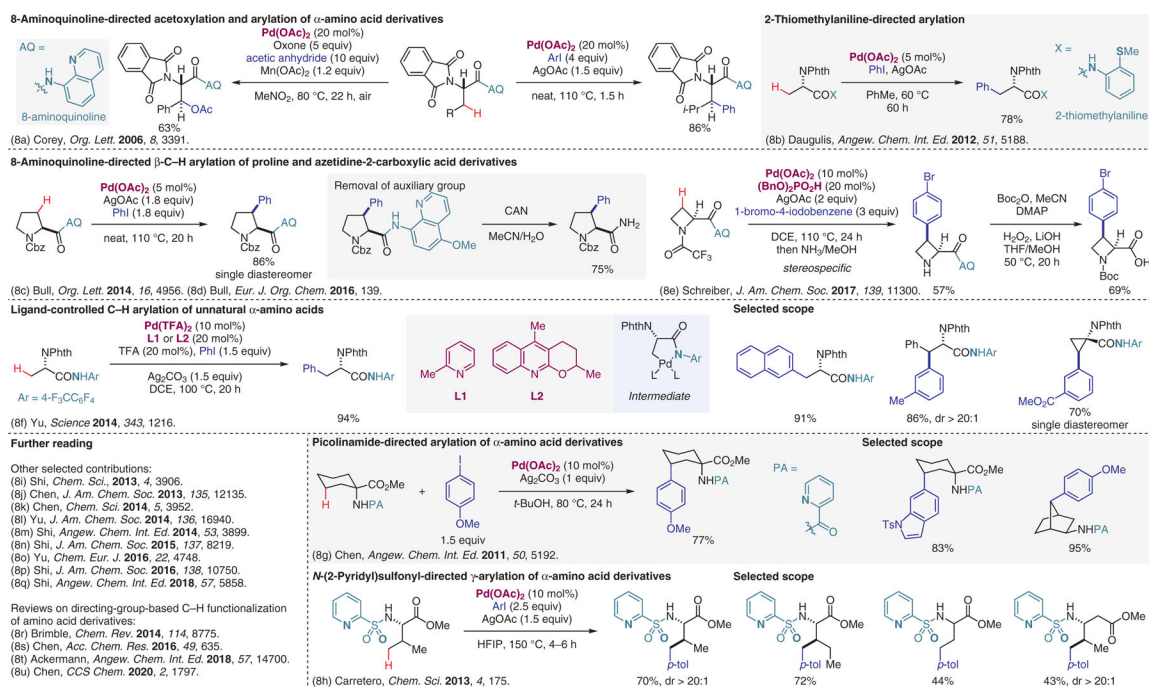


Figure 8. Transition-metal-catalyzed reactions with substrates containing directing groups, functionalization of amino acid derivatives.⁸

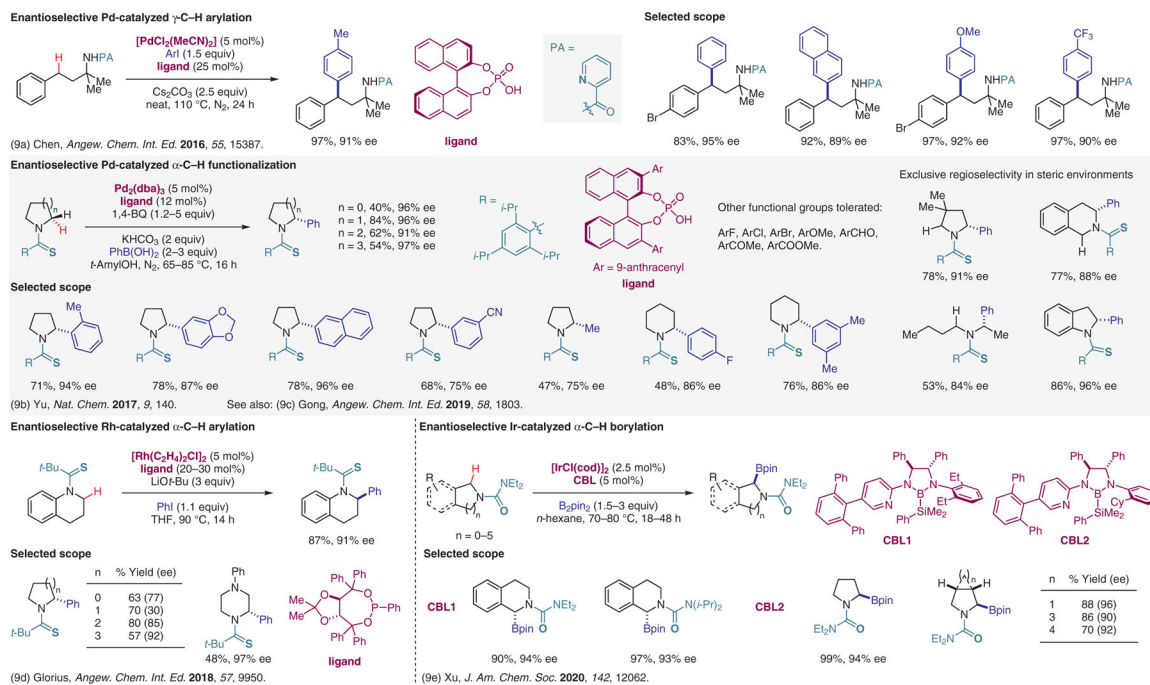


Figure 9. Transition-metal-catalyzed reactions with substrates containing directing groups, catalytic enantioselective approaches.⁹

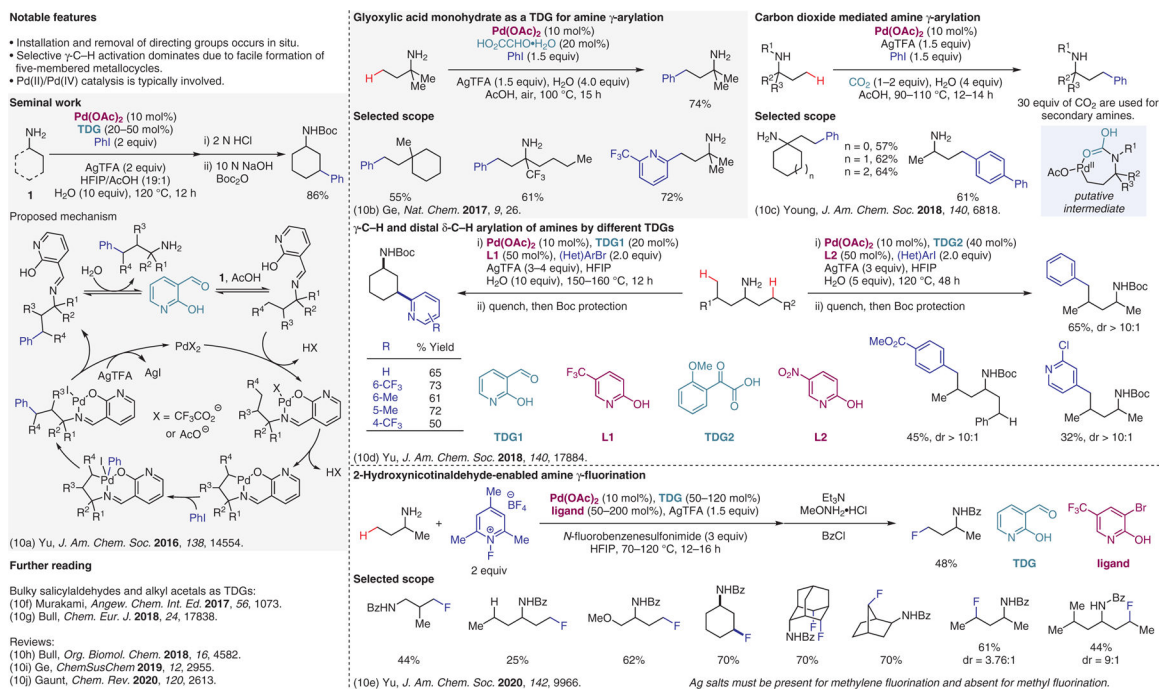


Figure 10. Transition-metal-catalyzed reactions involving transient directing groups (TDGs).¹⁰

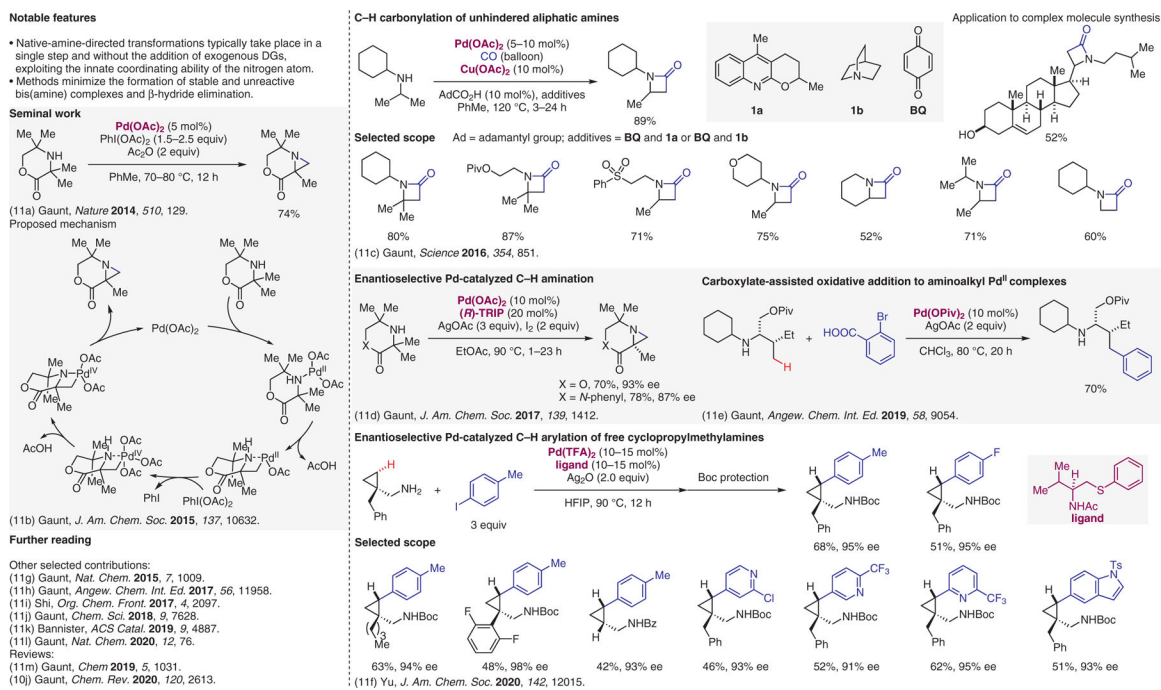


Figure 11. Native-amine-directed transition-metal-catalyzed reactions.¹¹

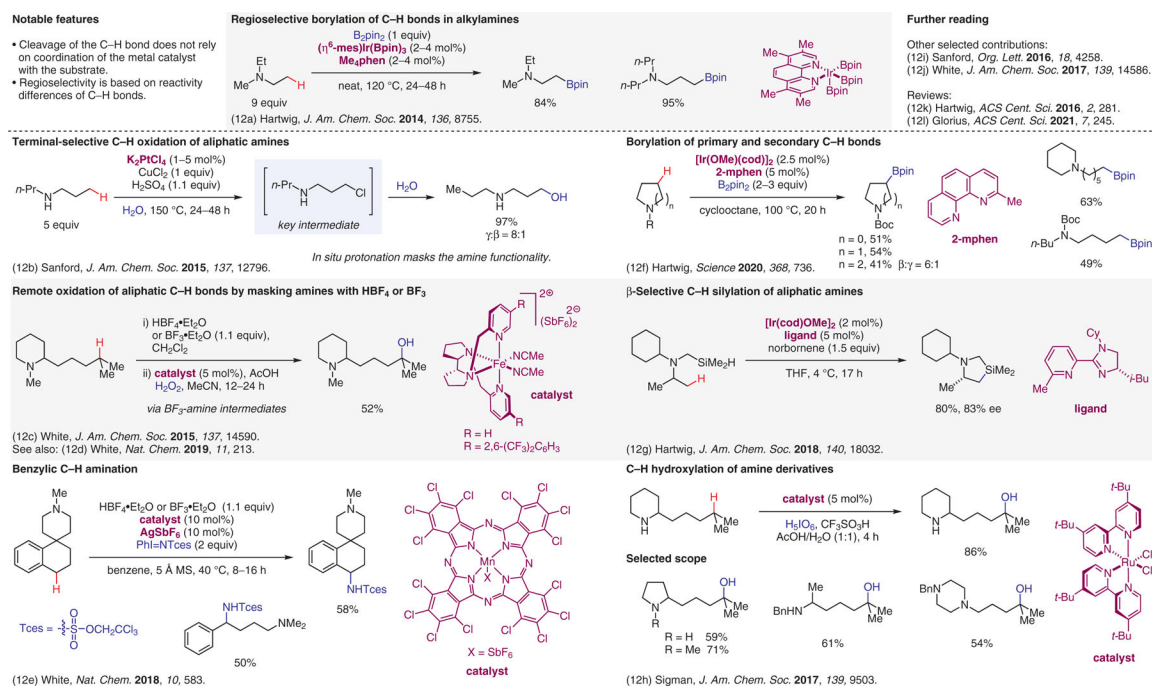
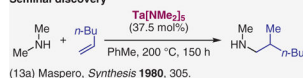


Figure 12.
 Undirected transition-metal-catalyzed reactions.¹²

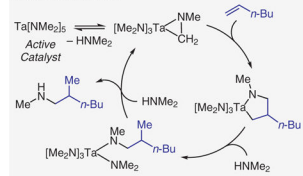
Notable features

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

Seminal discovery



Proposed mechanism:



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

Further reading

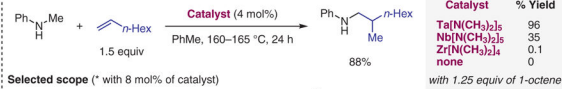
Reviews:

- (13) Roesky, *Angew. Chem. Int. Ed.* **2009**, 48, 4892.
 (13) Bellier, *ChemSusChem* **2009**, 2, 715.
 (13a) Schafer, *Synthesis* **2014**, 46, 2884.
 (13) 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, 6361.

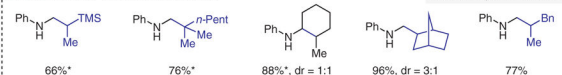
Other selected contributions:

- (13o) Doye, *Eur. J. Org. Chem.* **2001**, 4411.
 (13p) Odum, *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.

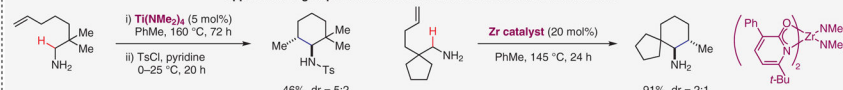
Application of group V metals to amine α -functionalization (13c) Hartwig, *J. Am. Chem. Soc.* **2007**, 129, 6690. (13d) Hartwig, *J. Am. Chem. Soc.* **2008**, 130, 14940.

The chloroamido complex [Cl₂Ta(NMePh)₂] catalyzes the same reaction effectively at 90 °C while Ta(NMe₂)₅ shows no activity at this temperature.

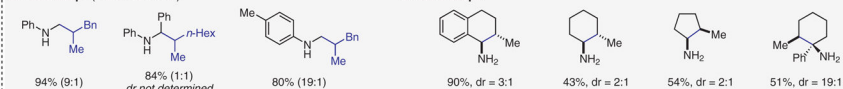
Selected scope (* with 8 mol% of catalyst)



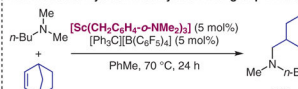
D retention Catalyst Ta(NMe₂)₅
 [Cl₂Ta(NMePh)₂]
 A mechanistic study suggests formation of an azametallacyclopropane (η^2 -imine complex) as the turnover-limiting step.

Application of group IV metals to intramolecular amine α -functionalization

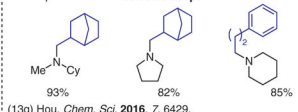
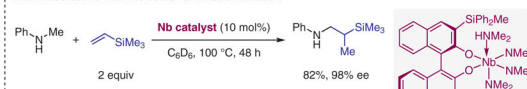
Selected scope (Branched:Linear)

(13e) Doye, *Angew. Chem. Int. Ed.* **2009**, 48, 1153.(13) Schafer, *J. Am. Chem. Soc.* **2009**, 131, 2116.

Intermolecular hydroaminoalkylation with group III metals



Selected scope

(13g) Hou, *Chem. Sci.* **2016**, 7, 6429.Enantioselective intermolecular α -functionalization

Selected scope

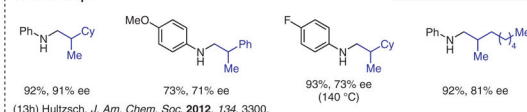
(13h) Hultsch, *J. Am. Chem. Soc.* **2012**, 134, 3300.

Figure 13.
Hydroaminoalkylation.¹³

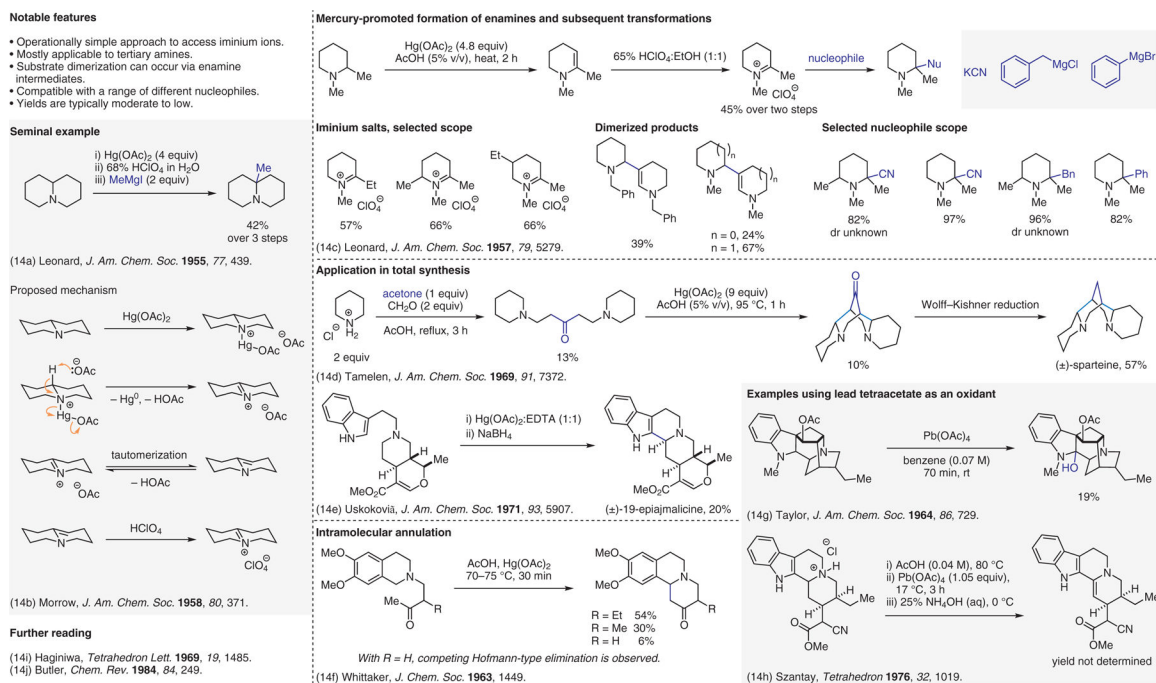


Figure 14.
Oxidative methods, stoichiometric metal-based oxidants.¹⁴

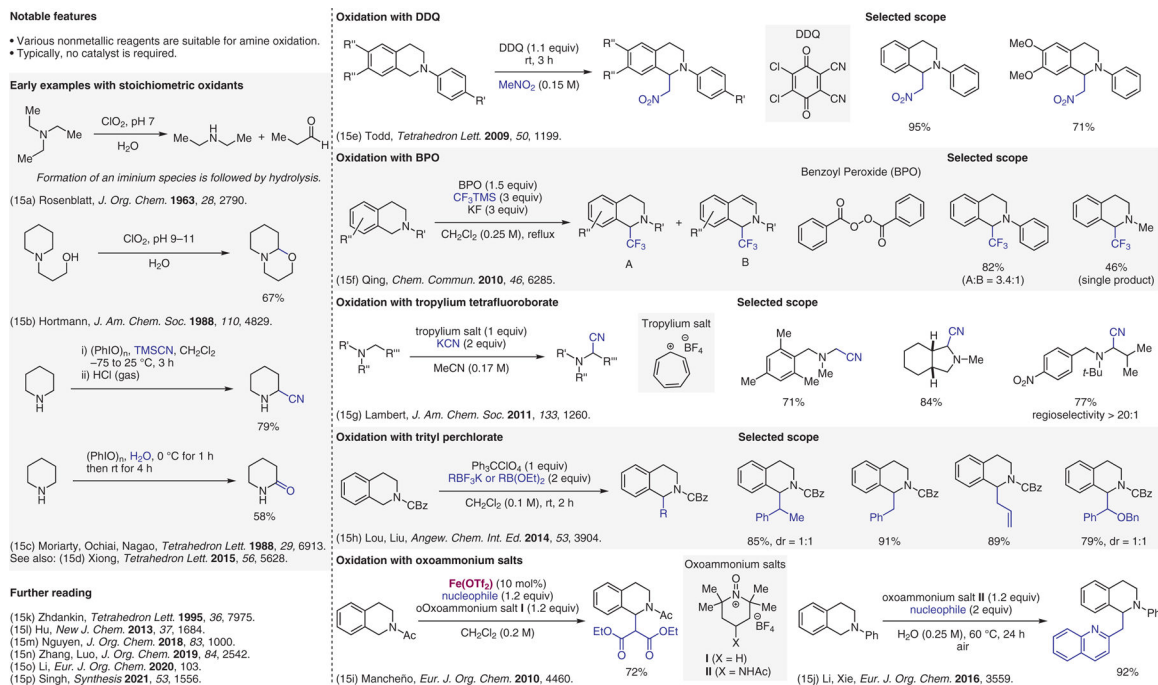


Figure 15.
Oxidative methods, stoichiometric nonmetallic oxidants.¹⁵

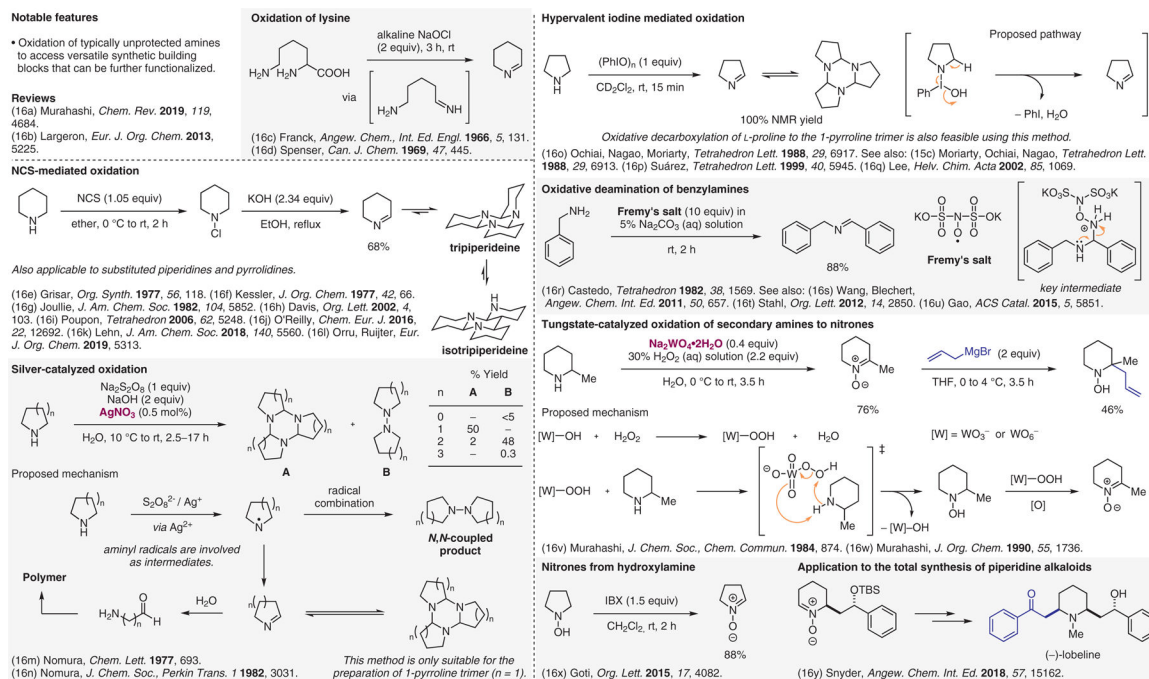


Figure 16.
Oxidative preparation of building blocks.¹⁶

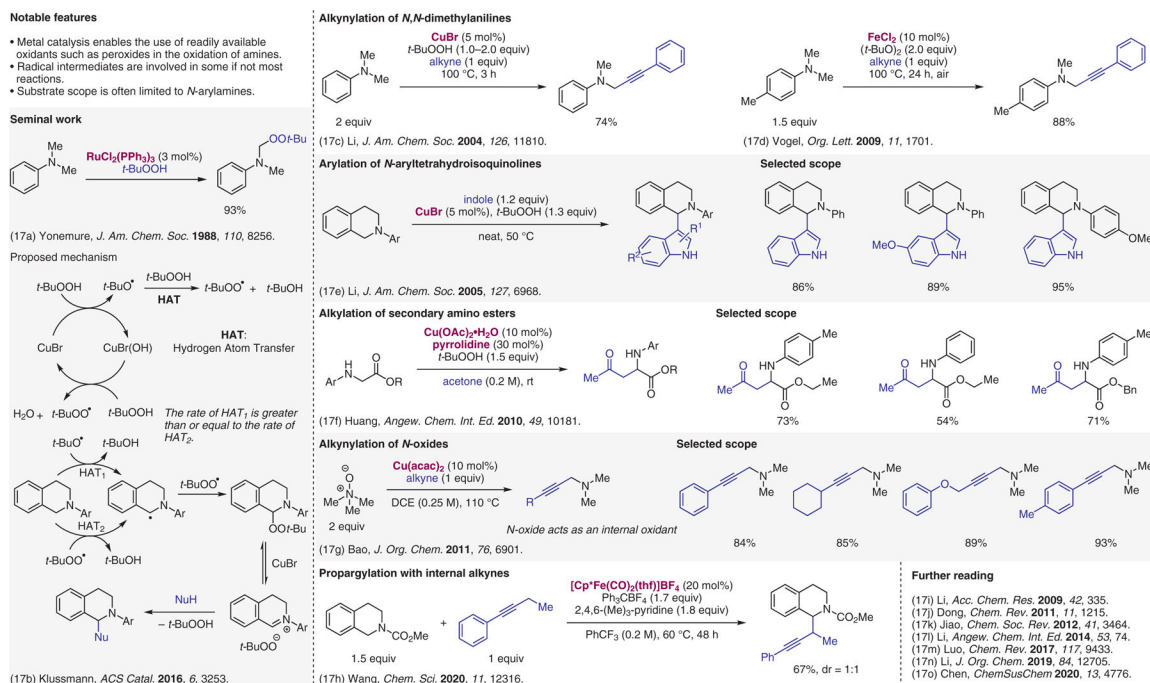


Figure 17. Metal-catalyzed cross-dehydrogenative-coupling (CDC) reactions.¹⁷

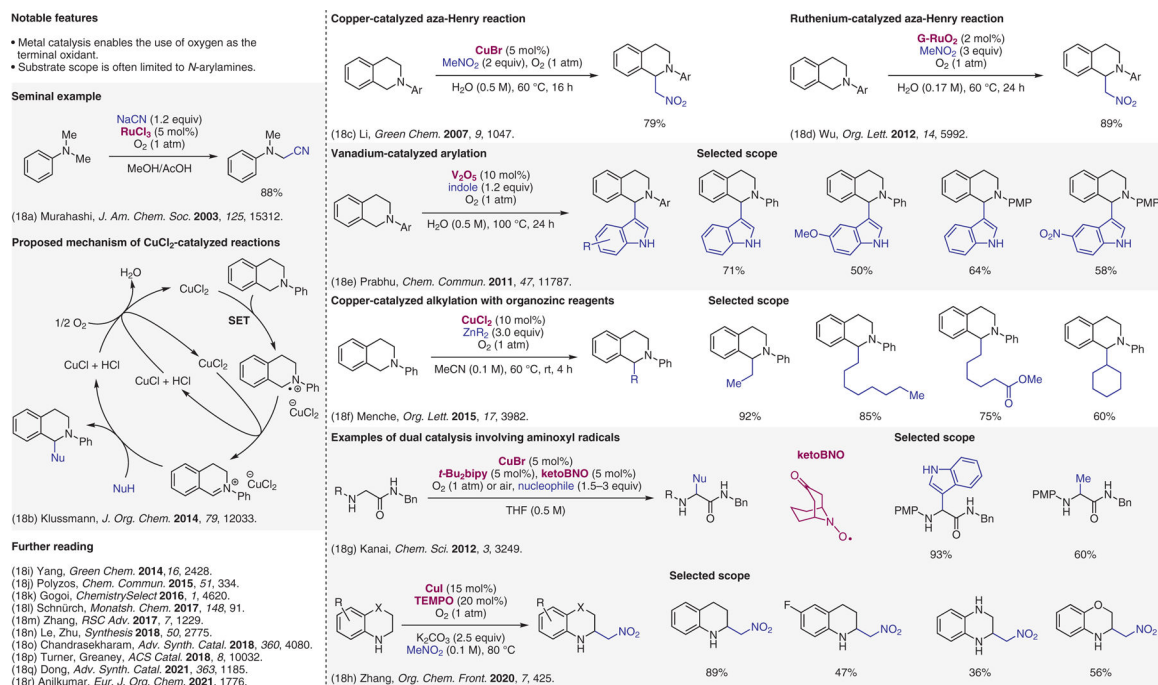


Figure 18. Metal-catalyzed cross-dehydrogenative-coupling (CDC) reactions with oxygen as the terminal oxidant.¹⁸

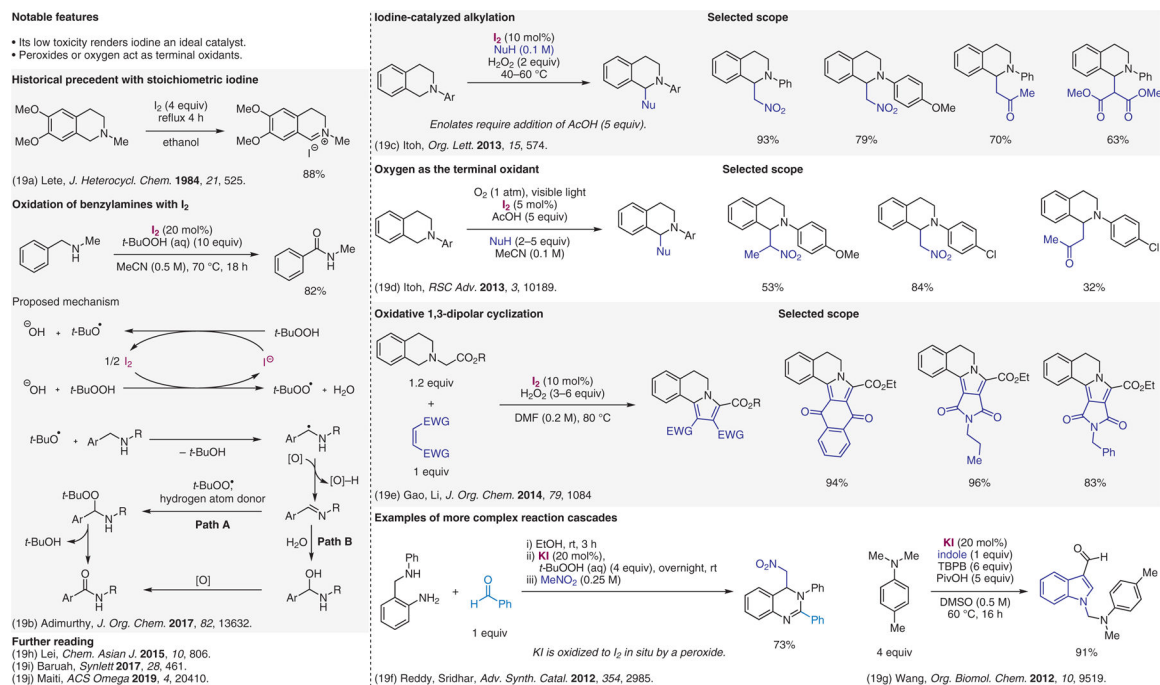


Figure 19. Iodine-catalyzed cross-dehydrogenative-coupling (CDC) reactions.¹⁹

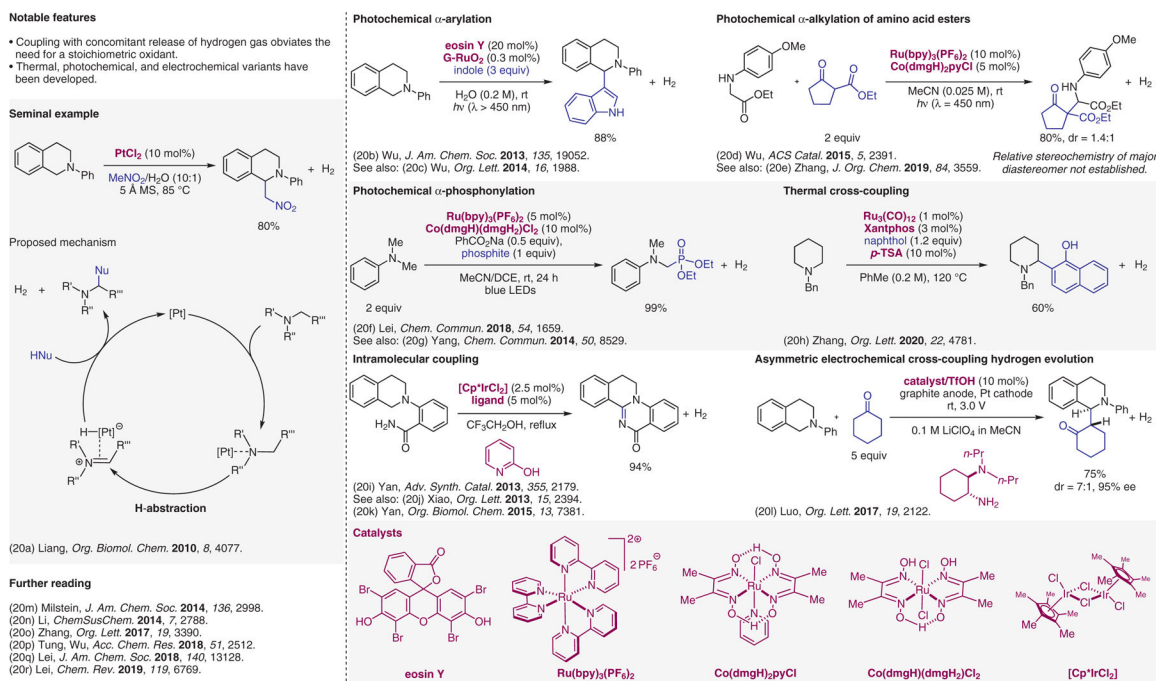


Figure 20. Acceptorless cross-dehydrogenative-coupling (CDC) reactions with hydrogen evolution.²⁰

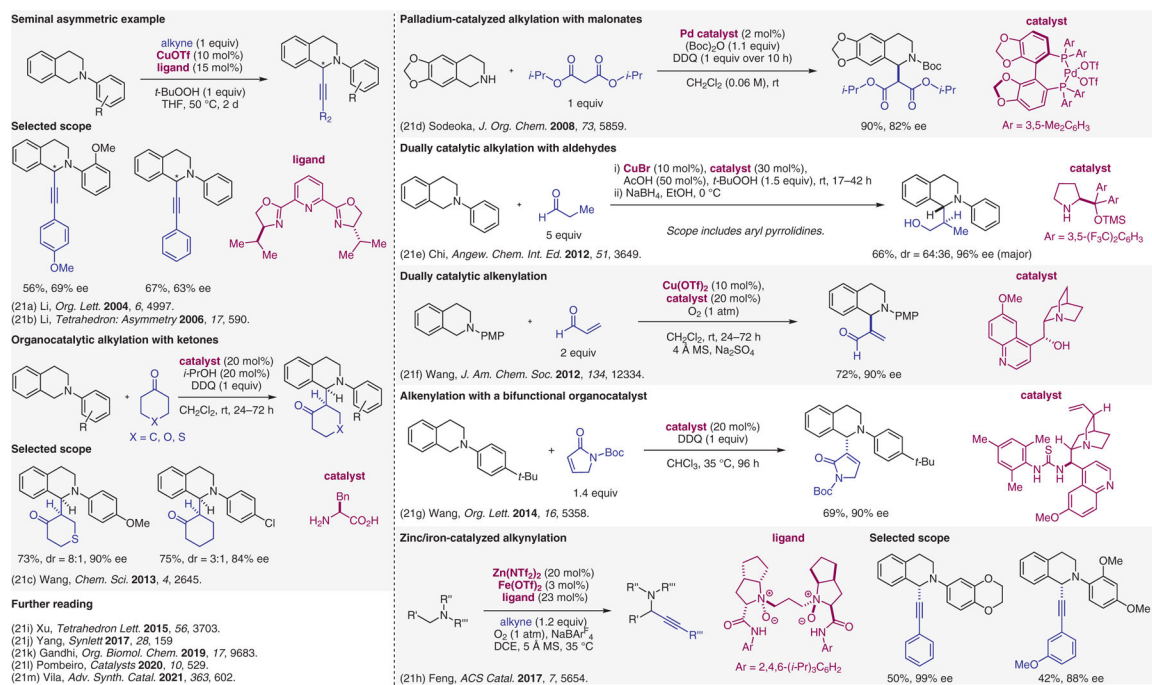
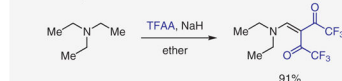


Figure 21.
Catalytic enantioselective cross-dehydrogenative-coupling (CDC) reactions.²¹

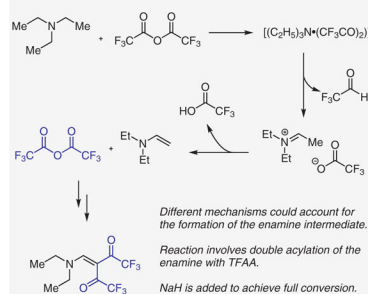
Notable features

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

Seminal example



Proposed mechanism

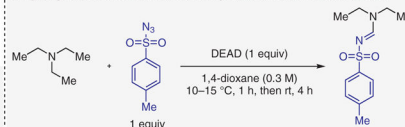


(22a) Schreiber, *Tetrahedron Lett.* **1980**, 21, 1027.

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.

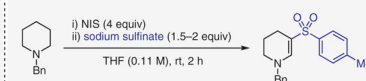
Dehydrogenation with DEAD followed by cascade reactions with azides



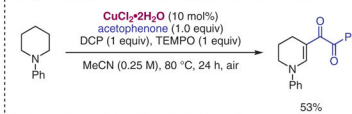
(22b) Weng, *J. Am. Chem. Soc.* **2008**, 130, 14048.
 See also: (22c) Zheng, Wang, *Chem. Commun.* **2009**, 47, 7372.

Platinum-catalyzed α,β -difunctionalization

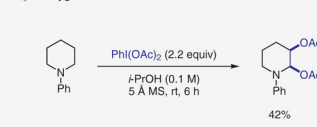
(22e) Liang, *J. Org. Chem.* **2010**, 75, 2893.

Oxidative β -sulfonylation with NIS

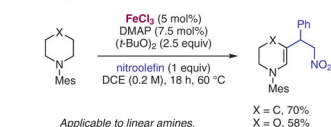
(22g) Talbot, Willis, *Chem. Sci.* **2018**, 9, 2295.
 See also: (22h) Fan, He, *J. Org. Chem.* **2020**, 85, 15600.

Complex reaction cascade leading to α -keto-enaminones

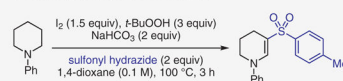
(22j) Fan, Zhang, *J. Org. Chem.* **2020**, 85, 2220.

 α,β -Dioxygenation with DIB

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

Iron-catalyzed β -alkylation

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

Oxidative β -sulfonylation with iodine

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

Selected scope

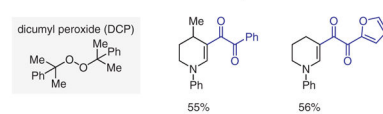


Figure 22.
Oxidative β -functionalization.²²

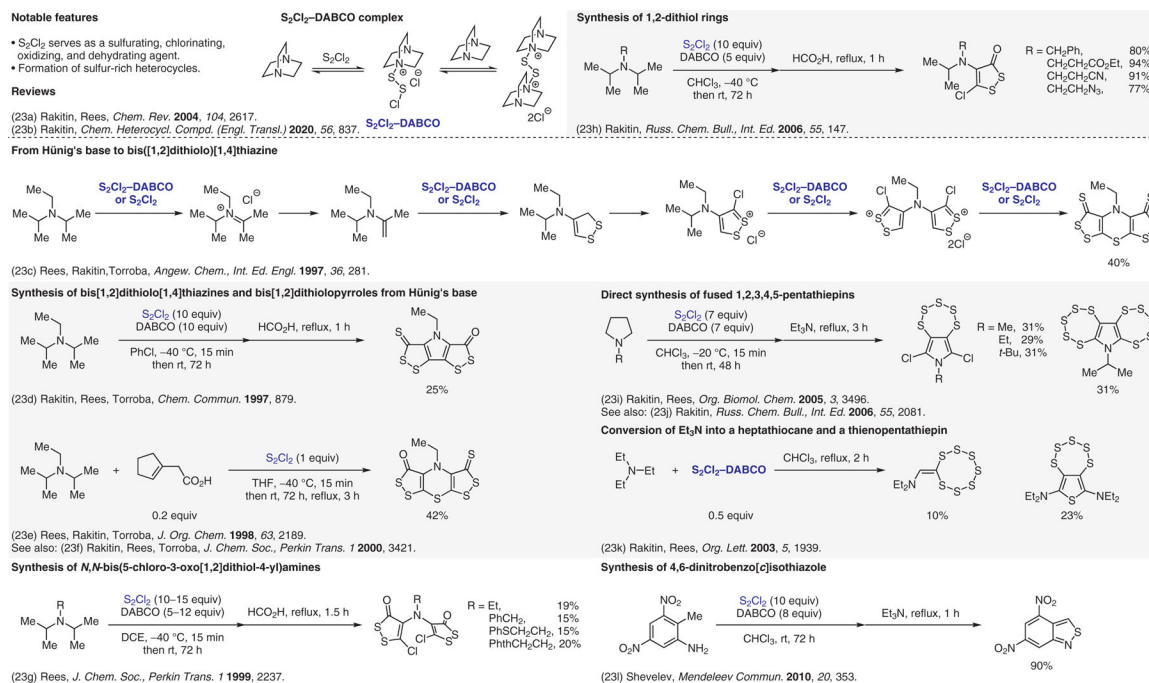


Figure 23.
Oxidative formation of sulfur-rich heterocycles.²³

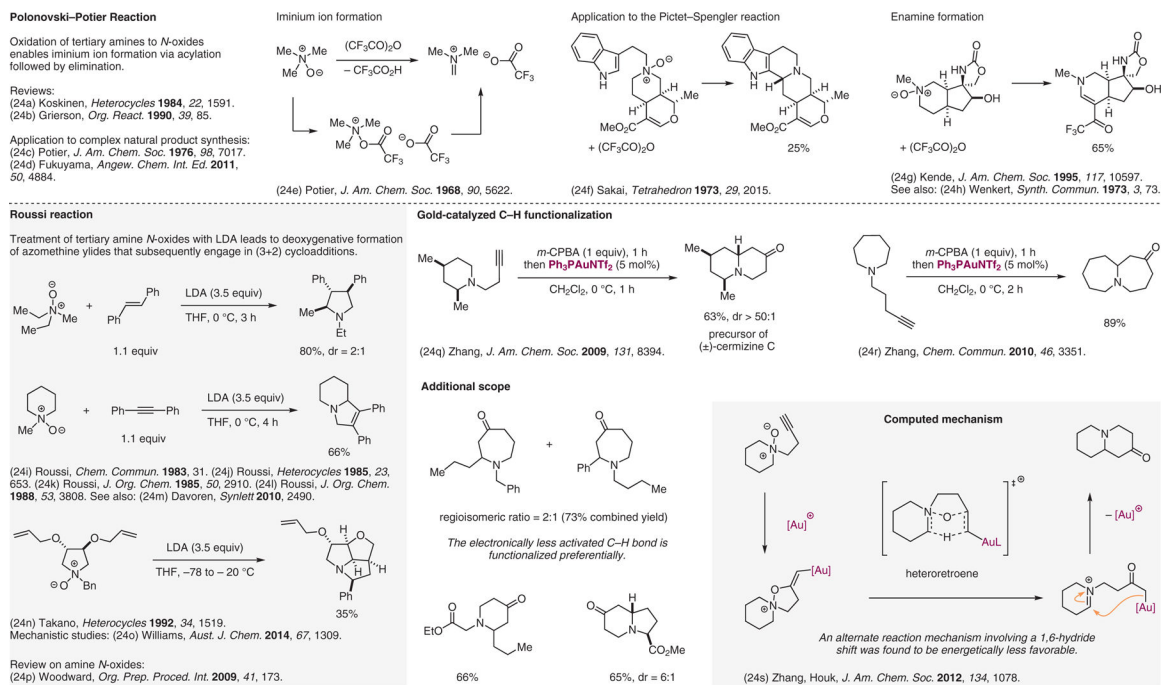


Figure 24.
 Reactions involving amine *N*-oxides.²⁴

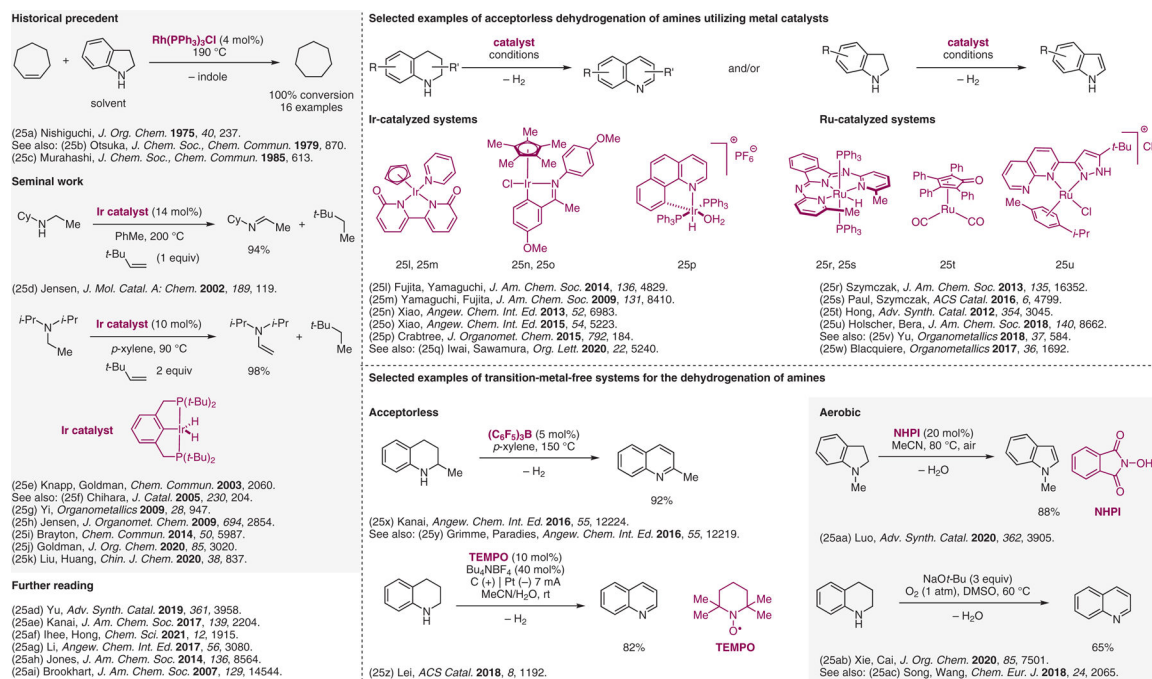


Figure 25.
Dehydrogenation/aromatization.²⁵

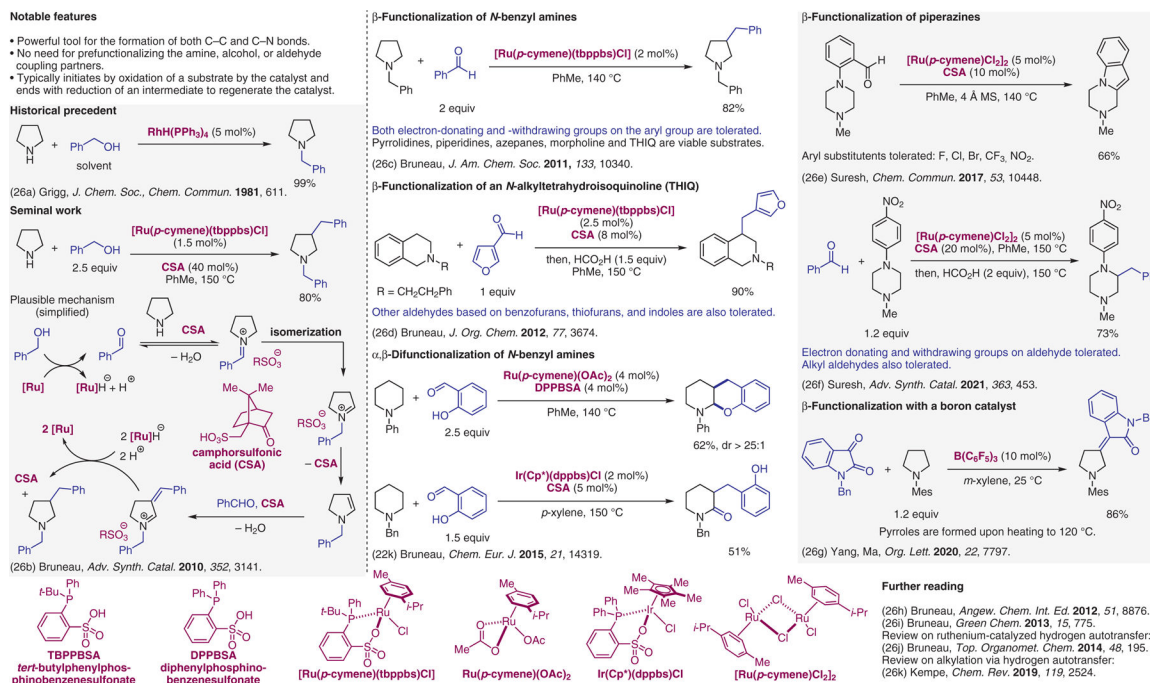
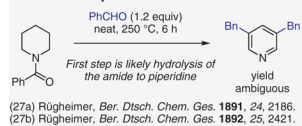


Figure 26.
 Hydrogen borrowing.²⁶

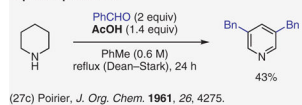
Notable features

- 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.

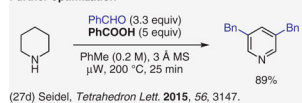
Seminal discovery



Improved procedure



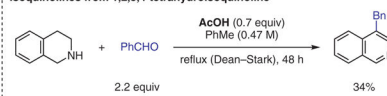
Further optimization



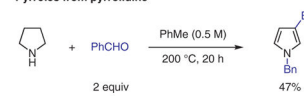
Other selected contributions

- (27e) Burrows, *J. Org. Chem.* **1962**, 27, 316.
 (27f) Sainsbury, *Tetrahedron* **1968**, 24, 427.
 (27g) Dannhardt, *Arch. Pharm.* **1966**, 319, 977.
 (27h) Cook, *Lett. Org. Chem.* **2004**, 1, 1.
 (27i) Toma, *Synth. Commun.* **2009**, 39, 1871.
 (27j) Yu, *Org. Lett.* **2011**, 13, 5054.
 (27k) Lodeiro, *Chem. Eur. J.* **2014**, 20, 6684.

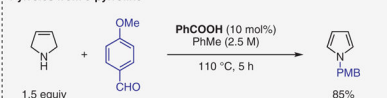
Isoquinolines from 1,2,3,4-tetrahydroisoquinoline



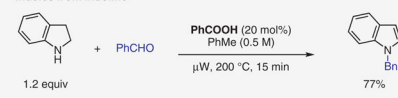
Pyrroles from pyrrolidine



Pyrroles from 3-pyrroline



Indoles from indoline



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

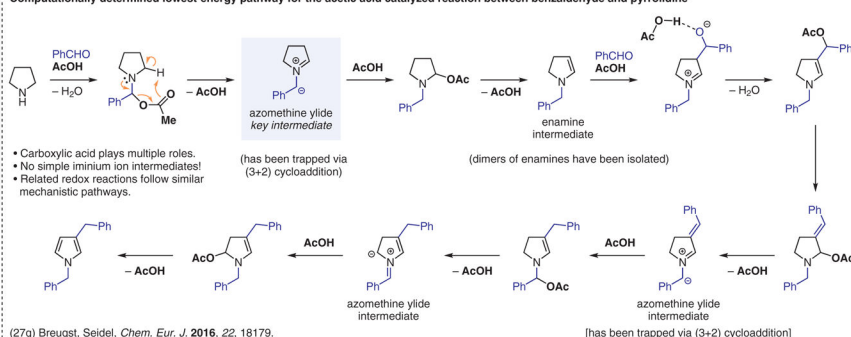


Figure 27. Condensation-based methods involving azomethine ylide intermediates, aromatization.²⁷

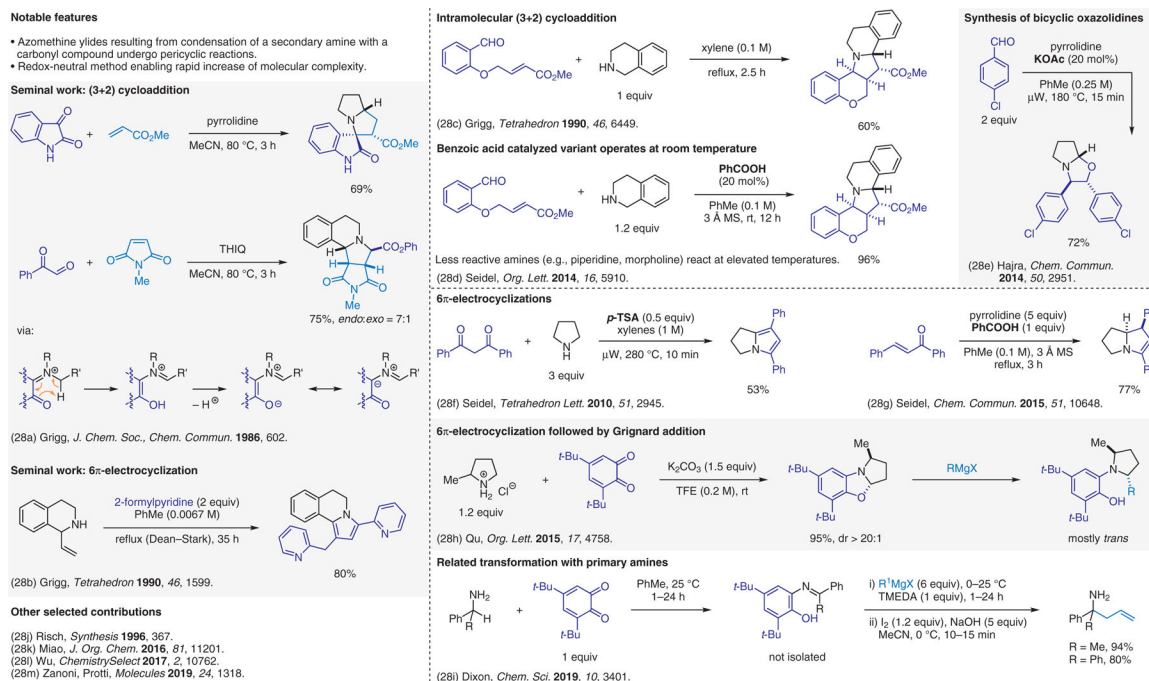


Figure 28.
 Condensation-based methods involving azomethine ylide intermediates, pericyclic reactions.²⁸

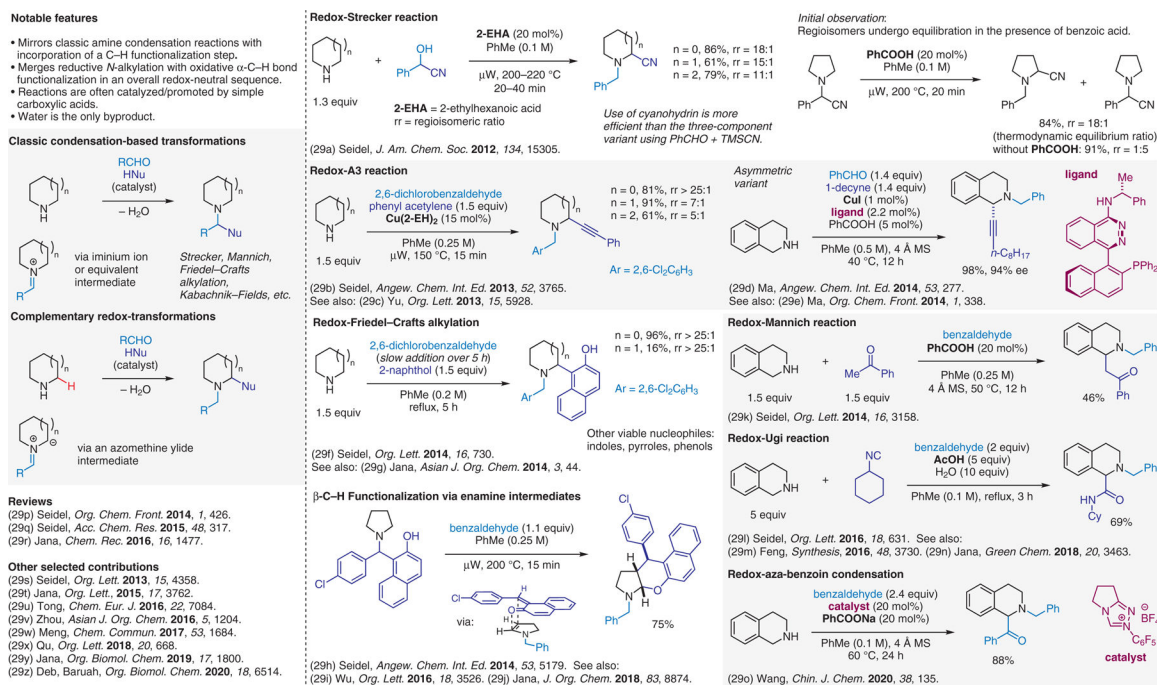
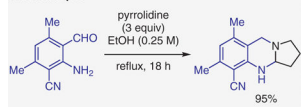


Figure 29. Condensation-based methods involving azomethine ylide intermediates, redox-neutral 3-component coupling reactions.²⁹

Notable features

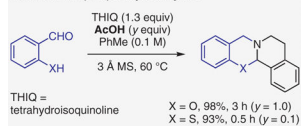
- Powerful method for generating polycyclic amines via redox-neutral ring-annulation of alicyclic amines.
- Azomethine ylides are key intermediates.
- Reactions are often catalyzed/promoted by simple carboxylic acids.
- Water is the only byproduct.

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.

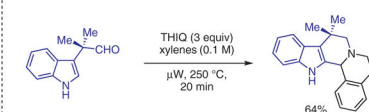
Reviews

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

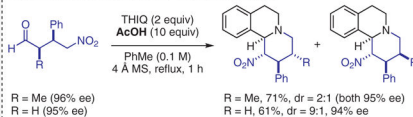
Other selected contributions

(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

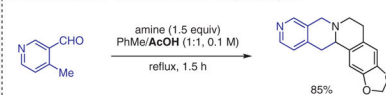


(30i) Seidel, *Chem. Sci.* **2011**, *2*, 233.

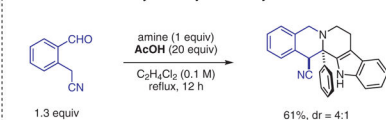
Asymmetric redox-annulations of γ -nitroaldehydes

R = Me (96% ee) R = H (95% ee)
 R = Me, 71%, dr = 2:1 (both 95% ee)
 R = H, 61%, dr = 9:1, 94% ee

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

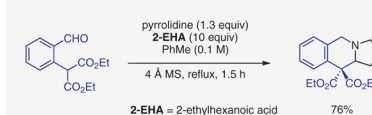
Redox-annulations of heteroaromatic α -alkyl aldehydes

(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.

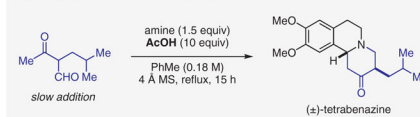
Redox-annulations of α -cyanomethyl benzaldehydes

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

Redox-annulations of 2-formylaryl malonates

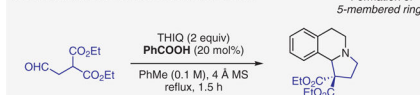


(30j) Seidel, *Chem. Eur. J.* **2015**, *21*, 12908.

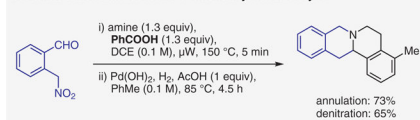
Redox-annulations of β -ketoaldehydes

(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 α -nitromethyl benzaldehyde

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

Figure 30. Condensation-based methods involving azomethine ylide intermediates, redox-annulations.³⁰

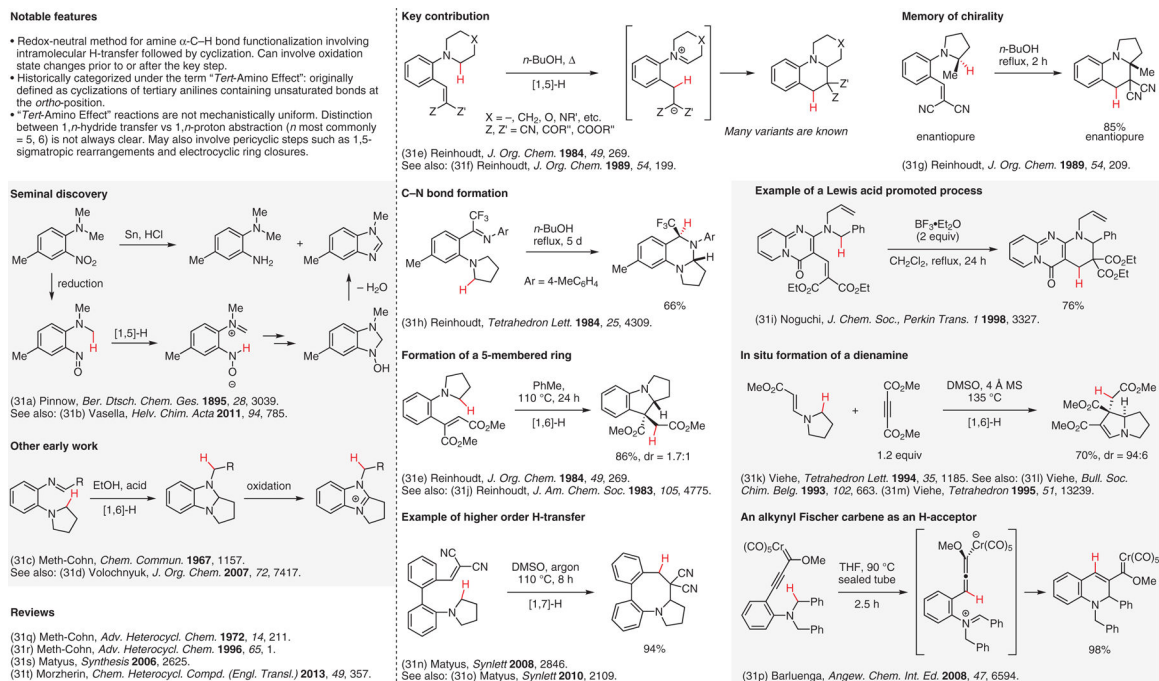


Figure 31. Internal redox transformations involving [1,*n*]-H transfers, the 'tert-amino effect'.³¹

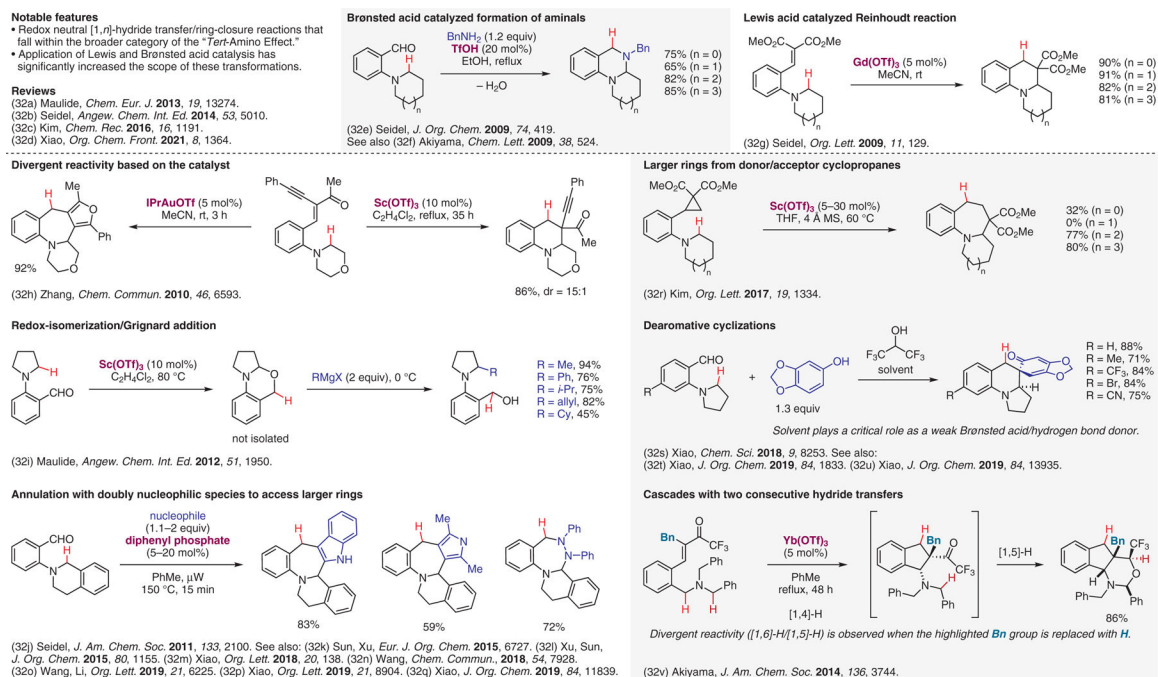


Figure 32.
 Lewis and Brønsted acid catalyzed internal redox transformations involving [1,*n*]-H transfers.³²

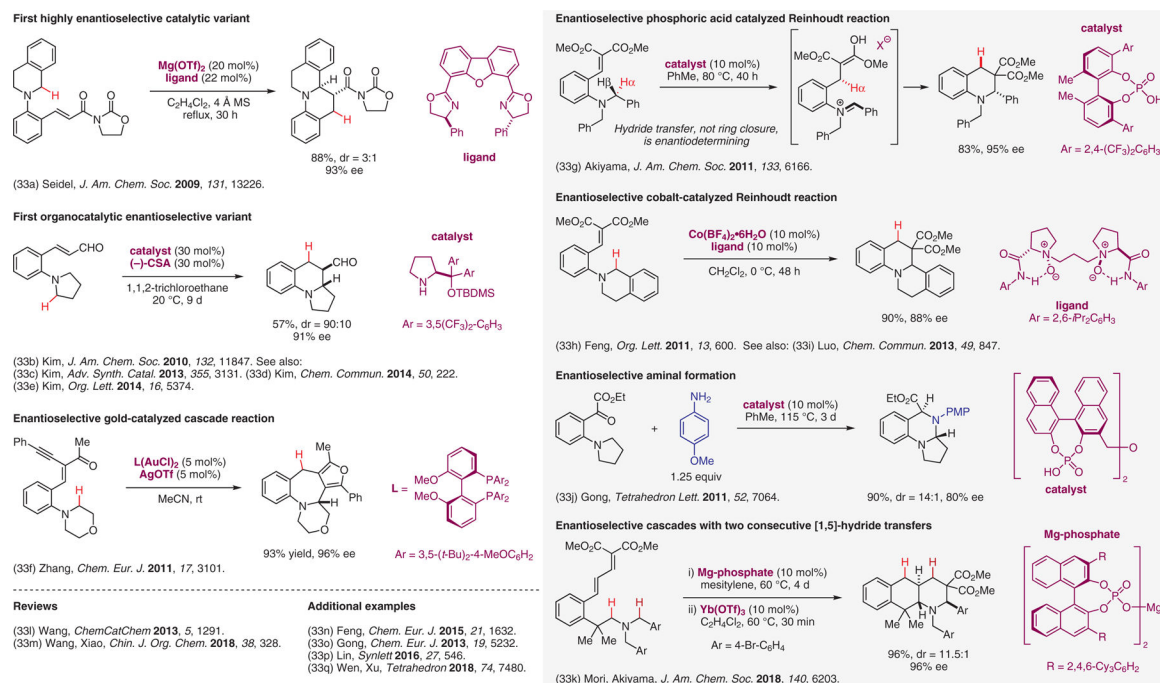


Figure 33. Catalytic enantioselective internal redox transformations involving [1,*n*]-H transfers.³³

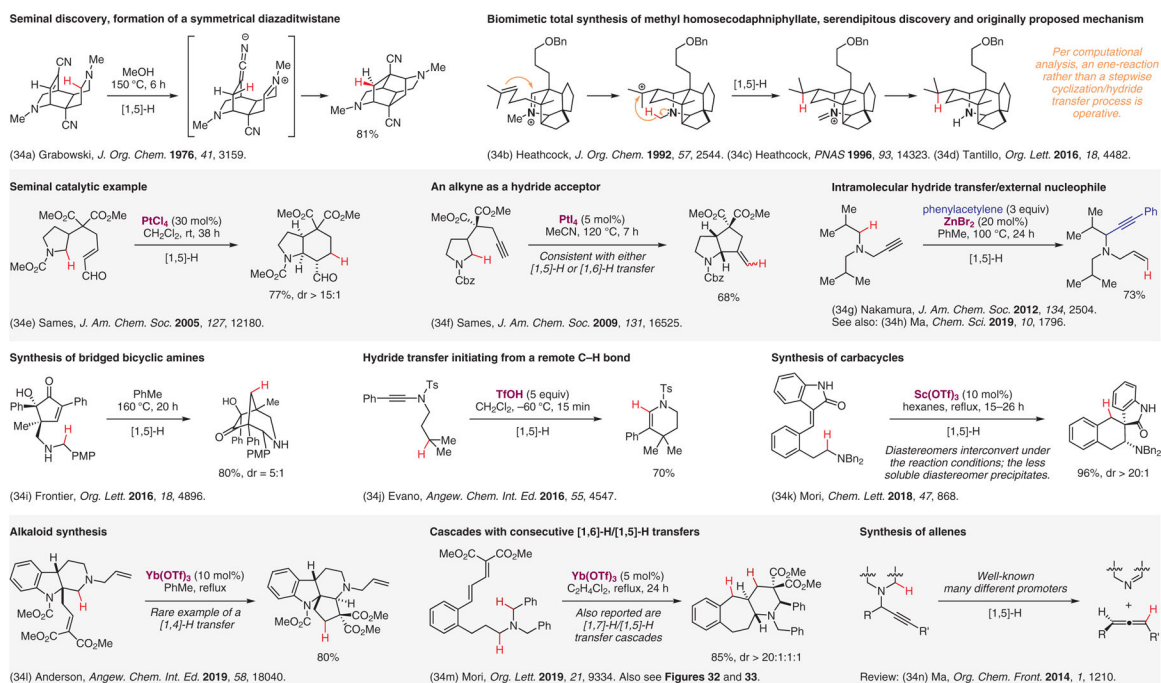
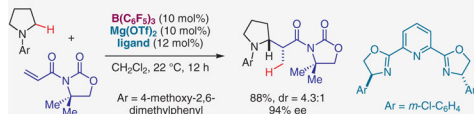
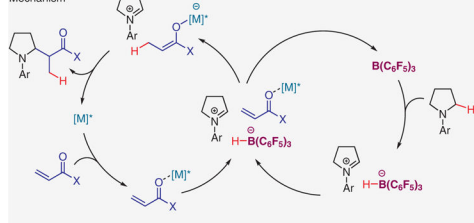


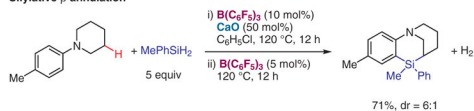
Figure 34. Internal redox transformations involving [1,*n*]-H transfers in non-conjugated systems.³⁴

Notable features

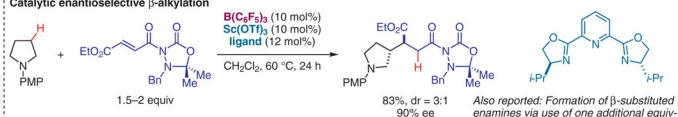
- Intermolecular hydride transfer from amine to $B(C_6F_5)_3$ generates an iminium ion and a $H-B(C_6F_5)_3$ anion. The iminium ion is alkylated directly or undergoes deprotonation to form an enamine which typically reacts further. The $H-B(C_6F_5)_3$ anion reacts with a pronucleophile or reduces the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

Landmark study: Catalytic enantioselective α -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 β -annulation

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

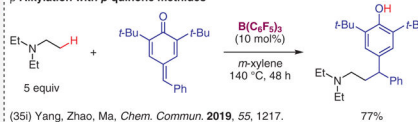
Catalytic enantioselective β -alkylation

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

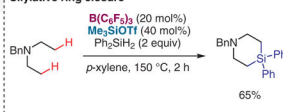
Catalytic enantioselective α -alkynylation with alkynylsilanes: (35g) Wasa, *J. Am. Chem. Soc.* **2020**, *142*, 16493.

 α -Alkylation with silyl ketene acetals

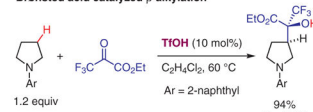
(35h) Wasa, *Org. Lett.* **2019**, *21*, 984.

 β -Alkylation with p -quinone methides

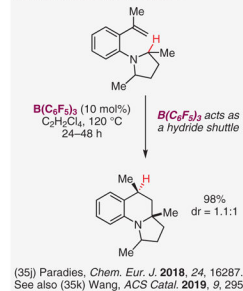
(35i) Yang, Zhao, Ma, *Chem. Commun.* **2019**, *55*, 1217.

Silylative ring closure

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

Bronsted acid catalyzed β -alkylation

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

Pseudo-intramolecular reaction

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

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) Pullis, *Chem. Soc. Rev.* **2021**, *50*, 3720.

Figure 35.
 (Redox-neutral) methods involving intermolecular hydride transfer.³⁵

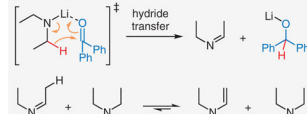
Notable features

- Rapid access to imines from unprotected alicyclic amines via their in situ generated Li-amides.
 - Oxidation of Li-amide is fast at -78°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



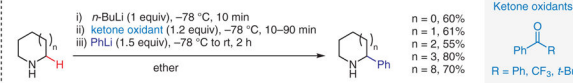
Proposed mechanism



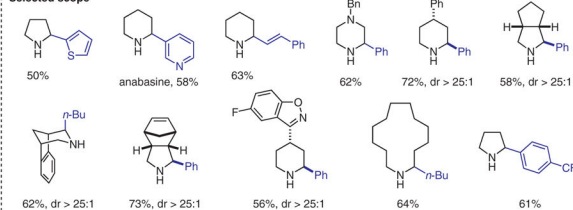
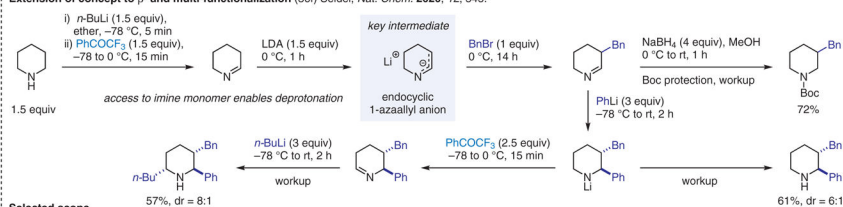
- (36b) Wittig, *Chem. Ber.* **1962**, *95*, 2377. See also:
 (36c) Wittig, *Liebigs Ann. Chem.* **1971**, *746*, 174.
 (36d) Wittig, *Liebigs Ann. Chem.* **1971**, *746*, 185.

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 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 α -functionalization (36e) Seidel, *Nat. Chem.* **2018**, *10*, 165.

Selected scope

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

Selected scope

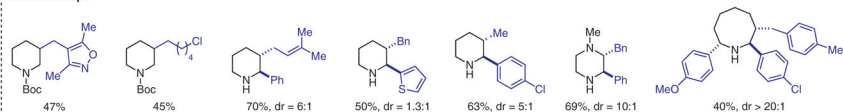


Figure 36. Li-amide-based imine and 1-azaallyl anion generation from unprotected azacycles.³⁶

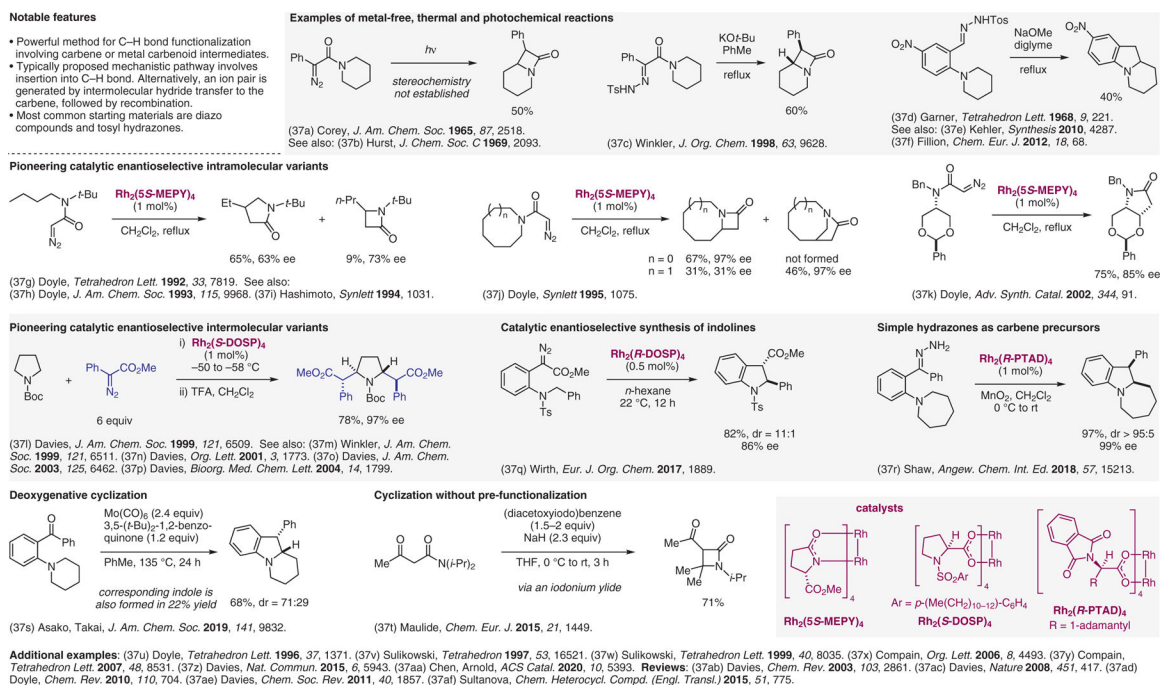


Figure 37.
Reactions involving carbenes or metal carbenoids.³⁷

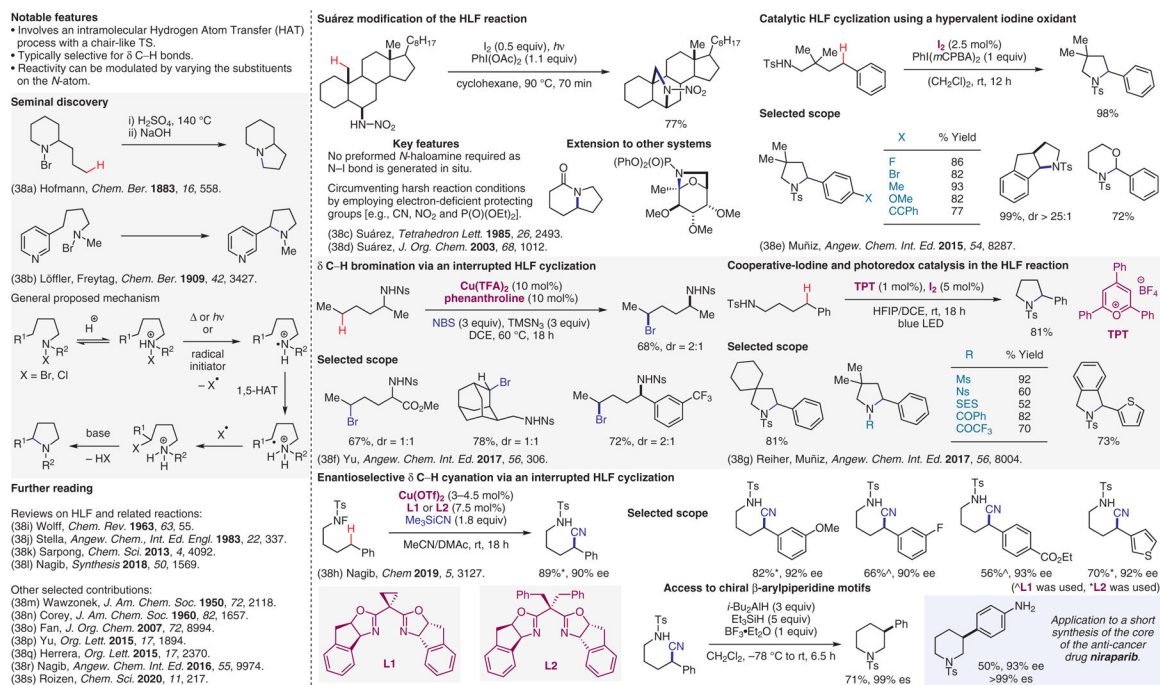
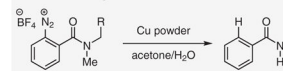


Figure 38.
Hofmann–Löffler–Freytag (HLF) reaction.³⁸

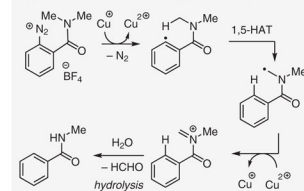
Notable features

- HAT reactivity dependent on BDE and bond strength.
- Energy difference between C(sp²) and C(sp³) 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

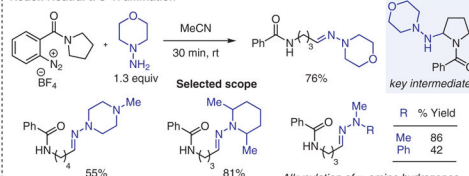
(39a) Hey, Turpin, *J. Chem. Soc.* **1954**, 2471.

Proposed mechanism of the Cu(I)-catalyzed process

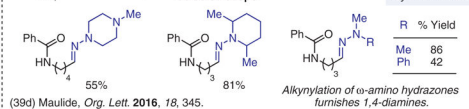
(39b) Cohen, *Tetrahedron* **1966**, 22, 1527.
See also: (39c) Cohen, *J. Am. Chem. Soc.* **1968**, 90, 6866.

Further reading

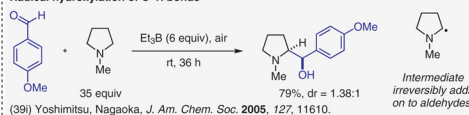
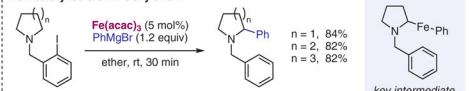
- Reviews on HAT chemistry:
- (38f) Nagib, *Synthesis* **2018**, 50, 1569.
 (39f) Gevorgyan, *Chem. Sci.* **2020**, 11, 12974.
 Other selected contributions:
- (39m) Robertson, *Tetrahedron Lett.* **1996**, 37, 5825.
 (39n) Murphy, *Org. Lett.* **2003**, 5, 2971.
 (39o) Storey, *Angew. Chem. Int. Ed.* **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) Raghains, *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 α -C-H amination(39d) Maulide, *Org. Lett.* **2016**, 18, 345.

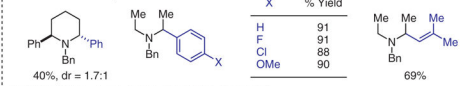
Selected scope

Alkynylation of ω -amino hydrazones furnishes 1,4-diamines.

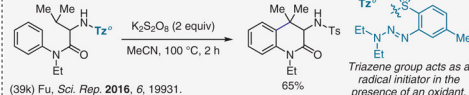
Radical hydroxylation of C-H bonds

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

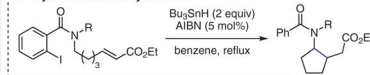
Other substrate scope

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

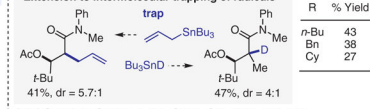
Intramolecular C-H arylation mediated by 1,6-HAT

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

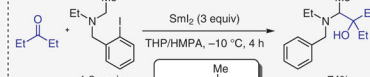
Tin hydride mediated cyclization



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.(39h) Ito, *J. Org. Chem.* **1992**, 57, 793.Extension to intermolecular α -C-H alkylation(39i) Ito, *J. Org. Chem.* **1992**, 57, 793.

Selected scope

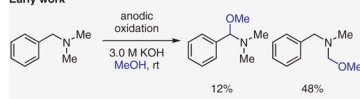
(39h) Undheim, *Tetrahedron* **1994**, 50, 13697.

Figure 39.
Miscellaneous radical-based methods.³⁹

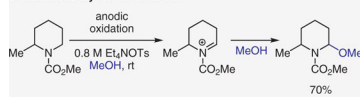
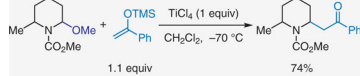
Notable features

- 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

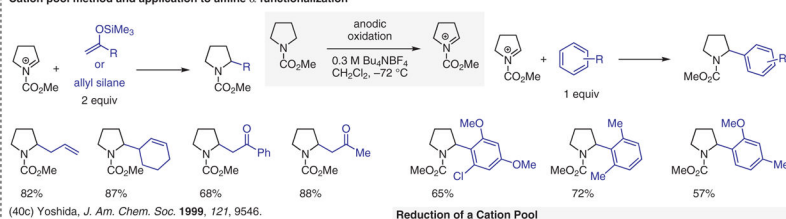
(40a) Weinberg, *J. Org. Chem.* **1966**, *31*, 4058.

Landmark study: Shono oxidation

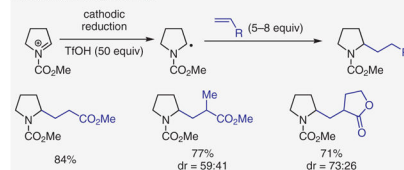
(40b) Shono, *J. Am. Chem. Soc.* **1981**, *103*, 1172.(40b) Shono, *J. Am. Chem. Soc.* **1981**, *103*, 1172.

Further reading

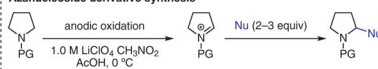
'Indirect' cation pool method:
 (40h) Yoshida, *J. Am. Chem. Soc.* **2006**, *128*, 7710.
 Use of electroauxiliaries to lower potentials and direct oxidation:
 (40i) Yoshida, *Tetrahedron Lett.* **1987**, *28*, 6621.
 (40j) Yoshida, *Electrochim. Acta* **1997**, *42*, 1995.
 Application of electroauxiliaries for amine α -functionalization of C-Si and C-S bonds:
 (40k) Yoshida, *Electrochemistry* **2006**, *74*, 672.
 (40l) Suga, *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 α -functionalization(40c) Yoshida, *J. Am. Chem. Soc.* **1999**, *121*, 9546.

Reduction of a Cation Pool

(40e) Yoshida, *J. Am. Chem. Soc.* **2002**, *124*, 30.

Azanucleoside derivative synthesis

(40d) Yoshida, *Tetrahedron Lett.* **2001**, *42*, 2173.

allyl silanes and electron-rich aromatics also tolerated

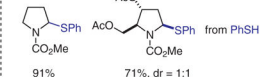
(40f) Chiba, *Chem. Commun.* **2013**, *49*, 6525.(40g) Chiba, *Angew. Chem. Int. Ed.* **2017**, *56*, 4011

Figure 40.
 Electrochemical approaches, cation pool method.⁴⁰

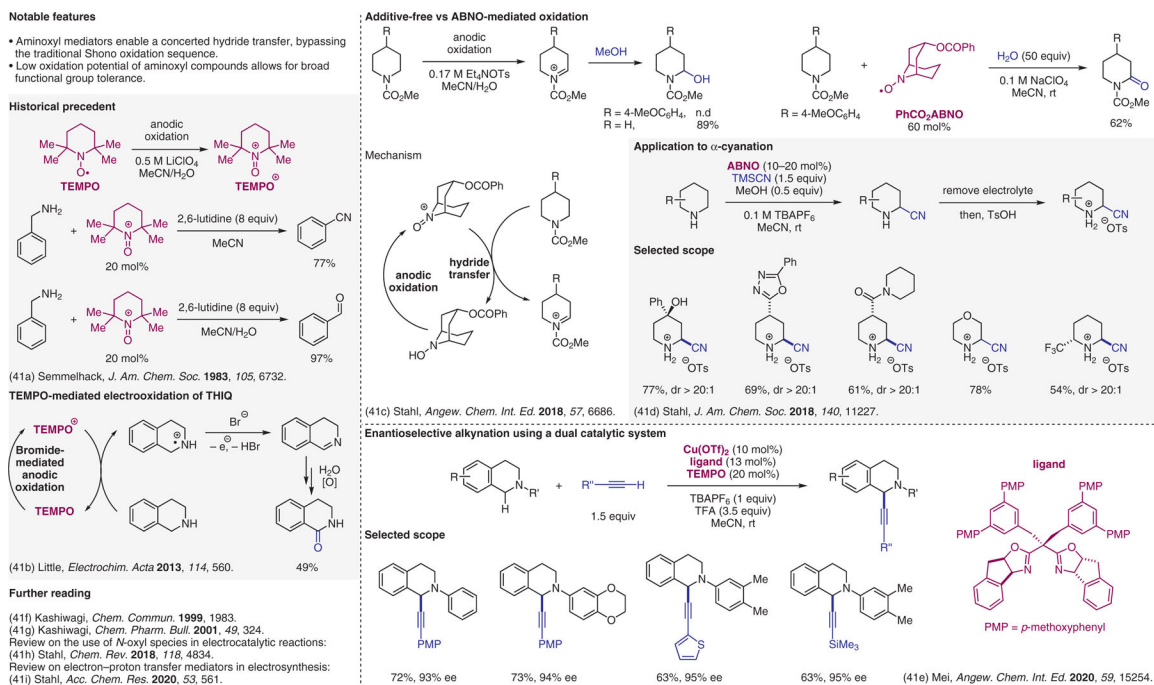
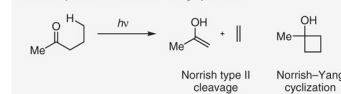


Figure 41. Electrochemical approaches, 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO) catalysis.⁴¹

Notable features

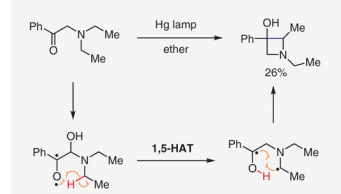
- Intramolecular Hydrogen Atom Transfer (HAT) represents a key step in many photochemical C–H bond functionalizations of amine derivatives.
- Initial products are useful starting materials for further transformations.

Historical precedent: Norrish–Yang cyclization



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

Seminal work



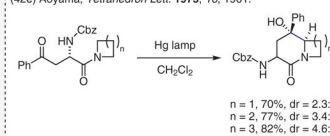
(42c) Clasen, Sealers, *Chem. Commun.* **1966**, 289.
See also: (42d) Cohen, *Chem. Rev.* **1973**, *73*, 141.

Further reading

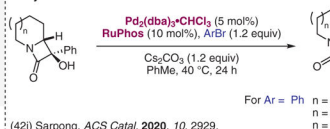
- Other 1,6-HAT reactions:
(42l) Griesbeck, *Tetrahedron Lett.* **1999**, *40*, 3137.
(42m) Peñehory, *J. Org. Chem.* **2009**, *74*, 1223.
- 1,8-HAT reactions:
(42n) Nishio, *Helv. Chim. Acta* **2005**, *88*, 78.
(42o) Nishio, *Helv. Chim. Acta* **2005**, *88*, 996.
(42p) Nishio, *Helv. Chim. Acta* **2005**, *88*, 2603.
- Reviews:
(42q) Nechab, Bertrand, *Chem. Eur. J.* **2014**, *20*, 16034.
(39l) Gevorgyan, *Chem. Sci.* **2020**, *11*, 12974.

Synthesis of β -, γ -, and δ -lactams

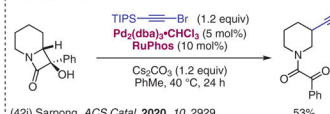
(42e) Aoyama, *Tetrahedron Lett.* **1975**, *16*, 1901.



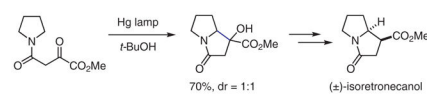
(42f) Wessig, *Tetrahedron: Asymmetry* **1998**, *9*, 4459.

Cyclization of α -ketoamides and subsequent applications α -Arylation

(42j) Sarpong, *ACS Catal.* **2020**, *10*, 2929.

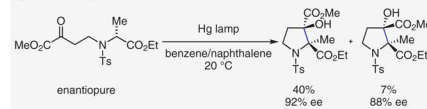
 β -Alkynylation

(42j) Sarpong, *ACS Catal.* **2020**, *10*, 2929.



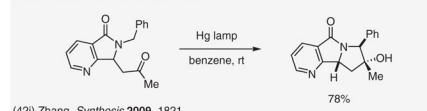
(42g) Gramain, *J. Org. Chem.* **1985**, *50*, 710.

Synthesis of pyrrolidines



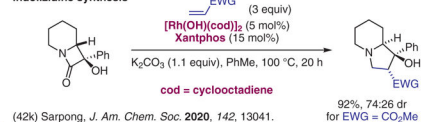
(42h) Giese, *Angew. Chem. Int. Ed.* **1999**, *38*, 2586.

Synthesis of benzopyrrolidinones



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

Indolizidine synthesis



(42k) Sarpong, *J. Am. Chem. Soc.* **2020**, *142*, 13041.

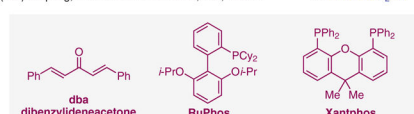
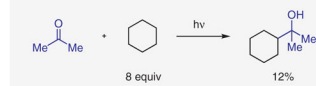


Figure 42.
Intramolecular hydrogen atom transfer (HAT).⁴²

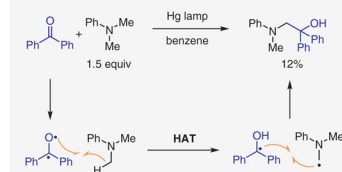
Notable features

- 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 α -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



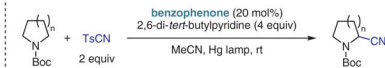
Seminal work



Further reading

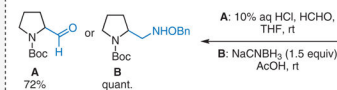
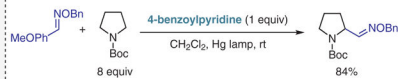
- Early review on photoreduction by amines:
 (42d) Cohen, *Chem. Rev.* **1973**, *73*, 141.
 A uranyl cation and eosin Y as HAT photocatalysts:
 (43i) Mei, Shi, *Chem. Eur. J.* **2020**, *26*, 16521.
 (43j) Singh, *Tetrahedron Lett.* **2019**, *60*, 1333.
 Polarity matching effect, and its application 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

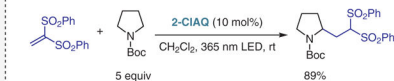


Morpholines and acyclic amines also tolerated.

Aldoximation and further functionalization



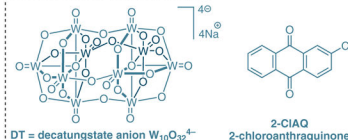
Alkylation



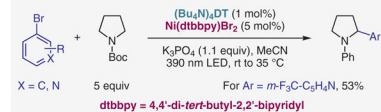
Morpholines and proline esters also tolerated.

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

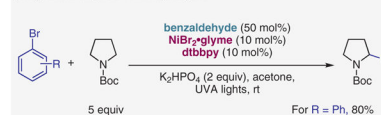
Direct Hydrogen Atom Transfer agents



Arylation



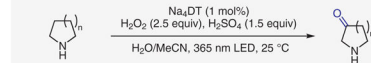
Functional groups on aryl group tolerated: F, CF_3 , Me, OMe, CN, CF_3 .
 Alkyl bromides also tolerated as coupling partners.



Functional groups on aryl group tolerated: F, CF_3 , Me, OMe, CN, CF_3 .
 Alkyl bromides also tolerated as coupling partners.

(43f) Hashmi, *Org. Lett.* **2019**, *21*, 6329.

Oxidation

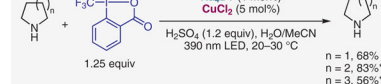


Protonation of the amine deactivates the α -C-H bond, allowing HAT to occur at the β - or γ -positions. Selective hydroxylations and iminations also possible.

(43g) Schultz, *Angew. Chem. Int. Ed.* **2017**, *56*, 15274.

* mixture of regioisomers.

Trifluoromethylation at distal positions



* mixture of regioisomers.

Figure 43.
 Direct hydrogen atom transfer (HAT).⁴³

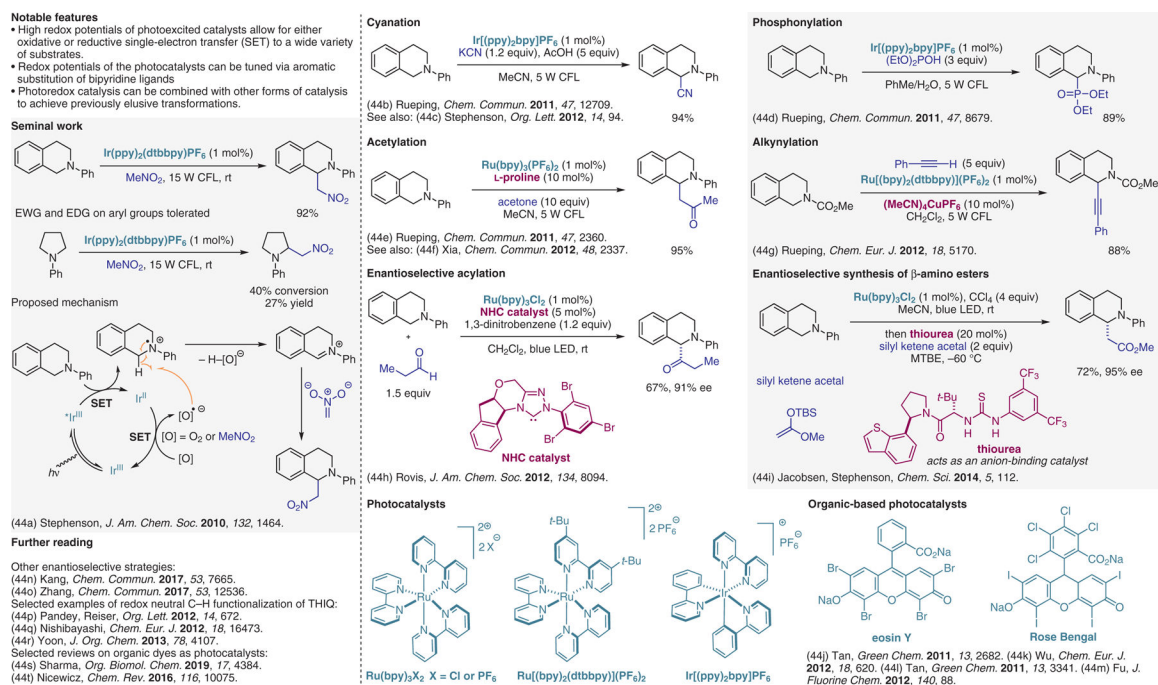


Figure 44.
 Photoredox approaches, part I.⁴⁴

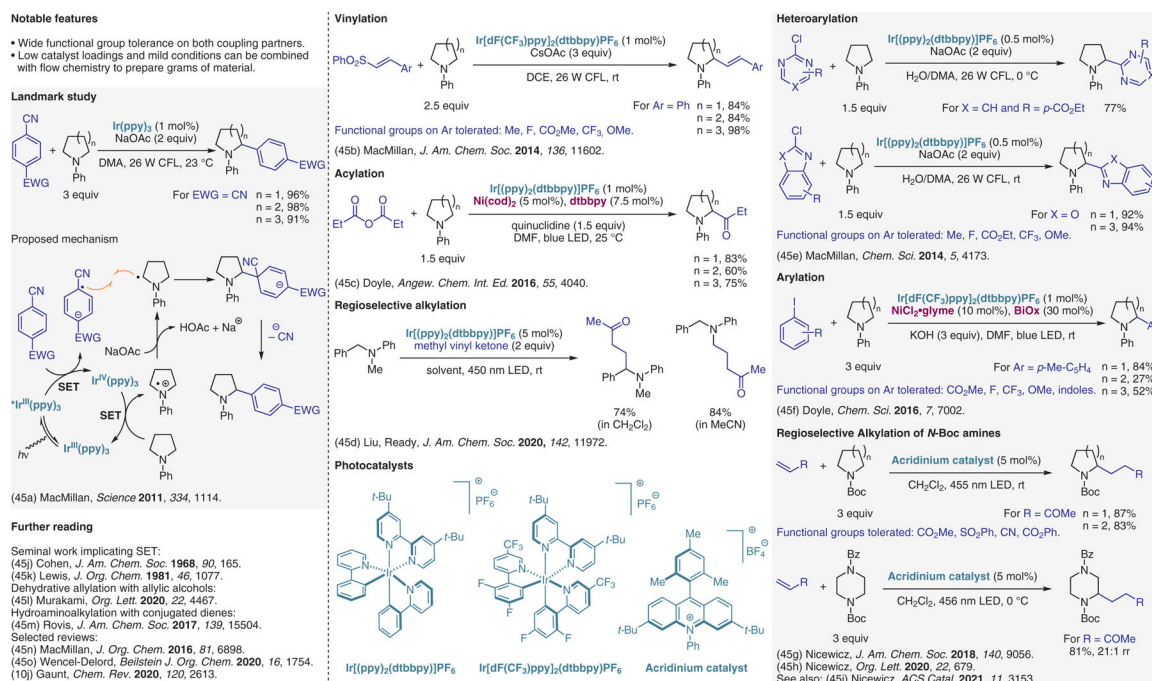


Figure 45.
 Photoredox approaches, part II.⁴⁵

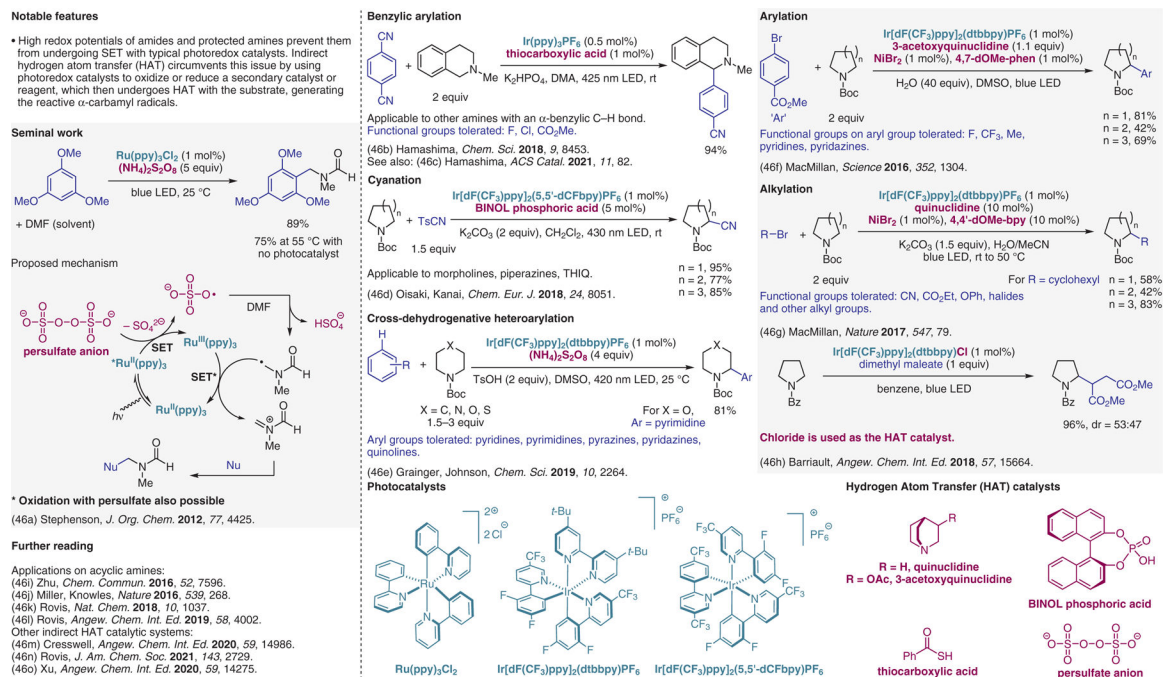
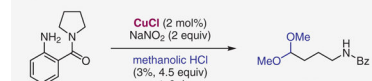


Figure 46.
Indirect hydrogen atom transfer (HAT).⁴⁶

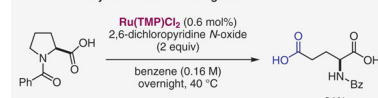
Notable features

- 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



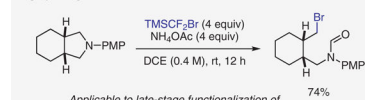
Ruthenium-catalyzed oxidative cleavage of amides



TMP = tetramesitylporphyrin

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

Ring opening with difluorocarbenes

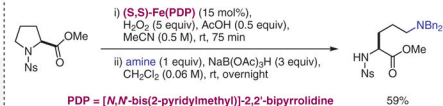


(47c) Seo, Chang, *Nat. Commun.* **2020**, 11, 4761.

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) Huijgens, *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.

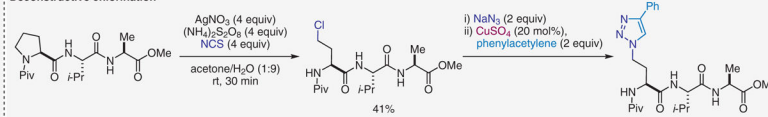
Deconstructive amination



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

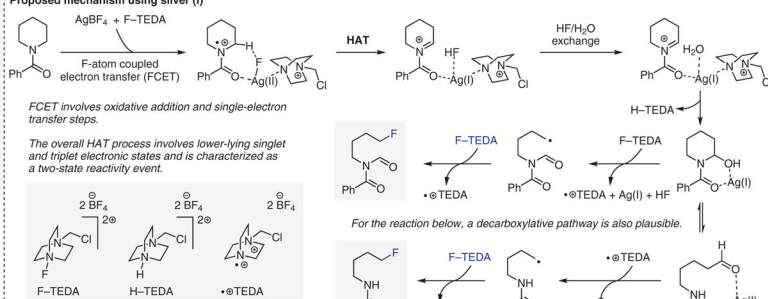
(47d) White, *Nature* **2016**, 537, 214.

Deconstructive chlorination



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

Proposed mechanism using silver (I)



(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.⁴⁷