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

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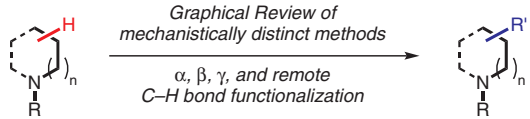

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Abstract This Graphical Review provides a concise overview of the manifold and mechanistically diverse methods that enable the functionalization of sp^3 C–H bonds in amines and their derivatives.

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.

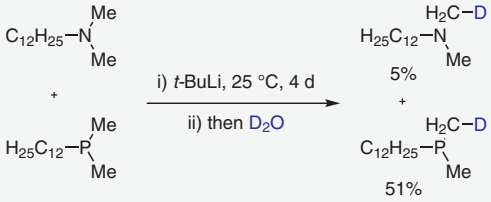
Daniel Valles was born in Caracas, Venezuela and raised in Weston, Florida, USA. He attended the California Institute of Technology (Caltech) (USA) working with Prof. Peter Dervan, Prof. Sarah Reisman, and Dr. Scott Virgil. In 2018, he started his Ph.D. research at the University of Florida under the 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).

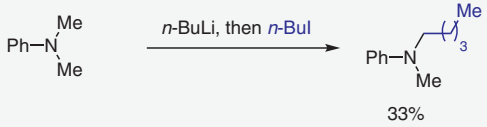
Notable features

- 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

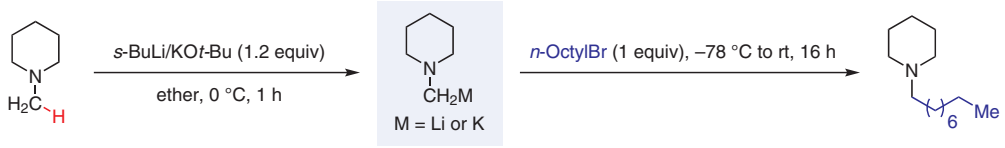
Additional seminal work:
(1i) Lepley, *J. Org. Chem.* **1966**, 31, 2061.
(1j) Lepley, *Chem. Commun. (London)* **1967**, 1198.

Reviews on α-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 superbase

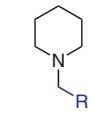


key intermediate

70%

(1c) Ahlbrecht, *Tetrahedron Lett.* **1984**, *25*, 1353.

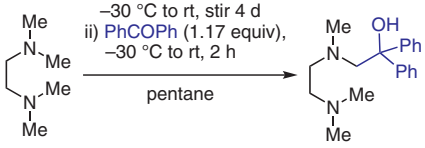
Selected scope



R	% Yield
PhCHOH	73
t-BuCHOH	41
i-PrCHOH	62

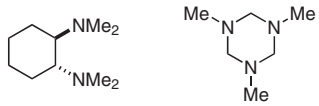
This methodology is also applicable to *N*-methylpyrrolidine and triethylamine.

Intramolecular activation of amines containing a second donor atom

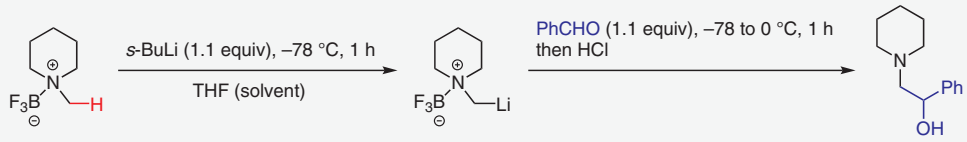


(1d) Strohmann, *J. Am. Chem. Soc.* **2008**, *130*, 14412.

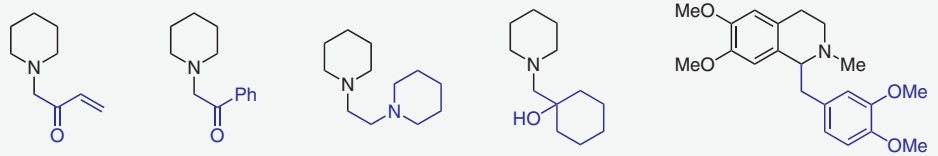
Other systems where similar deprotonation and trapping is observed:



Lewis acid complexed α-metalation of tertiary amines



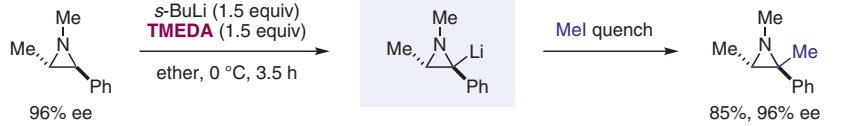
Selected scope with other electrophiles



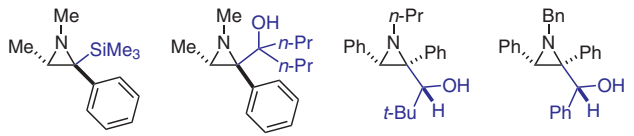
69% from *methyl acrylate* | 50% from *benzonitrile* | 65% from *iodine* | 88% from *cyclohexanone* | synthesis of (±)-laudanosine 41%

(1e) Kessar, *J. Chem. Soc., Chem. Commun.* **1991**, 568. (1f) Kessar, *Tetrahedron Lett.* **1991**, *32*, 3221.

Functionalization of enantioenriched aziridines



Selected scope



65%, 96% ee | 84%, 96% ee | 62%*, dr = 98:2 96% ee | 56%*, dr = 87:13 96% ee

(* THF was used as the solvent)

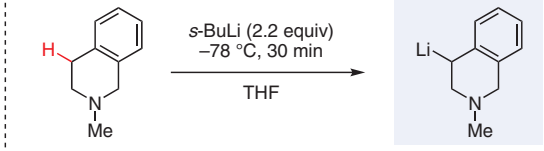
Key features

Temperature-dependent regioselective lithiation.

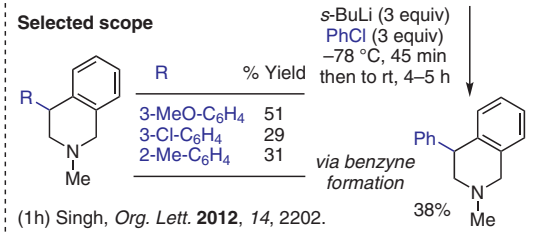
Solvent-dependent stereochemical outcome.

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

Addition of β-amino carbanions to arenes



Selected scope



R	% Yield
3-MeO-C_6H_4	51
3-Cl-C_6H_4	29
2-Me-C_6H_4	31

via benzyne formation

38%

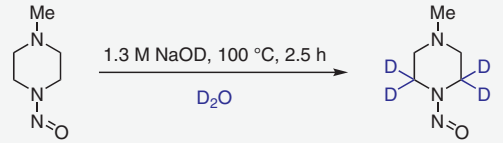
(1h) Singh, *Org. Lett.* **2012**, *14*, 2202.

Figure 1 Deprotonation of tertiary amines.[1]

Notable features

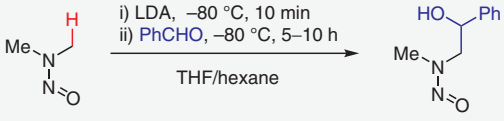
- Rate of deprotonation depends on stabilization of the electron-rich C–Li bond by a nearby empty orbital or electron-withdrawing group.
- Precomplexation of the substrate with the organolithium occurs prior to deprotonation.
- Lithiate stabilized by dipoles of amide (or similar functional groups) and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

Seminal discovery



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

First example of C–C bond formation

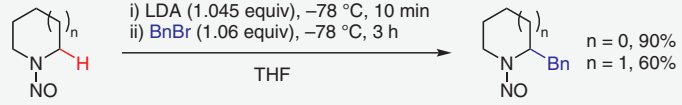


(2b) Seebach, *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 301.

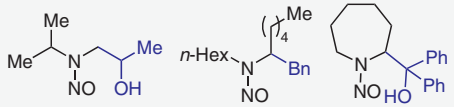
Further reading

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



Key features

Directed lithiation to a tertiary carbon atom is feasible.

Facile denitrosation using Raney Ni/H_2.

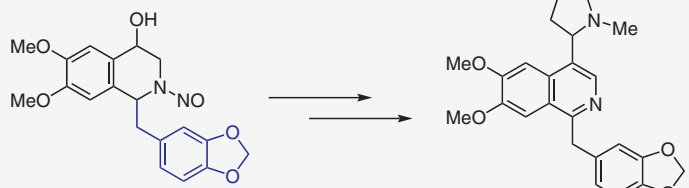
(2c) Seebach, *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1101.
(2d) Seebach, *Synthesis* **1979**, 423.
See also: (2e) Seebach, *J. Med. Chem.* **1974**, *17*, 1225.

Access to α,α'-difunctionalized pyrrolidines

Key constituents of the venom of the South African fire ant, *Solinopsis punctaticeps*.

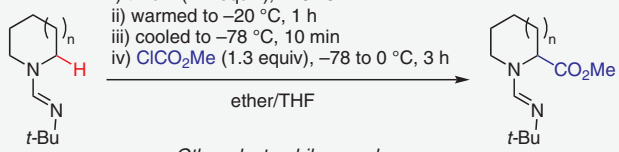
(2f) Fraser, *Synthesis* **1976**, 540.

Application to natural product synthesis



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

Formamidines as substrates

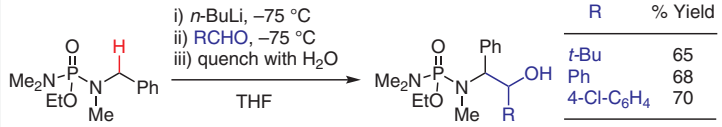


Other electrophiles used:
PhCHO, PhSeSePh, $Br(CH_2)_3Cl$, *n*-BuI

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

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

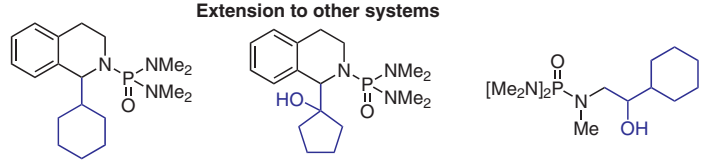
Phosphoramides as substrates



R	% Yield
t-Bu	65
Ph	68
4-Cl-C_6H_4	70

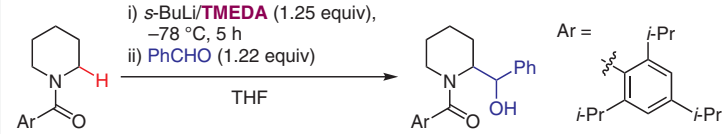
(2h) Savignac, *Tetrahedron Lett.* **1974**, *15*, 2651. (2i) Savignac, *J. Organomet. Chem.* **1973**, *57*, C47. See also: (2j) Magnus, *Synthesis* **1980**, 575. (2k) Seebach, *Helv. Chim. Acta* **1981**, *64*, 643.

Extension to other systems



Deprotection is facile by refluxing with aqueous methanolic hydrochloric acid.

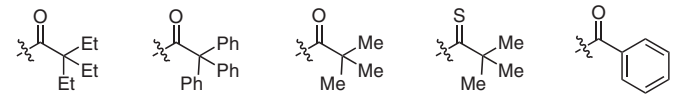
Amides as substrates



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

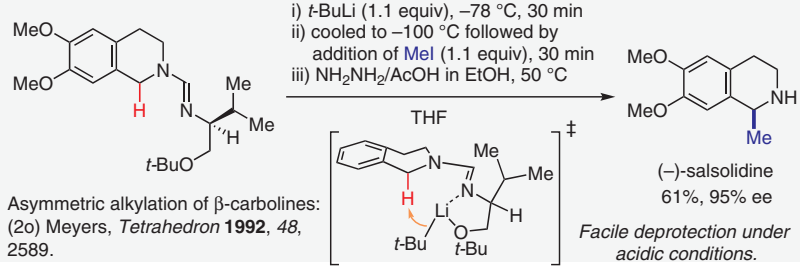
Disadvantage: Harsh deprotection conditions required.

Other protecting groups used



Chiral Formamidines in asymmetric synthesis

(2n) Meyers, *Tetrahedron* **1987**, *43*, 5095.



Asymmetric alkylation of β-carbolines: (2o) Meyers, *Tetrahedron* **1992**, *48*, 2589.

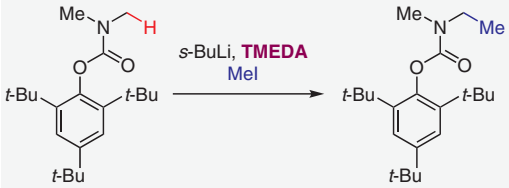
Facile deprotection under acidic conditions.

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

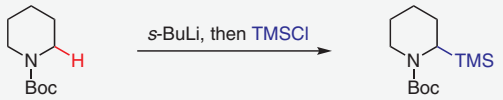
Notable features

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

Historical precedent



(2w) Seebach, *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 274.



(3a) Beak, *Tetrahedron Lett.* **1989**, *30*, 1197.
See also: (3b) Beak, *J. Org. Chem.* **1990**, *55*, 2578.

Further reading

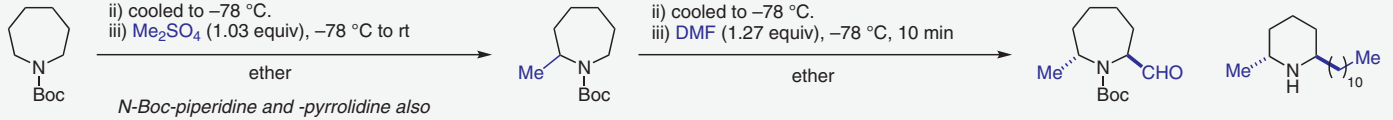
Extension of lithiation trapping to other systems:
(3n) O'Brien, *Org. Lett.* **2005**, *7*, 4459.
(3o) van Maarseveen, *Tetrahedron Lett.* **2005**, *46*, 2369.
(3p) Hodgson, *Angew. Chem. Int. Ed.* **2007**, *46*, 2245.
(3q) Coldham, *Chem. Eur. J.* **2013**, *19*, 7724.

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

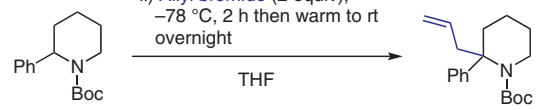


N-Boc-piperidine and -pyrrolidine also underwent sequential difunctionalization.

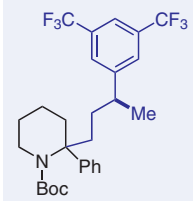
62% 63% *dr not determined* 49%, dr > 20:1

(3c) Beak, *J. Org. Chem.* **1993**, *58*, 1109.

Access to *gem*-disubstituted piperidines



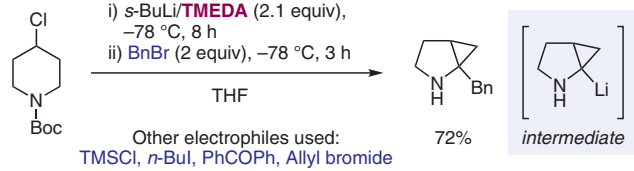
43%



61%, dr = 1:1
synthesis of NK_1 receptor antagonist

(3d) Xiao, Lavey, *Tetrahedron Lett.* **2005**, *46*, 7653.
See also: (3e) Coldham, *Synlett* **2017**, *28*, 2765.

Intramolecular cyclization



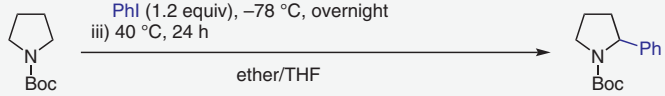
Other electrophiles used:
TMSCl, *n*-BuI, PhCOPh, Allyl bromide

72% *intermediate*

Relatively high acidity of the cyclopropyl hydrogen facilitates deprotonation of the tertiary position in the presence of an available secondary position.

(3f) Beak, *J. Org. Chem.* **1994**, *59*, 276.

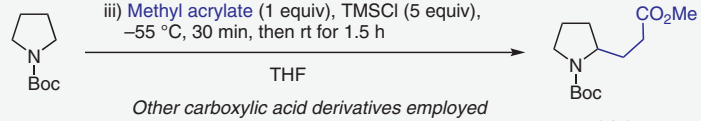
Copper cyanide/palladium-catalyzed coupling with aryl iodides



47%

(3g) Dieter, *Tetrahedron Lett.* **1995**, *36*, 3613.
Improved procedure: (3h) Dieter, *J. Org. Chem.* **1997**, *62*, 7726.
See also: (3i) Dieter, *J. Org. Chem.* **1996**, *61*, 2930.

Transmetalation to α-aminoalkyl cuprates

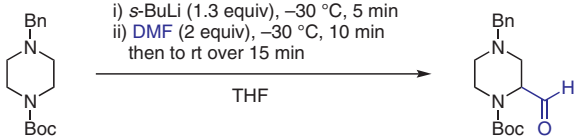


Other carboxylic acid derivatives employed include amides and thioesters

94%

(3j) Dieter, *J. Org. Chem.* **1997**, *62*, 3798.
See also: (3k) Dieter, *J. Org. Chem.* **2000**, *65*, 8715.

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

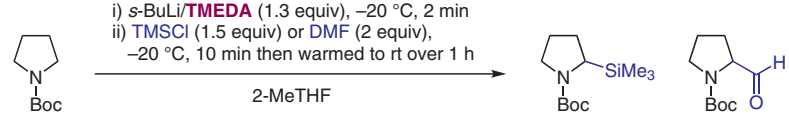


71%

- *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.*

(3l) O'Brien, *Org. Lett.* **2010**, *12*, 4176.

High temperature batch and flow lithiation trapping of *N*-Boc-pyrrolidine

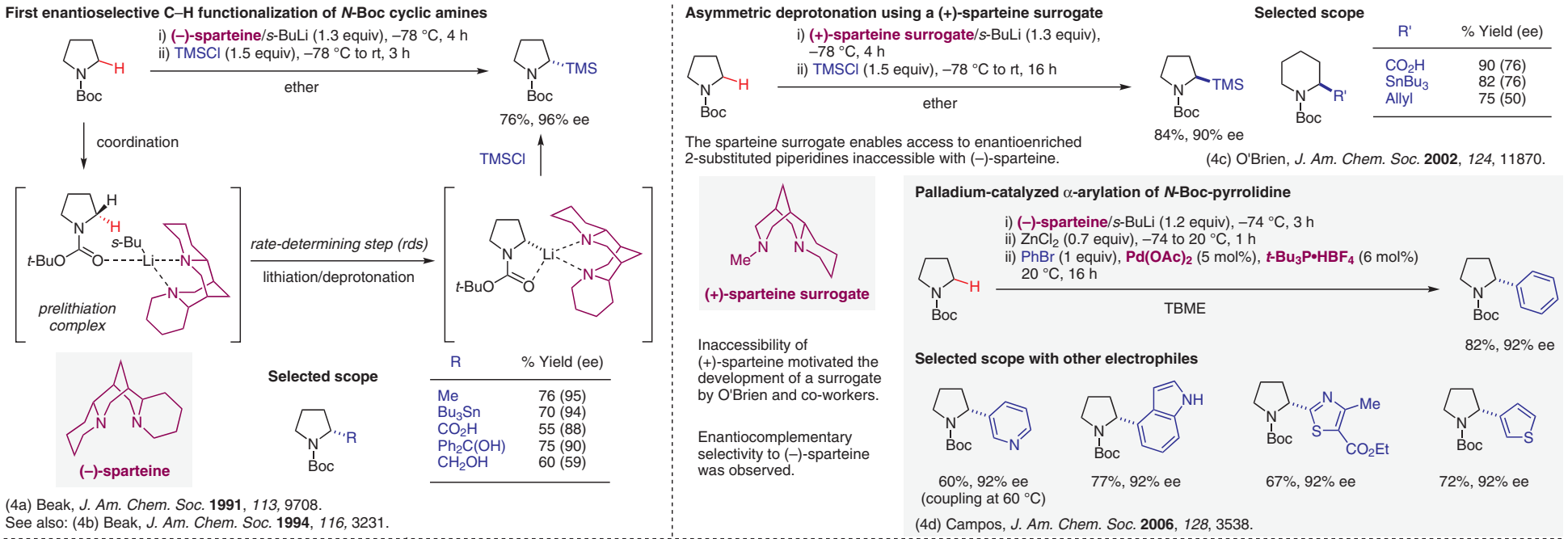


	68%	66%
without TMEDA	52%	52%

Under flow, lithiation can be performed at 0 °C in THF. However, short lithiation times of 3–4 s and the use of TMEDA are critical to the reaction efficiency.

(3m) O'Brien, *Tetrahedron* **2021**, *81*, 131899.

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



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) Kozlowski, *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.

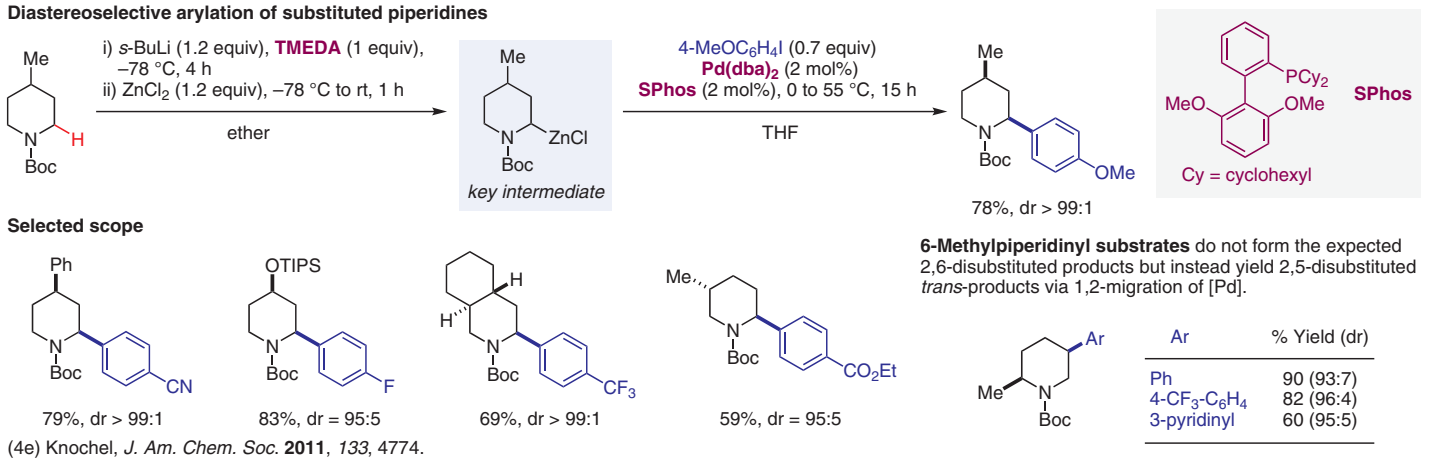
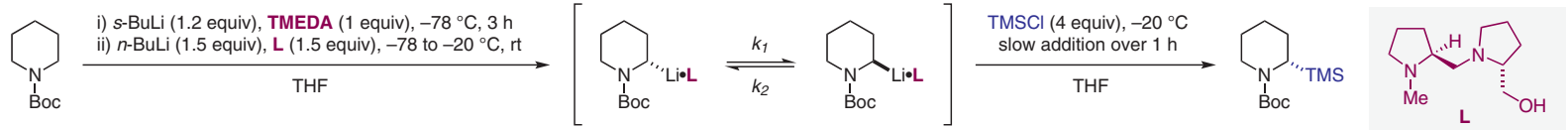


Figure 4 Deprotonation of protected amines, part III.[4]

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



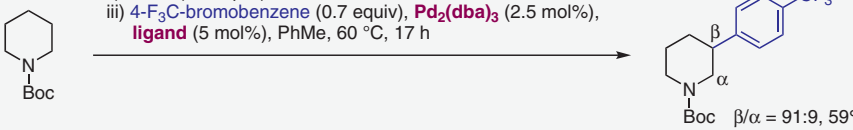
(5a) Coldham, *Chem. Eur. J.* **2010**, *16*, 4082.

60%, 90% ee

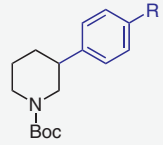
Limitation

Enantioselectivity is dependent on the electrophile, limiting the scope.

β-C–H Arylation of *N*-Boc-piperidines

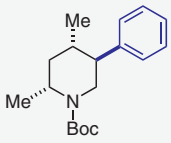


Selected scope

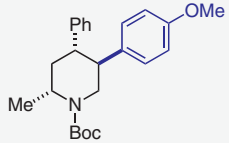


R	% Yield (β/α)
CN	51 (85:15)
CO_2Me	57 (82:18)
Me	70 (82:18)
OMe	55 (88:12)
NMe_2	48 (78:22)

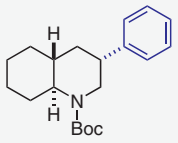
Reactions of substituted *N*-Boc-piperidines and *trans*-decahydroquinoline are diastereoselective.



β/α > 98:2, 76%*



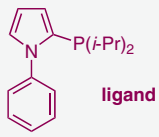
β/α > 98:2, 61%*

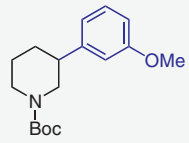


β/α = 96:4, 57%*

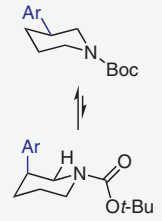
(* coupling at 80 °C)

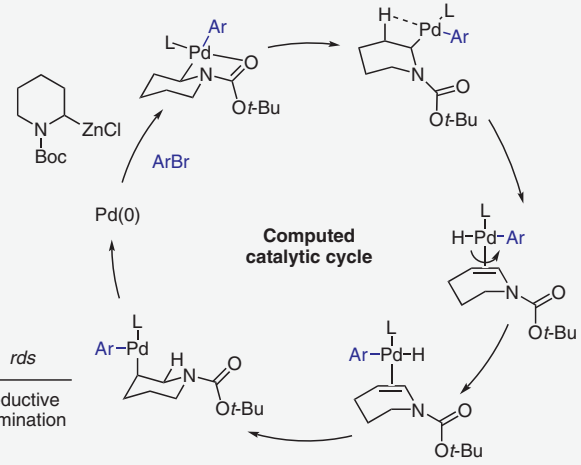
(5b) Baudoin, *Chem. Sci.* **2013**, *4*, 2241.



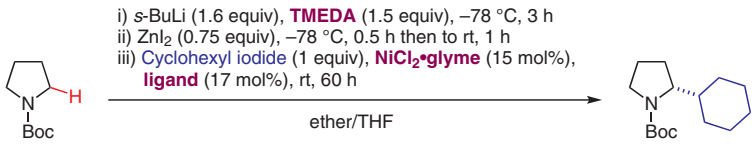


β/α = 86:14, 71%
Formal synthesis of preclamol

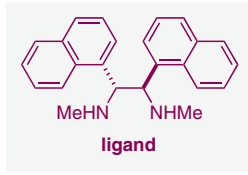




Enantioconvergent Negishi cross-coupling with unactivated secondary alkyl electrophiles



86%, 93% ee

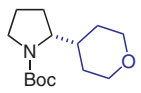


Key features

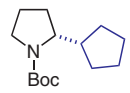
Access to enantioenriched 2-alkyl pyrrolidines starting from racemic metalated carbamates and achiral alkyl iodides.

Further extension of this methodology to control **vicinal stereocenters** with good selectivity.

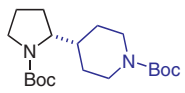
Selected scope with other electrophiles



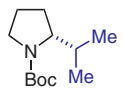
96%, 92% ee



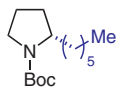
91%, 82% ee



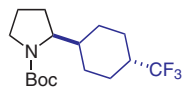
96%, 94% ee



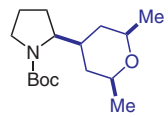
85%, 90% ee



85%, 58% ee



82%, dr > 99:1
91% ee



82%, dr > 99:1
91% ee

(5c) Fu, *J. Am. Chem. Soc.* **2013**, *135*, 10946. (5d) Fu, *Angew. Chem. Int. Ed.* **2017**, *56*, 5821.

Further reading

Reviews on α-deprotonation and functionalization:
(5e) Beak, *Acc. Chem. Res.* **1996**, *29*, 552.
(5f) Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069.
(5g) Maes, *Chem. Eur. J.* **2012**, *18*, 10092.

Dynamic thermodynamic resolution and catalytic dynamic resolution:
(5h) Coldham, *Angew. Chem. Int. Ed.* **2002**, *41*, 3887.
(5i) Gawley, *J. Am. Chem. Soc.* **2010**, *132*, 12216.

α- and β-arylation of Boc-protected acyclic amines:
(5j) Baudoin, *Angew. Chem. Int. Ed.* **2014**, *53*, 2678.

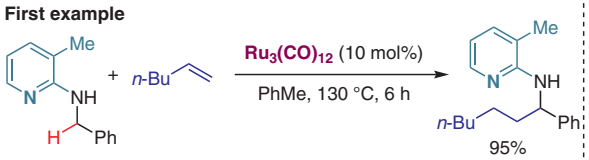
Application to potential pharmaceuticals and natural product synthesis:
(5k) Dieter, Snyder, *J. Org. Chem.* **2004**, *69*, 6105.
(5l) Campos, *J. Org. Chem.* **2008**, *73*, 4986.
(5m) Campos, O'Brien, *J. Org. Chem.* **2011**, *76*, 5936.

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

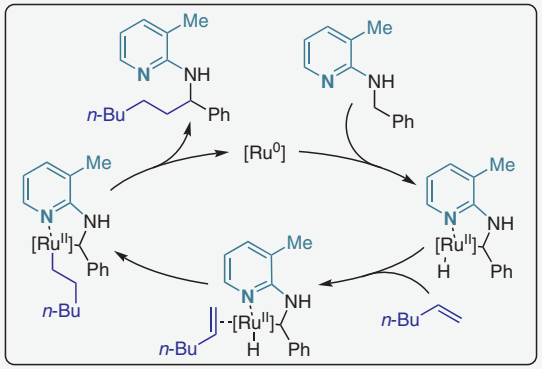
Notable features

- Functionalization of relatively unactived 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



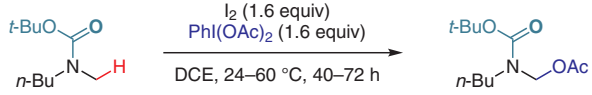
(6a) Jun, *Chem. Commun.* **1998**, 1405.

Further reading

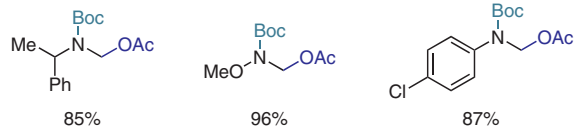
Other selected contributions:
(6f) Murai, *J. Am. Chem. Soc.* **2001**, *123*, 10935.
(6g) Shibata, *Org. Lett.* **2009**, *11*, 1821.
(6h) Ackermann, *Org. Lett.* **2014**, *16*, 1876.
(6i) Opatz, *Org. Lett.* **2014**, *16*, 4201.
(6j) Yu, *J. Am. Chem. Soc.* **2015**, *137*, 11876.
(6k) Yu, *Angew. 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

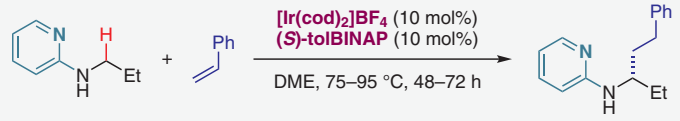


Selected scope



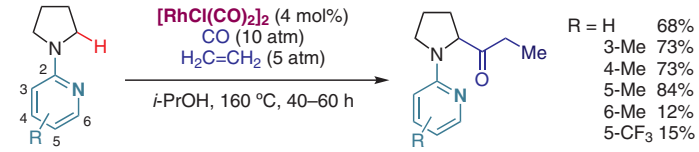
(6b) Yu, *Org. Lett.* **2006**, *8*, 3387.

Iridium



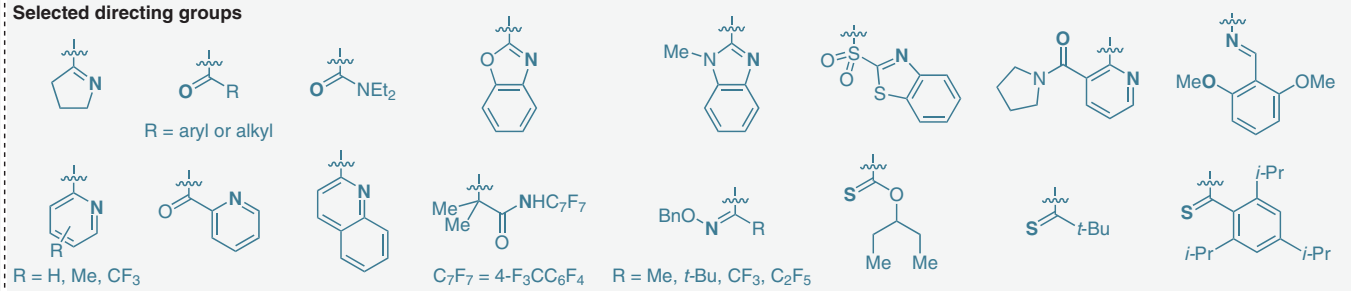
(6c) Shibata, *Org. Lett.* **2011**, *13*, 4692. 69%, 83% ee

Rhodium

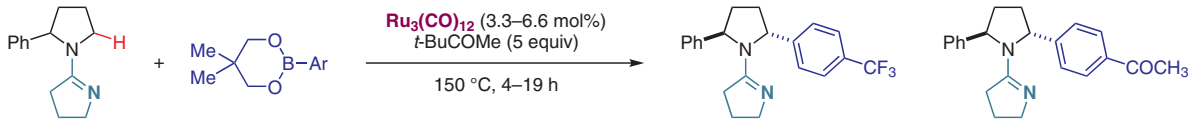


(6d) Murai, *J. Am. Chem. Soc.* **2000**, *122*, 12882.

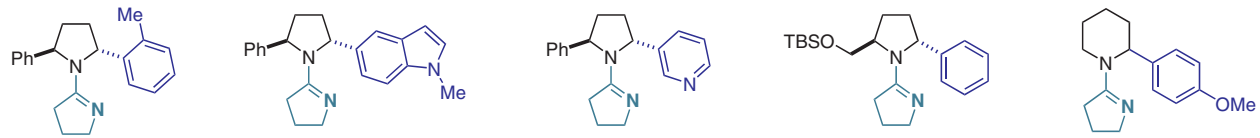
Selected directing groups



Ru-catalyzed α-C–H arylation



Selected scope



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

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

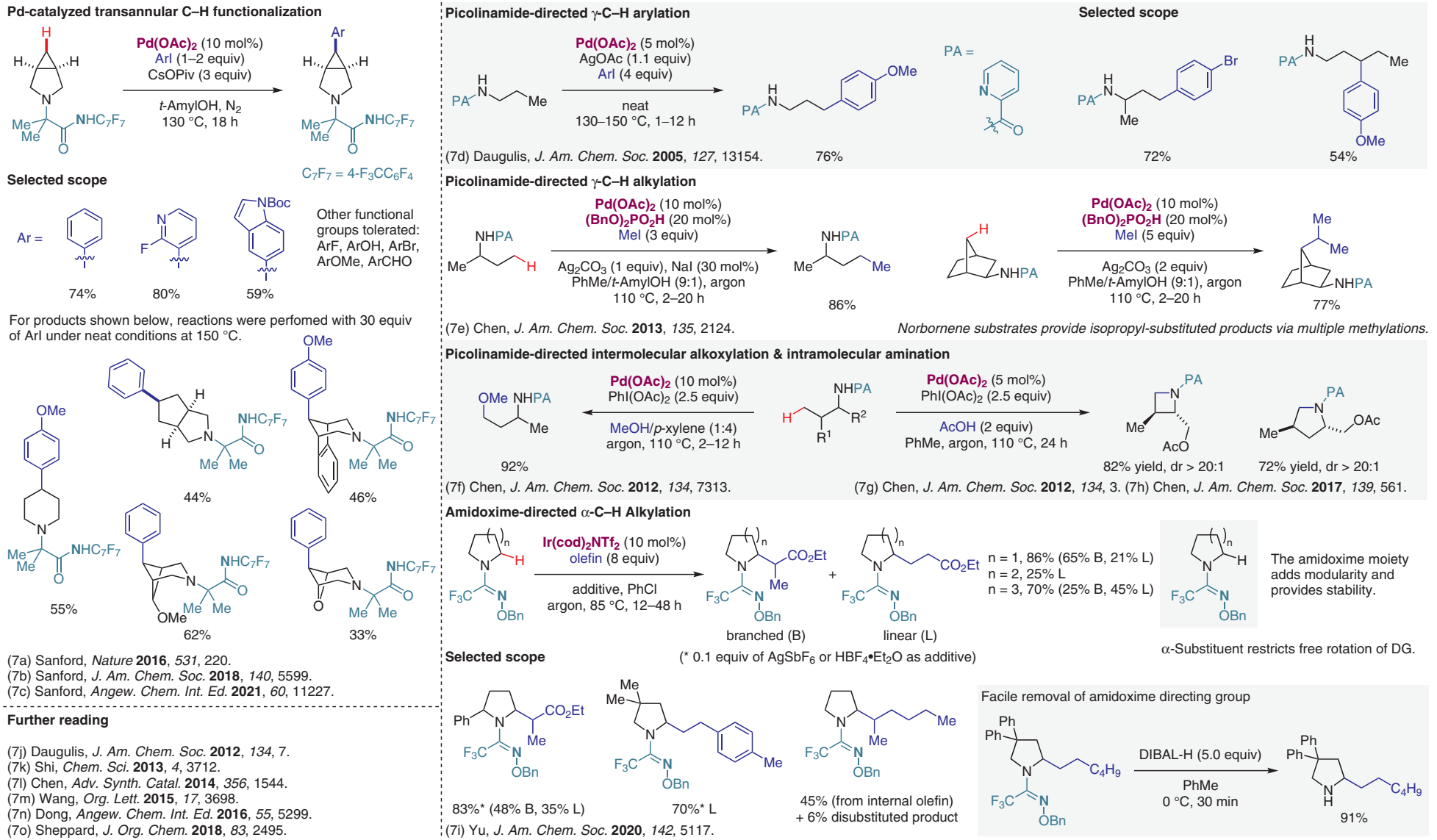


Figure 7 Transition-metal-catalyzed reactions with substrates containing directing groups, part II.[7]

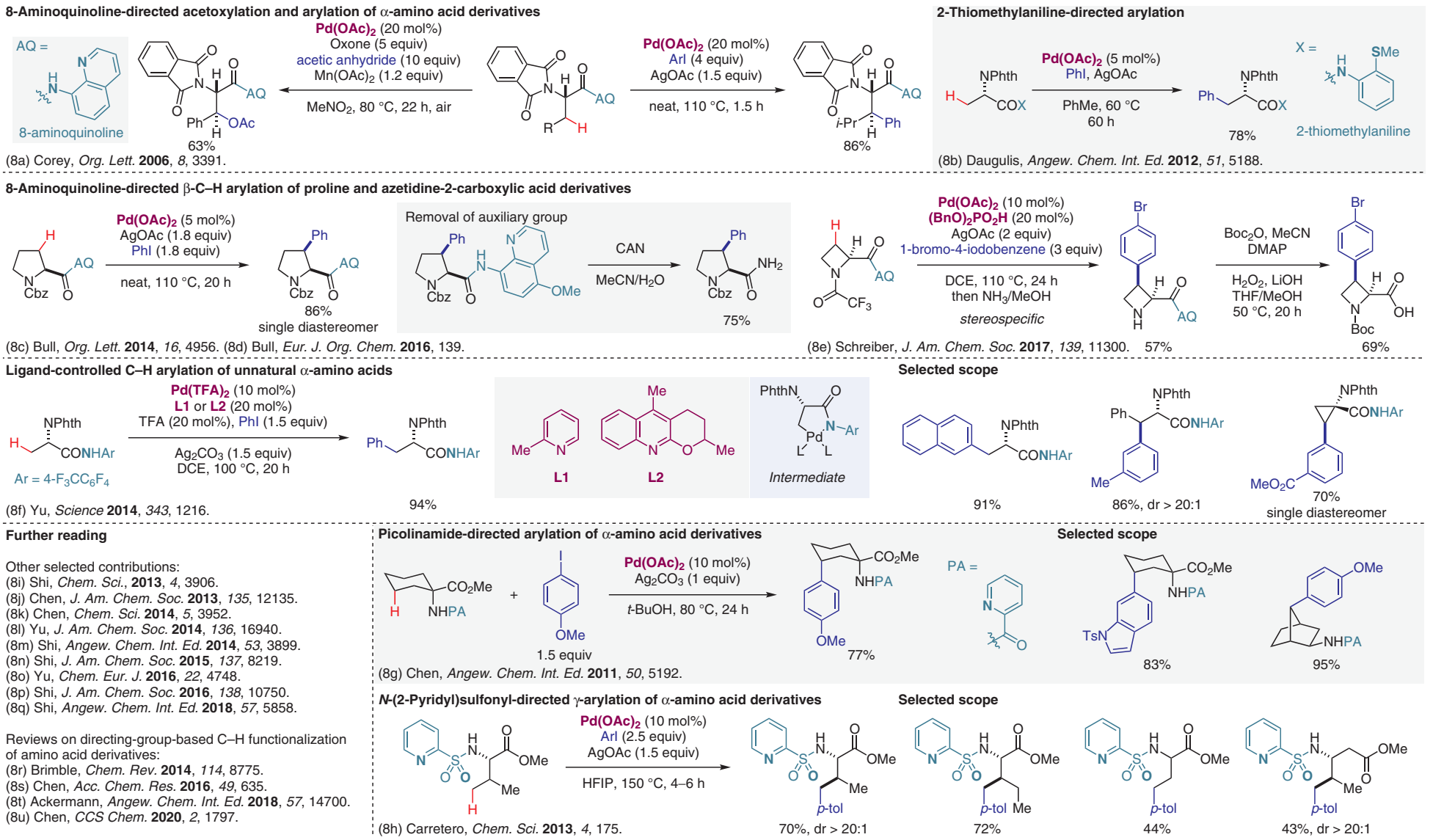


Figure 8 Transition-metal-catalyzed reactions with substrates containing directing groups, functionalization of amino acid derivatives.[8]

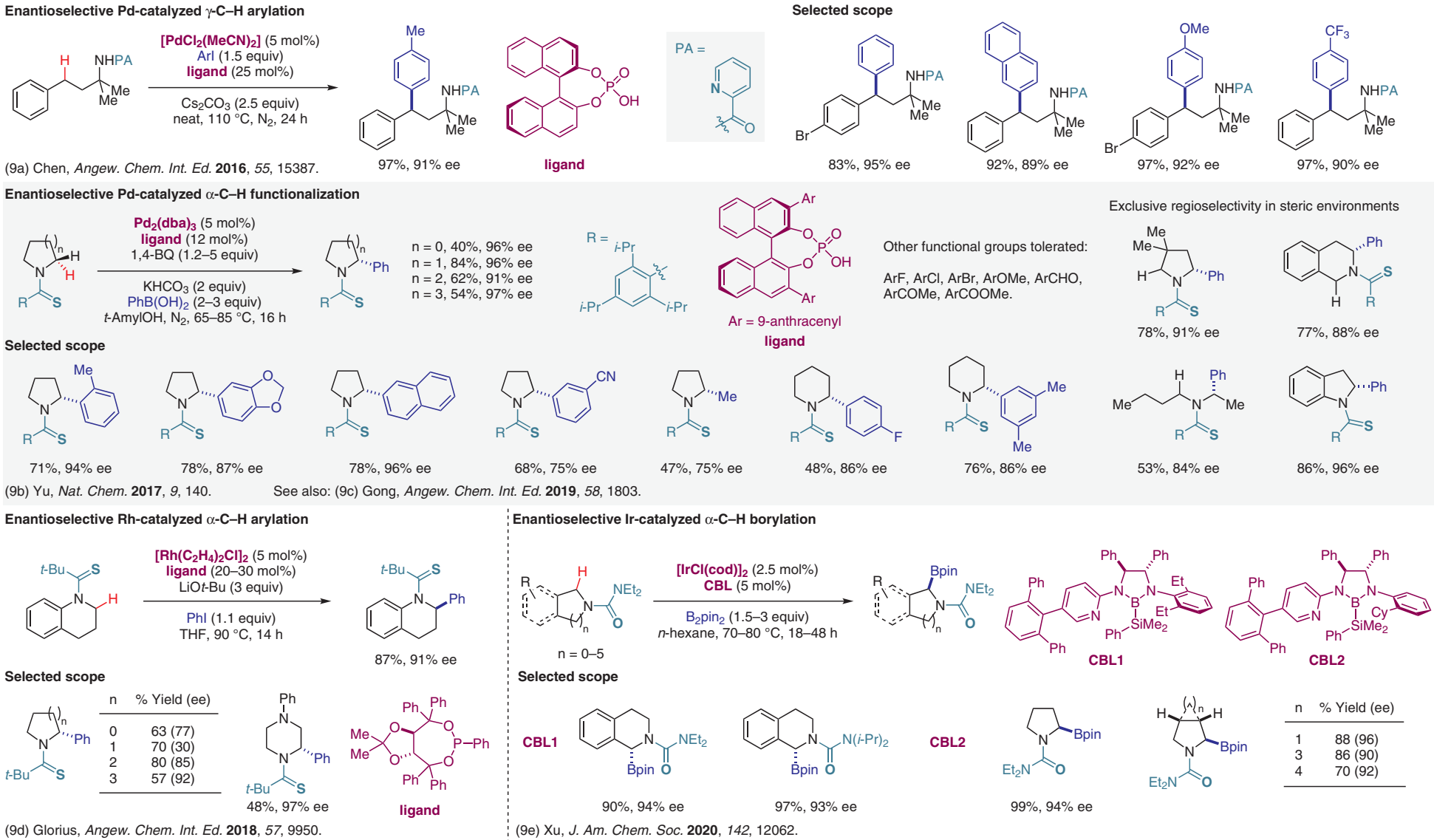
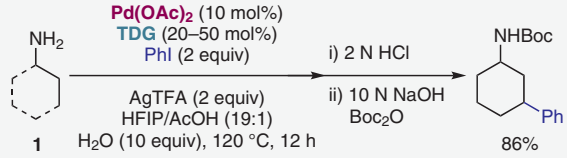


Figure 9 Transition-metal-catalyzed reactions with substrates containing directing groups, catalytic enantioselective approaches.[9]

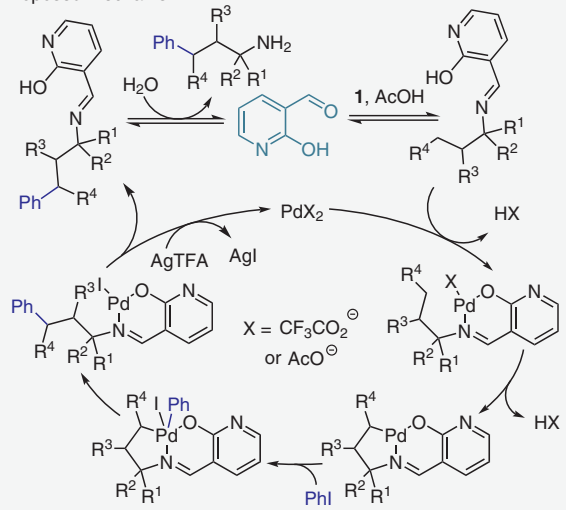
Notable features

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

Seminal work



Proposed mechanism



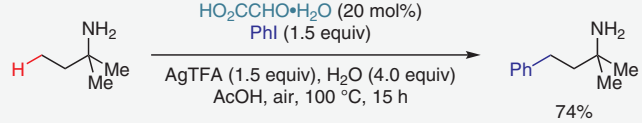
(10a) Yu, *J. Am. Chem. Soc.* **2016**, *138*, 14554.

Further reading

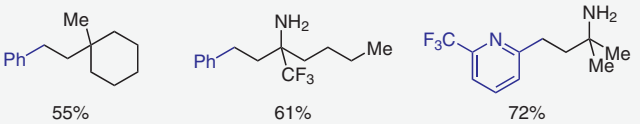
Bulky salicylaldehydes and alkyl acetals as TDGs:
(10f) Murakami, *Angew. Chem. Int. Ed.* **2017**, *56*, 1073.
(10g) Bull, *Chem. Eur. J.* **2018**, *24*, 17838.

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 γ-arylation

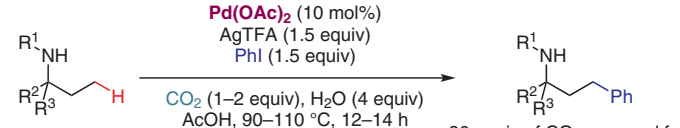


Selected scope

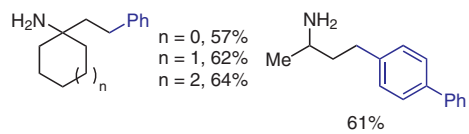


(10b) Ge, *Nat. Chem.* **2017**, *9*, 26.

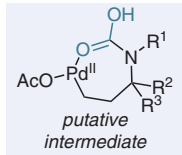
Carbon dioxide mediated amine γ-arylation



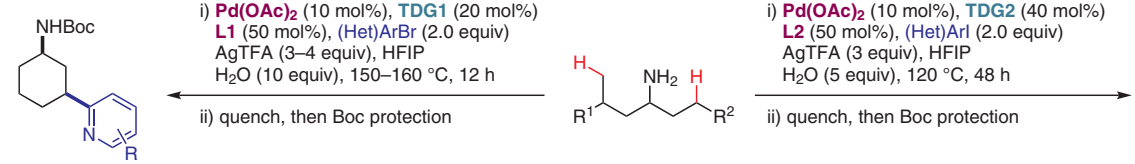
Selected scope



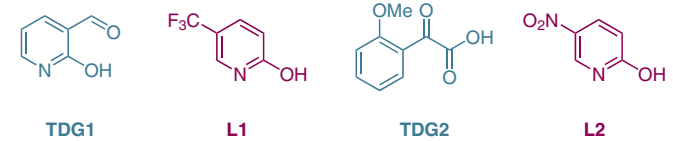
(10c) Young, *J. Am. Chem. Soc.* **2018**, *140*, 6818.

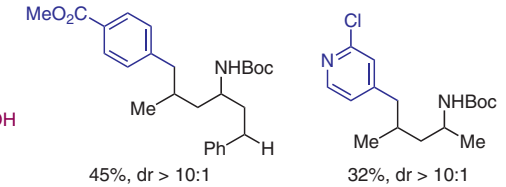


γ-C–H and distal δ-C–H arylation of amines by different TDGs



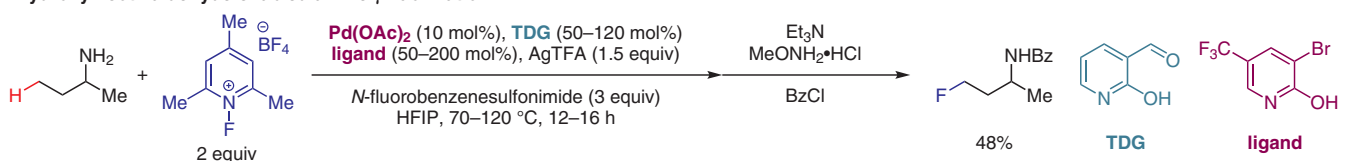
R	% Yield
H	65
6-CF_3	73
6-Me	61
5-Me	72
4-CF_3	50



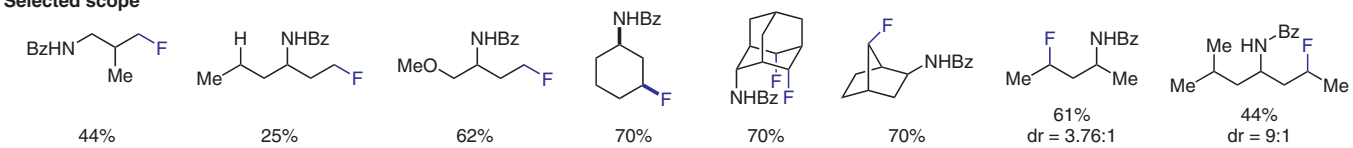


(10d) Yu, *J. Am. Chem. Soc.* **2018**, *140*, 17884.

2-Hydroxynicotinaldehyde-enabled amine γ-fluorination



Selected scope



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

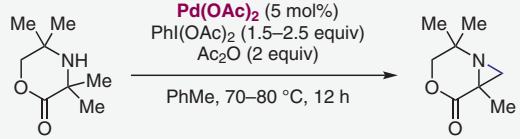
Ag salts must be present for methylene fluorination and absent for methyl fluorination.

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

Notable features

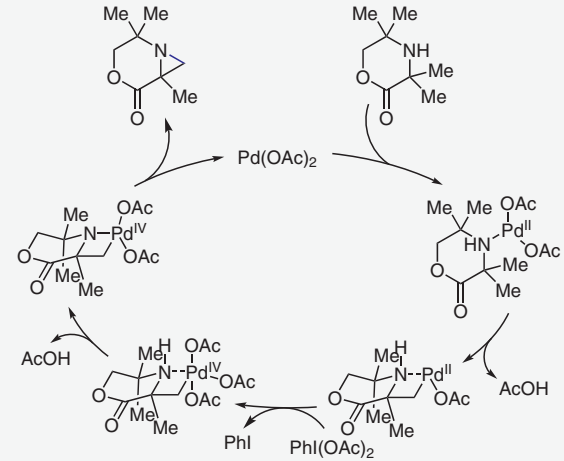
- Native-amine-directed transformations typically take place in a single step and without the addition of exogenous DGs, exploiting the innate coordinating ability of the nitrogen atom.
- Methods minimize the formation of stable and unreactive bis(amine) complexes and β-hydride elimination.

Seminal work



(11a) Gaunt, *Nature* **2014**, *510*, 129.

Proposed mechanism

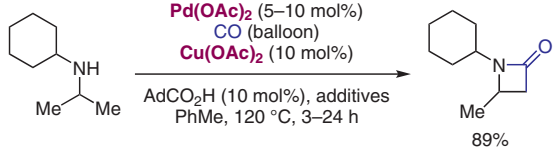


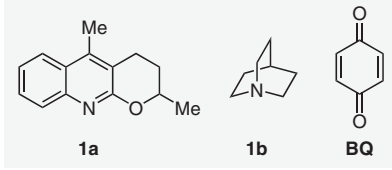
(11b) Gaunt, *J. Am. Chem. Soc.* **2015**, *137*, 10632.

Further reading

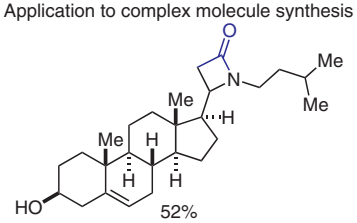
Other selected contributions:
(11g) Gaunt, *Nat. Chem.* **2015**, *7*, 1009.
(11h) Gaunt, *Angew. Chem. Int. Ed.* **2017**, *56*, 11958.
(11i) Shi, *Org. Chem. Front.* **2017**, *4*, 2097.
(11j) Gaunt, *Chem. Sci.* **2018**, *9*, 7628.
(11k) Bannister, *ACS Catal.* **2019**, *9*, 4887.
(11l) Gaunt, *Nat.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

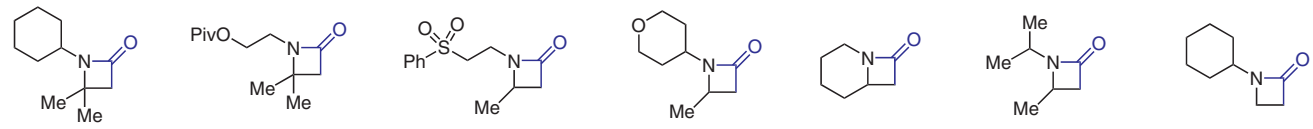




Application to complex molecule synthesis

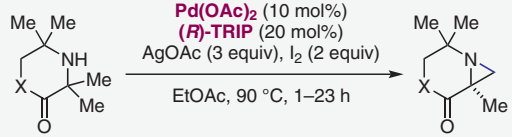


Selected scope Ad = adamantyl group; additives = **BQ** and **1a** or **BQ** and **1b**



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

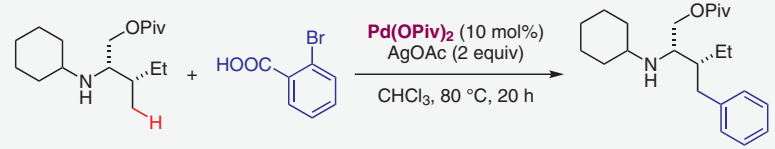
Enantioselective Pd-catalyzed C–H amination



X = O, 70%, 93% ee
X = *N*-phenyl, 78%, 87% ee

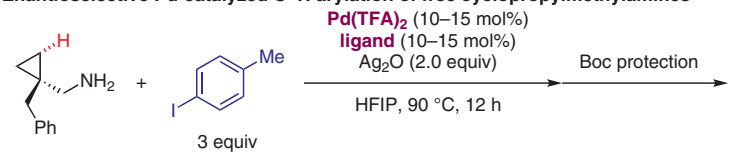
(11d) Gaunt, *J. Am. Chem. Soc.* **2017**, *139*, 1412.

Carboxylate-assisted oxidative addition to aminoalkyl Pd^{II} complexes

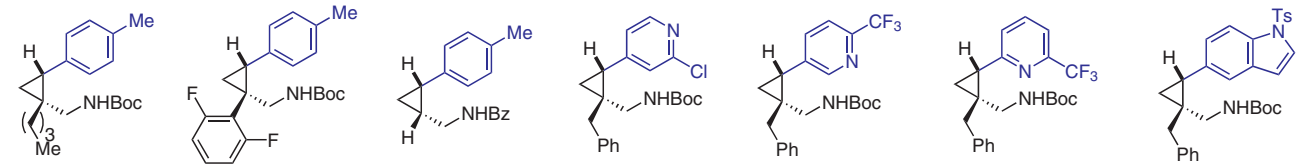


(11e) Gaunt, *Angew. Chem. Int. Ed.* **2019**, *58*, 9054.

Enantioselective Pd-catalyzed C–H arylation of free cyclopropylmethylamines



Selected scope



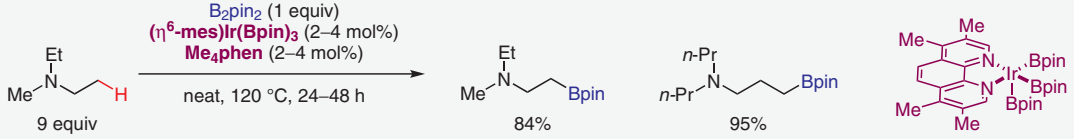
(11f) Yu, *J. Am. Chem. Soc.* **2020**, *142*, 12015.

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

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



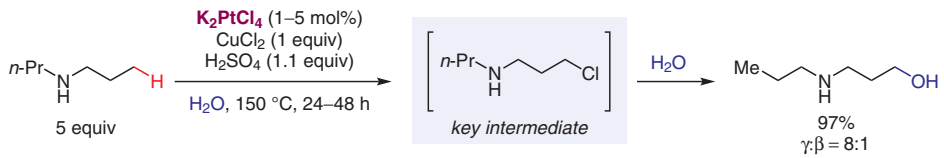
(12a) Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 8755.

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.

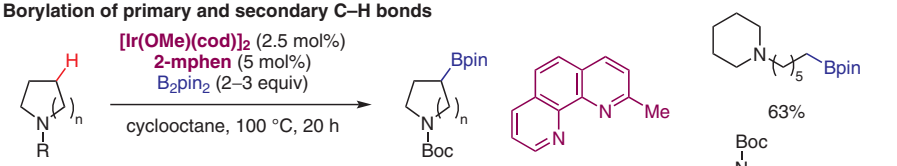
Terminal-selective C–H oxidation of aliphatic amines



In situ protonation masks the amine functionality.

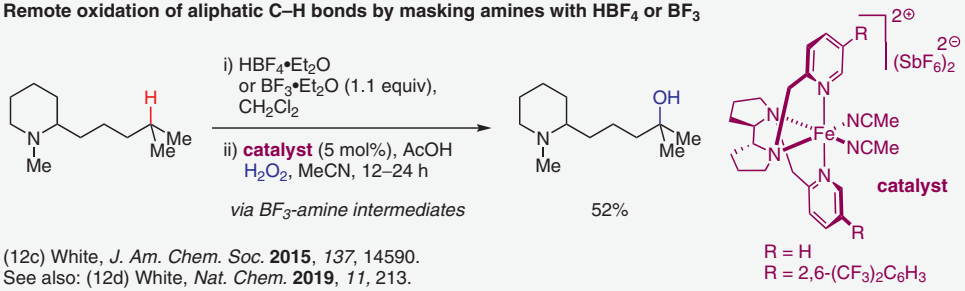
(12b) Sanford, *J. Am. Chem. Soc.* **2015**, *137*, 12796.

Borylation of primary and secondary C–H bonds



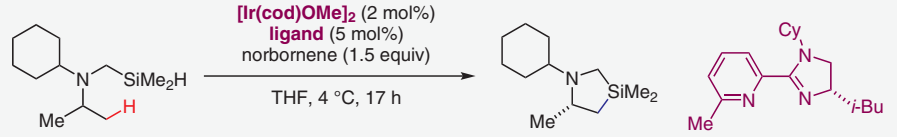
(12f) Hartwig, *Science* **2020**, *368*, 736.

Remote oxidation of aliphatic C–H bonds by masking amines with HBF_4 or BF_3



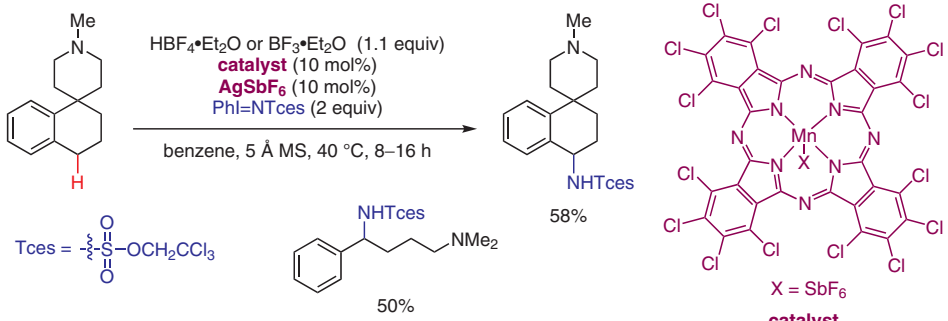
(12c) White, *J. Am. Chem. Soc.* **2015**, *137*, 14590.
See also: (12d) White, *Nat. Chem.* **2019**, *11*, 213.

β-Selective C–H silylation of aliphatic amines



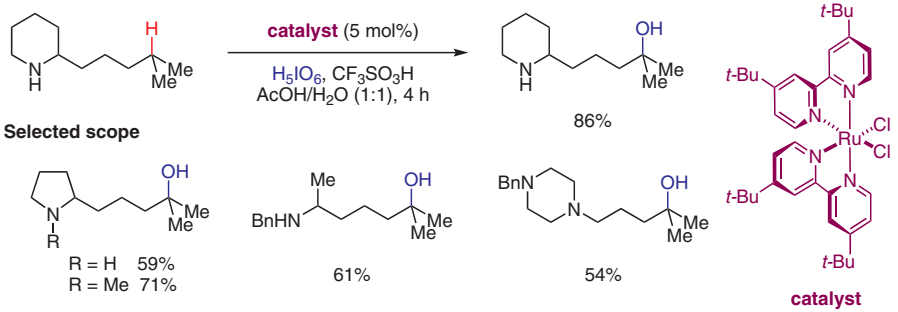
(12g) Hartwig, *J. Am. Chem. Soc.* **2018**, *140*, 18032.

Benzylic C–H amination



(12e) White, *Nat. Chem.* **2018**, *10*, 583.

C–H hydroxylation of amine derivatives



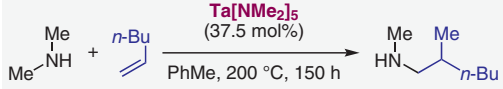
(12h) Sigman, *J. Am. Chem. Soc.* **2017**, *139*, 9503.

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

Notable features

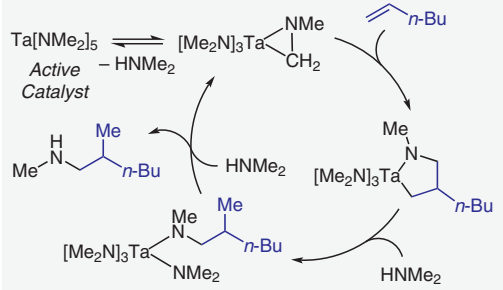
- Atom-economical process using early transition metals that are abundant and exhibit low toxicity.
- Reactions proceed through metalaziridine intermediates.

Seminal discovery



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

Proposed mechanism:



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

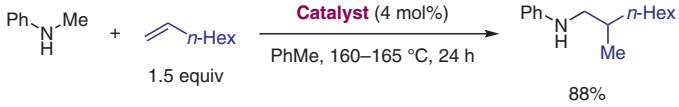
Further reading

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) Hultzsch, *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.

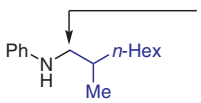
Application of group V metals to amine α-functionalization (13c) Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 6690. (13d) Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 14940.



Catalyst	% Yield
$Ta[N(CH_3)_2]_5$	96
$Nb[N(CH_3)_2]_5$	35
$Zr[N(CH_3)_2]_4$	0.1
none	0

with 1.25 equiv of 1-octene

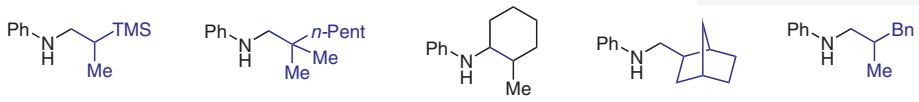
The chloroamido complex $[Cl_3Ta(NMePh)_2]_2$ catalyzes the same reaction effectively at 90 °C while $Ta(NMe_2)_5$ shows no activity at this temperature.



D retention	Catalyst
92%	$Ta(NMe_2)_5$
45%	$[Cl_3Ta(NMePh)_2]_2$

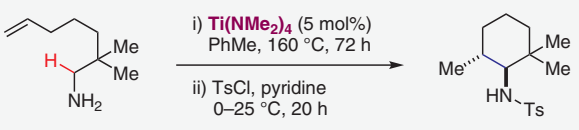
A mechanistic study suggests formation of an azametallacyclopropane (η^2-imine complex) as the turnover-limiting step.

Selected scope (* with 8 mol% of catalyst)

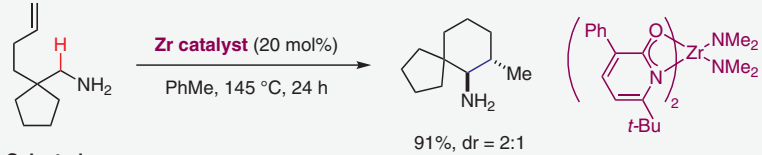


66%* 76%* 88%*, dr = 1:1 96%, dr = 3:1 77%

Application of group IV metals to intramolecular amine α-functionalization

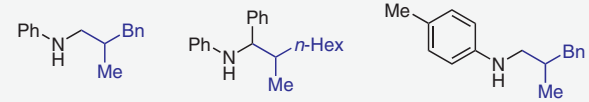


46%, dr = 5:2



91%, dr = 2:1

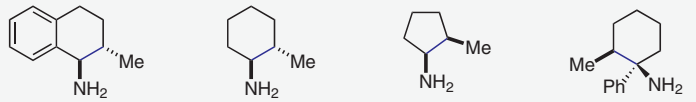
Selected scope (Branched:Linear)



94% (9:1) 84% (1:1) *dr not determined* 80% (19:1)

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

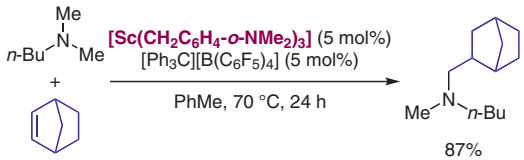
Selected scope



90%, dr = 3:1 43%, dr = 2:1 54%, dr = 2:1 51%, dr = 19:1

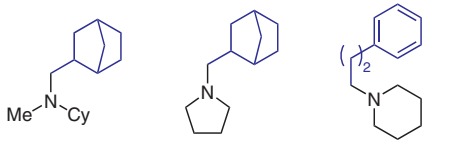
(13f) Schafer, *J. Am. Chem. Soc.* **2009**, *131*, 2116.

Intermolecular hydroaminoalkylation with group III metals



87%

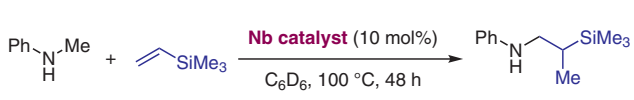
Selected scope



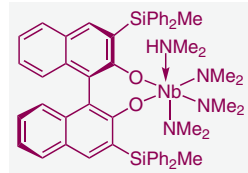
93% 82% 85%

(13g) Hou, *Chem. Sci.* **2016**, *7*, 6429.

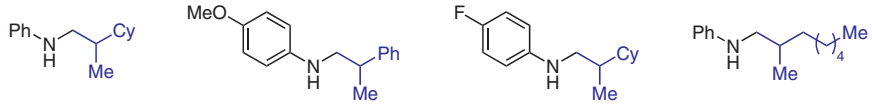
Enantioselective intermolecular α-functionalization



82%, 98% ee



Selected scope



92%, 91% ee 73%, 71% ee 93%, 73% ee (140 °C) 92%, 81% ee

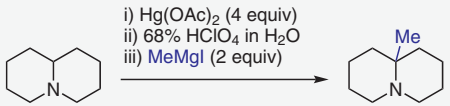
(13h) Hultzsch, *J. Am. Chem. Soc.* **2012**, *134*, 3300.

Figure 13 Hydroaminoalkylation.[13]

Notable features

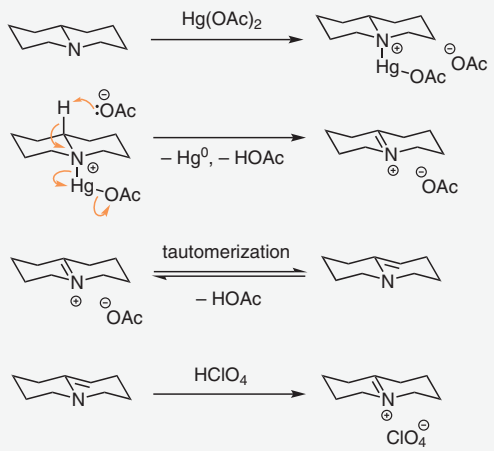
- Operationally simple approach to access iminium ions.
- Mostly applicable to tertiary amines.
- Substrate dimerization can occur via enamine intermediates.
- Compatible with a range of different nucleophiles.
- Yields are typically moderate to low.

Seminal example



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

Proposed mechanism

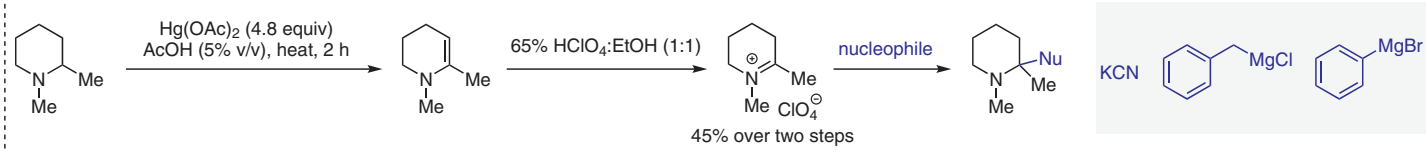


(14b) Morrow, *J. Am. Chem. Soc.* **1958**, *80*, 371.

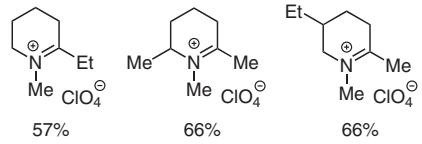
Further reading

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

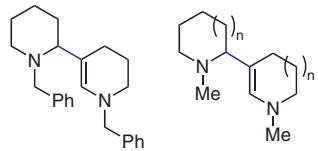
Mercury-promoted formation of enamines and subsequent transformations



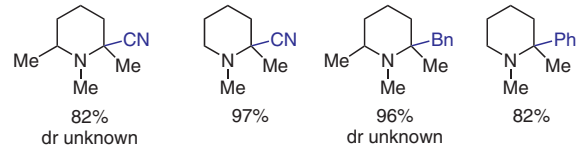
Iminium salts, selected scope



Dimerized products

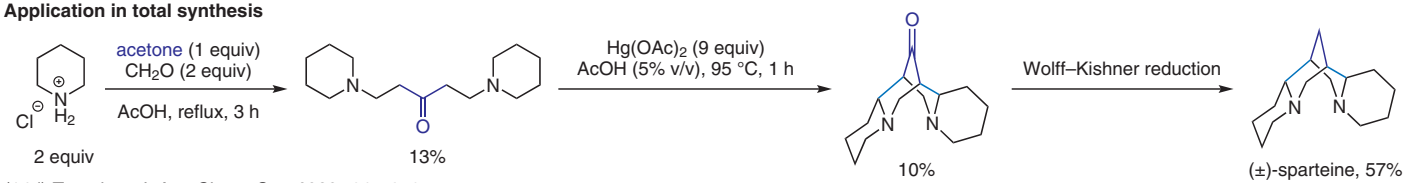


Selected nucleophile scope

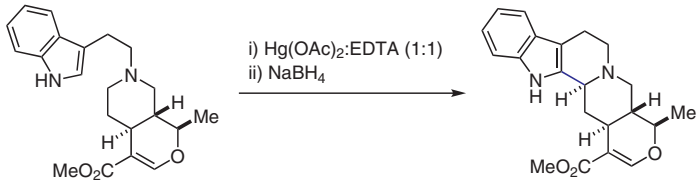


(14c) Leonard, *J. Am. Chem. Soc.* **1957**, *79*, 5279.

Application in total synthesis

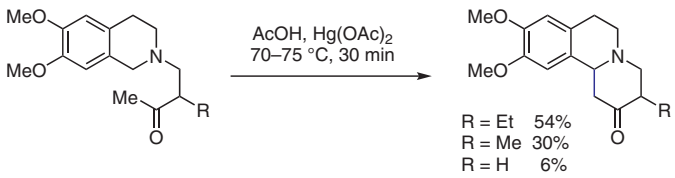


(14d) Tamelen, *J. Am. Chem. Soc.* **1969**, *91*, 7372.



(14e) Uskokoviã, *J. Am. Chem. Soc.* **1971**, *93*, 5907.

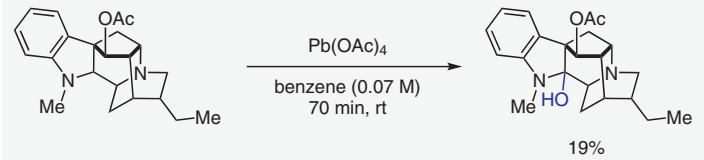
Intramolecular annulation



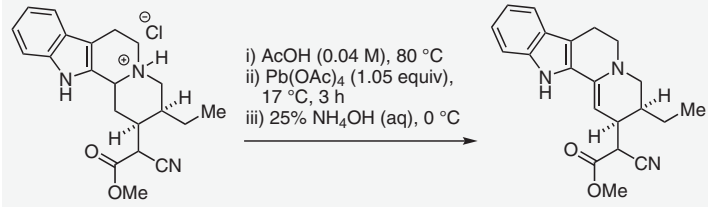
With R = H, competing Hofmann-type elimination is observed.

(14f) Whittaker, *J. Chem. Soc.* **1963**, 1449.

Examples using lead tetraacetate as an oxidant



(14g) Taylor, *J. Am. Chem. Soc.* **1964**, *86*, 729.



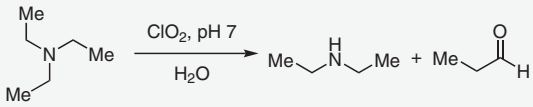
(14h) Szantay, *Tetrahedron* **1976**, *32*, 1019.

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

Notable features

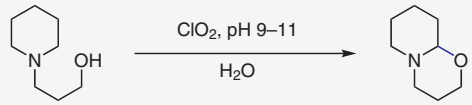
- Various nonmetallic reagents are suitable for amine oxidation.
- Typically, no catalyst is required.

Early examples with stoichiometric oxidants

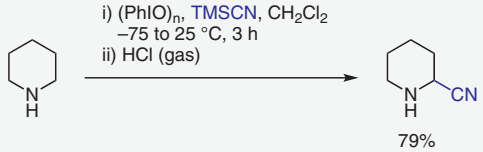


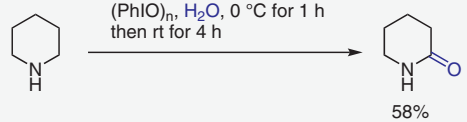
Formation of an iminium species is followed by hydrolysis.

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



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



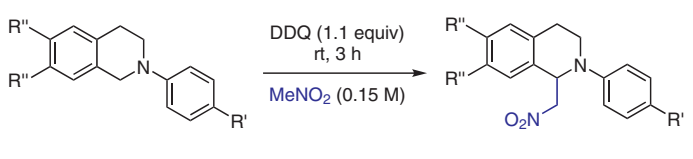


(15c) Moriarty, Ochiai, Nagao, *Tetrahedron Lett.* **1988**, *29*, 6913.
See also: (15d) Xiong, *Tetrahedron Lett.* **2015**, *56*, 5628.

Further reading

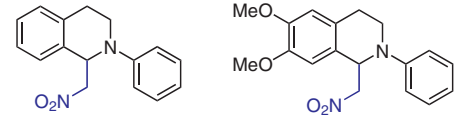
(15k) Zhdankin, *Tetrahedron Lett.* **1995**, *36*, 7975.
(15l) Hu, *New J. Chem.* **2013**, *37*, 1684.
(15m) Nguyen, *J. Org. Chem.* **2018**, *83*, 1000.
(15n) Zhang, Luo, *J. Org. Chem.* **2019**, *84*, 2542.
(15o) Li, *Eur. J. Org. Chem.* **2020**, 103.
(15p) Singh, *Synthesis* **2021**, *53*, 1556.

Oxidation with DDQ

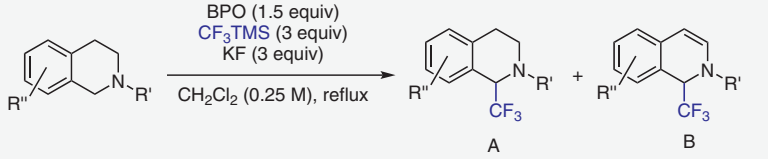


(15e) Todd, *Tetrahedron Lett.* **2009**, *50*, 1199.

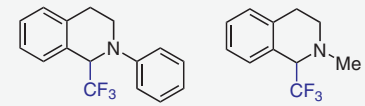
Selected scope



Oxidation with BPO

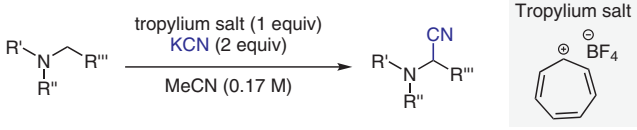


Selected scope

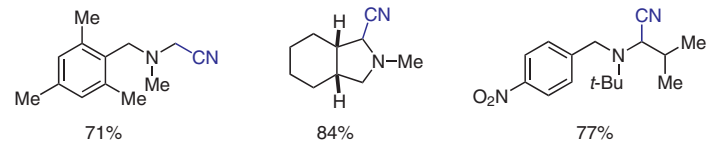


(15f) Qing, *Chem. Commun.* **2010**, *46*, 6285.

Oxidation with tropylium tetrafluoroborate

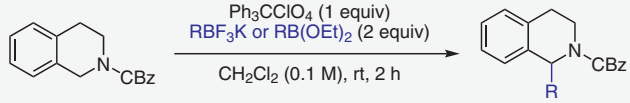


Selected scope

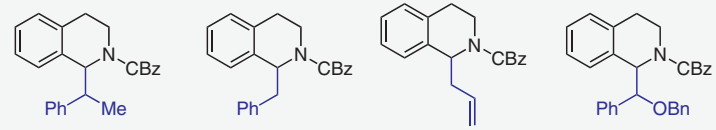


(15g) Lambert, *J. Am. Chem. Soc.* **2011**, *133*, 1260.

Oxidation with trityl perchlorate

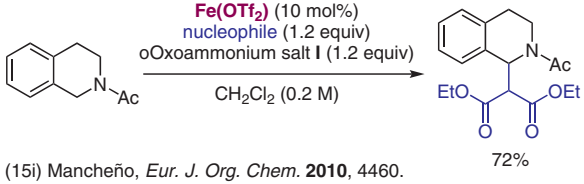


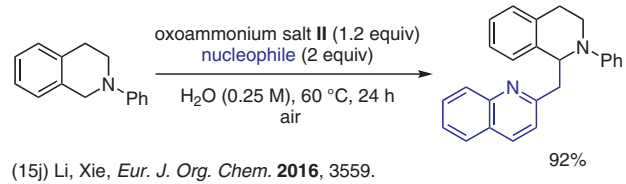
Selected scope



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

Oxidation with oxoammonium salts





(15i) Mancheño, *Eur. J. Org. Chem.* **2010**, 4460.
(15j) Li, Xie, *Eur. J. Org. Chem.* **2016**, 3559.

Figure 15 Oxidative methods, stoichiometric nonmetallic oxidants.[15]

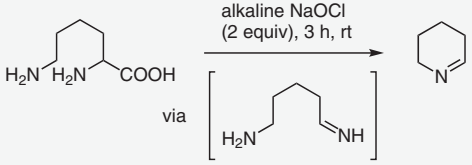
Notable features

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

Reviews

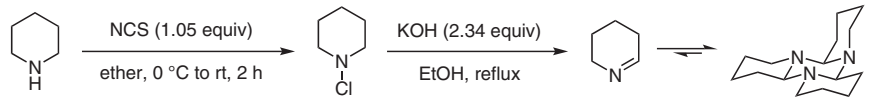
(16a) Murahashi, *Chem. Rev.* **2019**, *119*, 4684.
(16b) Largeron, *Eur. J. Org. Chem.* **2013**, 5225.

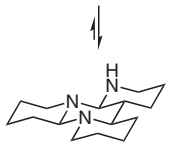
Oxidation of lysine



(16c) Franck, *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 131.
(16d) Spenser, *Can. J. Chem.* **1969**, *47*, 445.

NCS-mediated oxidation

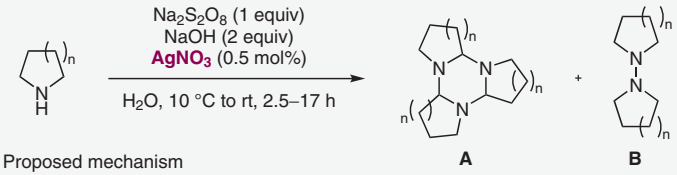




Also applicable to substituted piperidines and pyrrolidines.

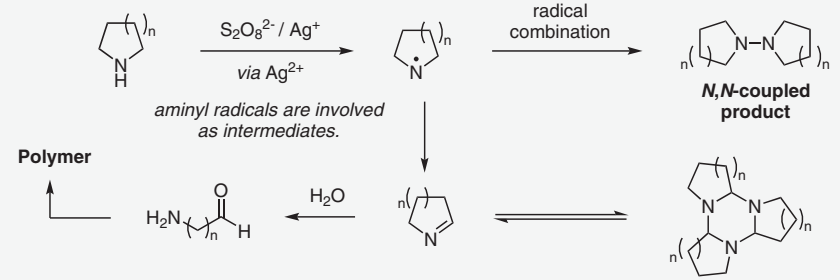
(16e) Grisar, *Org. Synth.* **1977**, *56*, 118. (16f) Kessler, *J. Org. Chem.* **1977**, *42*, 66. (16g) Joullie, *J. Am. Chem. Soc.* **1982**, *104*, 5852. (16h) Davis, *Org. Lett.* **2002**, *4*, 103. (16i) Poupon, *Tetrahedron* **2006**, *62*, 5248. (16j) O'Reilly, *Chem. Eur. J.* **2016**, *22*, 12692. (16k) Lehn, *J. Am. Chem. Soc.* **2018**, *140*, 5560. (16l) Orru, Ruijter, *Eur. J. Org. Chem.* **2019**, 5313.

Silver-catalyzed oxidation



n	% Yield A	B
0	–	<5
1	50	–
2	2	48
3	–	0.3

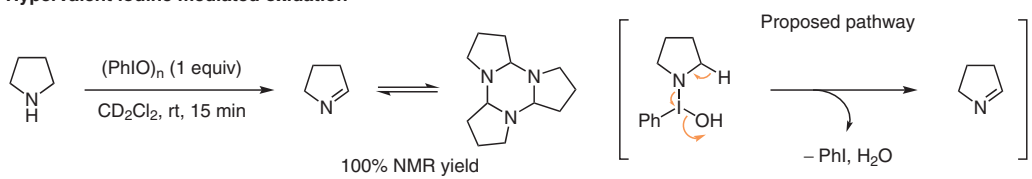
Proposed mechanism



(16m) Nomura, *Chem. Lett.* **1977**, 693.
(16n) Nomura, *J. Chem. Soc., Perkin Trans. 1* **1982**, 3031.

This method is only suitable for the preparation of 1-pyrroline trimer (n = 1).

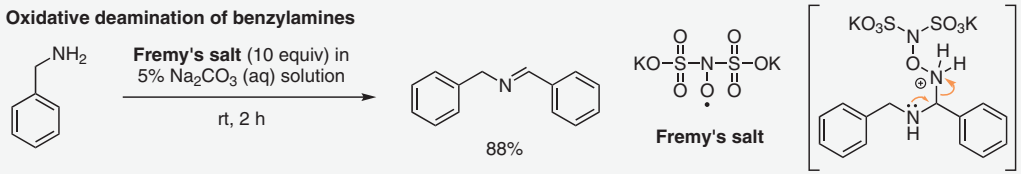
Hypervalent iodine mediated oxidation



Oxidative decarboxylation of L-proline to the 1-pyrroline trimer is also feasible using this method.

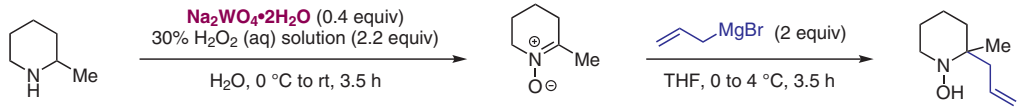
(16o) Ochiai, Nagao, Moriarty, *Tetrahedron Lett.* **1988**, *29*, 6917. See also: (15c) Moriarty, Ochiai, Nagao, *Tetrahedron Lett.* **1988**, *29*, 6913. (16p) Suárez, *Tetrahedron Lett.* **1999**, *40*, 5945. (16q) Lee, *Helv. Chim. Acta* **2002**, *85*, 1069.

Oxidative deamination of benzylamines

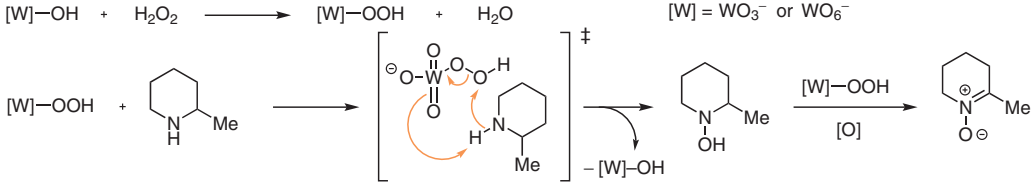


(16r) Castedo, *Tetrahedron* **1982**, *38*, 1569. See also: (16s) Wang, Blechert, *Angew. Chem. Int. Ed.* **2011**, *50*, 657. (16t) Stahl, *Org. Lett.* **2012**, *14*, 2850. (16u) Gao, *ACS Catal.* **2015**, *5*, 5851.

Tungstate-catalyzed oxidation of secondary amines to nitrones

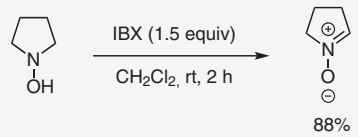


Proposed mechanism



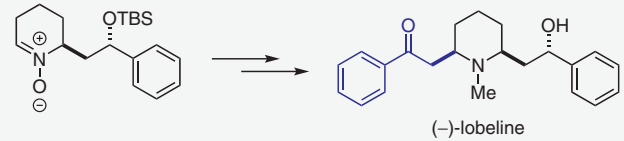
(16v) Murahashi, *J. Chem. Soc., Chem. Commun.* **1984**, 874. (16w) Murahashi, *J. Org. Chem.* **1990**, *55*, 1736.

Nitrones from hydroxylamine



(16x) Goti, *Org. Lett.* **2015**, *17*, 4082.

Application to the total synthesis of piperidine alkaloids



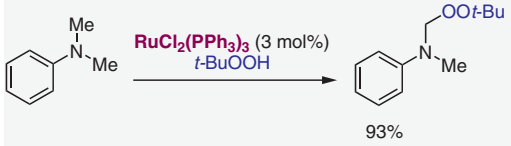
(16y) Snyder, *Angew. Chem. Int. Ed.* **2018**, *57*, 15162.

Figure 16 Oxidative preparation of building blocks.[16]

Notable features

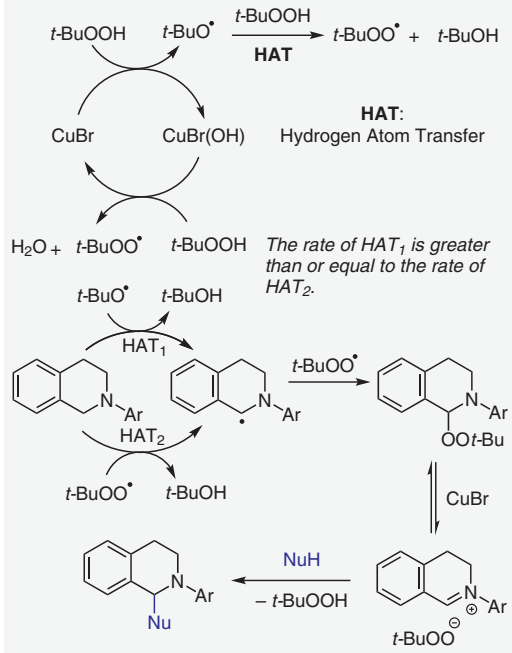
- Metal catalysis enables the use of readily available oxidants such as peroxides in the oxidation of amines.
- Radical intermediates are involved in some if not most reactions.
- Substrate scope is often limited to *N*-arylamines.

Seminal work



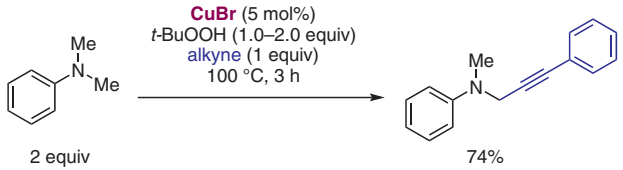
(17a) Yonemure, *J. Am. Chem. Soc.* **1988**, *110*, 8256.

Proposed mechanism

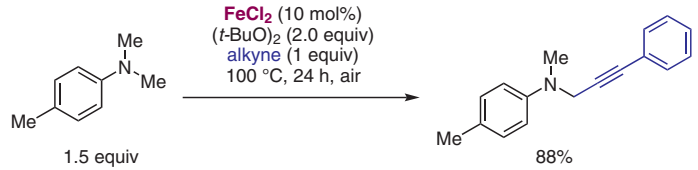


(17b) Klussmann, *ACS Catal.* **2016**, *6*, 3253.

Alkynylation of *N,N*-dimethylanilines

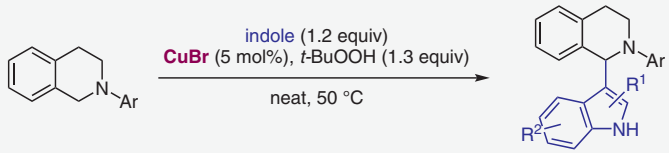


(17c) Li, *J. Am. Chem. Soc.* **2004**, *126*, 11810.



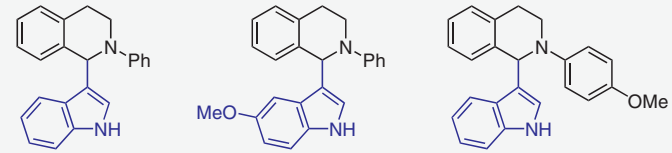
(17d) Vogel, *Org. Lett.* **2009**, *11*, 1701.

Arylation of *N*-aryltetrahydroisoquinolines

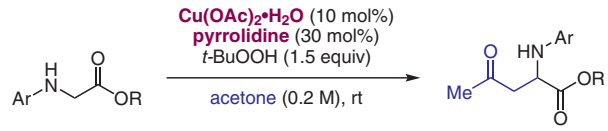


(17e) Li, *J. Am. Chem. Soc.* **2005**, *127*, 6968.

Selected scope

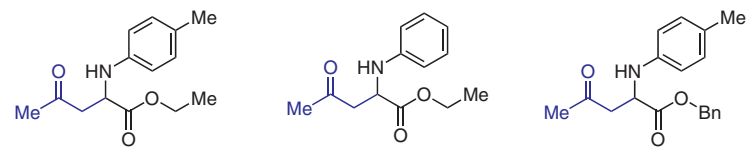


Alkylation of secondary amino esters

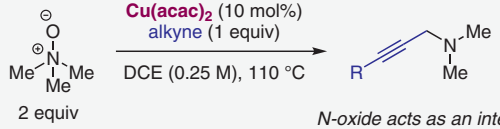


(17f) Huang, *Angew. Chem. Int. Ed.* **2010**, *49*, 10181.

Selected scope

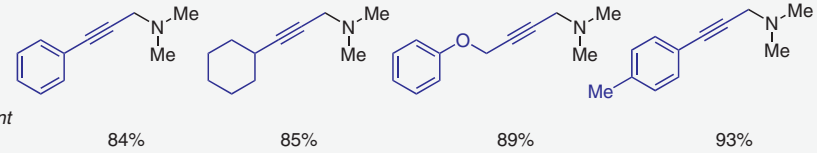


Alkynylation of *N*-oxides

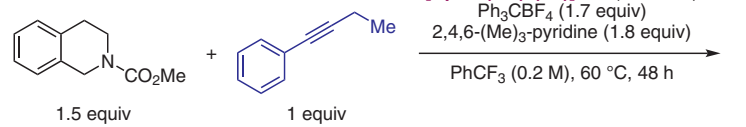


(17g) Bao, *J. Org. Chem.* **2011**, *76*, 6901.

Selected scope



Propargylation with internal alkynes



(17h) Wang, *Chem. Sci.* **2020**, *11*, 12316.

Further reading

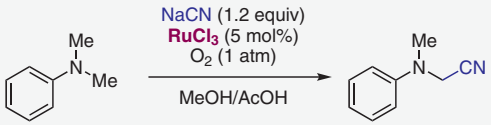
(17i) Li, *Acc. Chem. Res.* **2009**, *42*, 335.
(17j) Dong, *Chem. Rev.* **2011**, *11*, 1215.
(17k) Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3464.
(17l) Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74.
(17m) Luo, *Chem. Rev.* **2017**, *117*, 9433.
(17n) Li, *J. Org. Chem.* **2019**, *84*, 12705.
(17o)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

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

Notable features

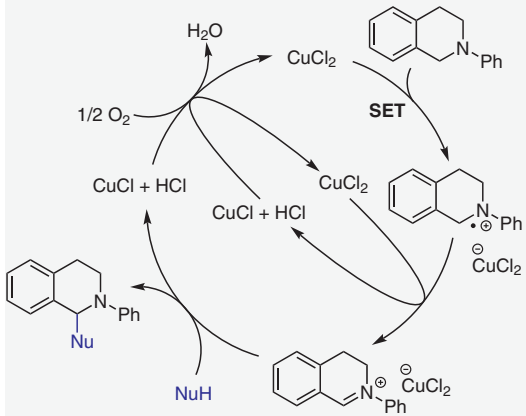
- Metal catalysis enables the use of oxygen as the terminal oxidant.
- Substrate scope is often limited to *N*-arylamines.

Seminal example



(18a) Murahashi, *J. Am. Chem. Soc.* **2003**, *125*, 15312.

Proposed mechanism of $CuCl_2$-catalyzed reactions

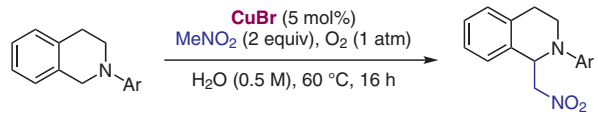


(18b) Klussmann, *J. Org. Chem.* **2014**, *79*, 12033.

Further reading

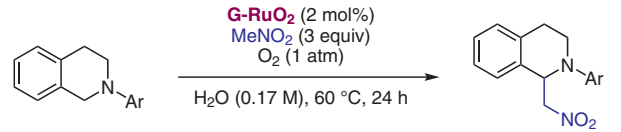
(18i) Yang, *Green Chem.* **2014**, *16*, 2428.
(18j) Polyzos, *Chem. Commun.* **2015**, *51*, 334.
(18k) Gogoi, *ChemistrySelect* **2016**, *1*, 4620.
(18l) Schnürch, *Monatsh. Chem.* **2017**, *148*, 91.
(18m) Zhang, *RSC Adv.* **2017**, *7*, 1229.
(18n) Le, Zhu, *Synthesis* **2018**, *50*, 2775.
(18o) 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



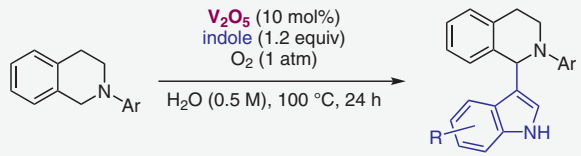
(18c) Li, *Green Chem.* **2007**, *9*, 1047.

Ruthenium-catalyzed aza-Henry reaction

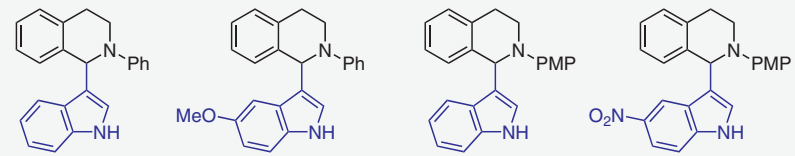


(18d) Wu, *Org. Lett.* **2012**, *14*, 5992.

Vanadium-catalyzed arylation

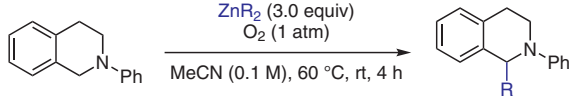


Selected scope

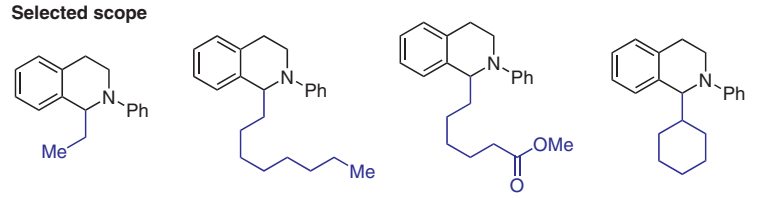


(18e) Prabhu, *Chem. Commun.* **2011**, *47*, 11787.

Copper-catalyzed alkylation with organozinc reagents

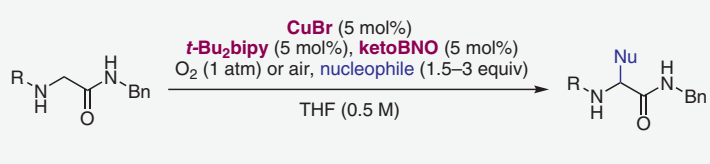


Selected scope

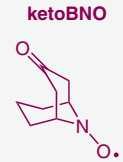


(18f) Menche, *Org. Lett.* **2015**, *17*, 3982.

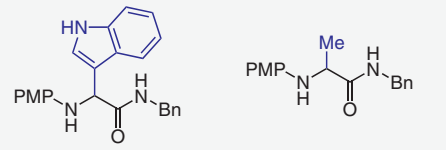
Examples of dual catalysis involving aminoxyl radicals



ketoBNO

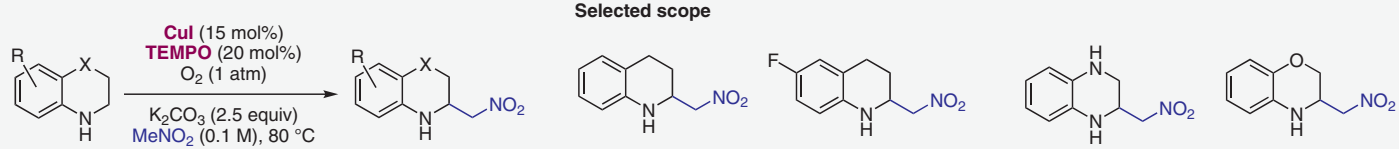


Selected scope



(18g) Kanai, *Chem. Sci.* **2012**, *3*, 3249.

Selected scope



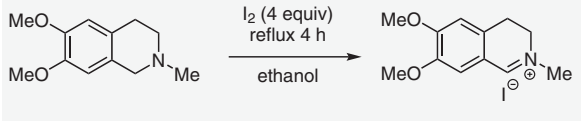
(18h) Zhang, *Org. Chem. Front.* **2020**, *7*, 425.

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

Notable features

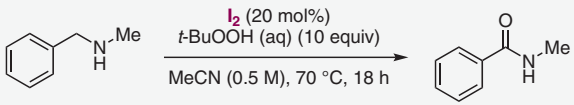
- Its low toxicity renders iodine an ideal catalyst.
- Peroxides or oxygen act as terminal oxidants.

Historical precedent with stoichiometric iodine

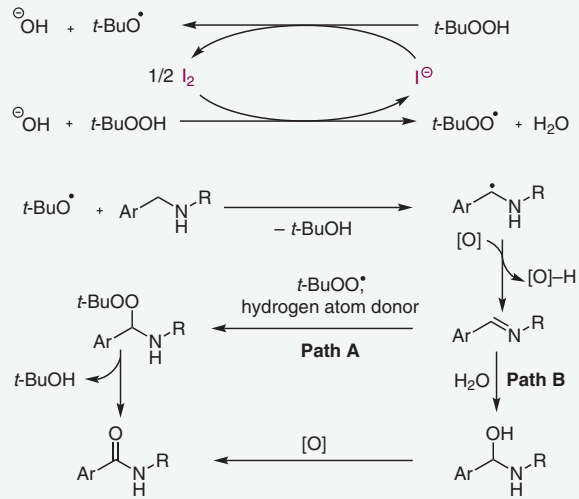


(19a) Lete, *J. Heterocycl. Chem.* **1984**, *21*, 525.

Oxidation of benzylamines with I_2



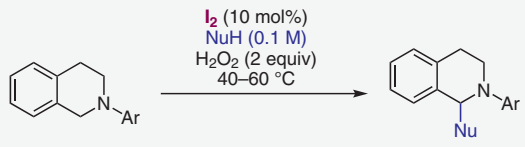
Proposed mechanism



(19b) Adimurthy, *J. Org. Chem.* **2017**, *82*, 13632.

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

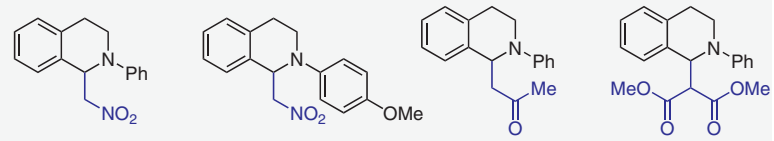
Iodine-catalyzed alkylation



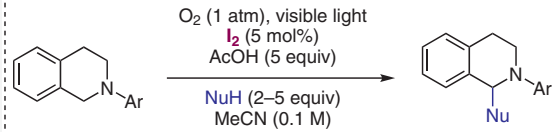
Enolates require addition of AcOH (5 equiv).

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

Selected scope

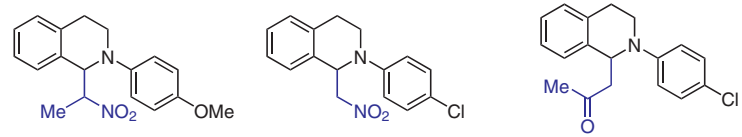


Oxygen as the terminal oxidant

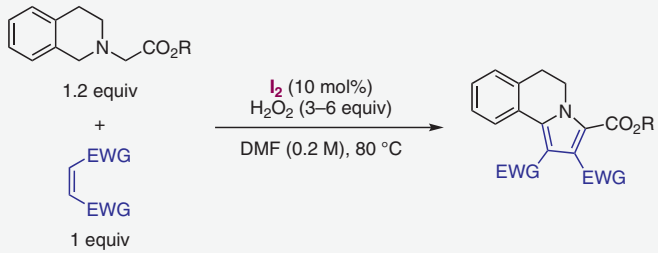


(19d) Itoh, *RSC Adv.* **2013**, *3*, 10189.

Selected scope

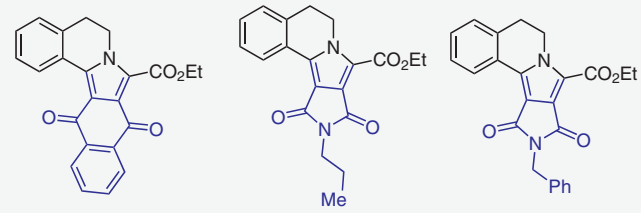


Oxidative 1,3-dipolar cyclization

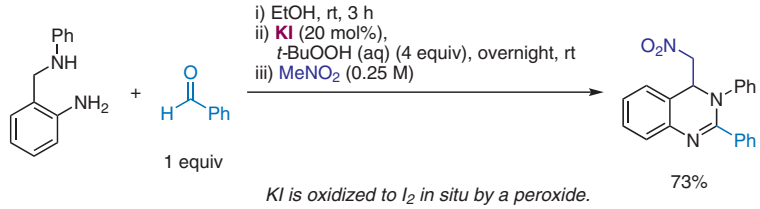


(19e) Gao, Li, *J. Org. Chem.* **2014**, *79*, 1084

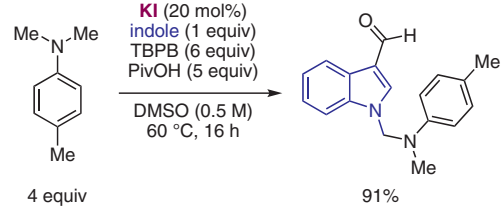
Selected scope



Examples of more complex reaction cascades



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



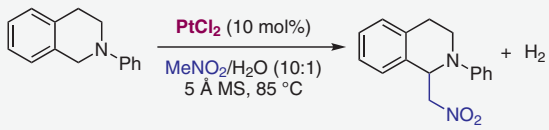
(19g) Wang, *Org. Biomol. Chem.* **2012**, *10*, 9519.

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

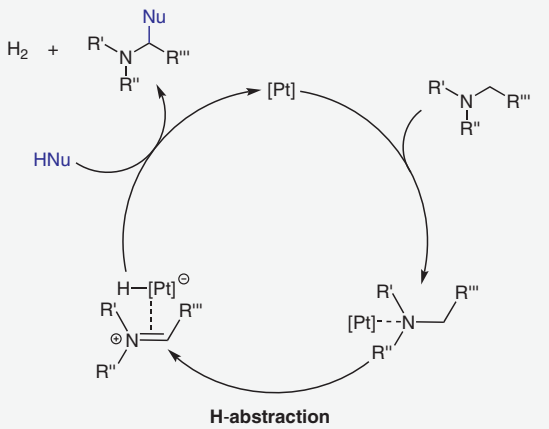
Notable features

- 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

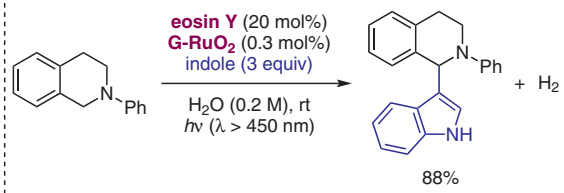


(20a) Liang, *Org. Biomol. Chem.* **2010**, *8*, 4077.

Further reading

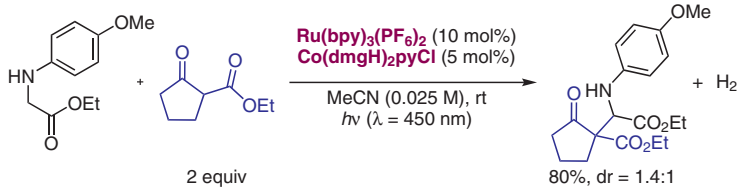
(20m) Milstein, *J. Am. Chem. Soc.* **2014**, *136*, 2998.
(20n) Li, *ChemSusChem.* **2014**, *7*, 2788.
(20o) Zhang, *Org. Lett.* **2017**, *19*, 3390.
(20p) Tung, Wu, *Acc. Chem. Res.* **2018**, *51*, 2512.
(20q) Lei, *J. Am. Chem. Soc.* **2018**, *140*, 13128.
(20r) Lei, *Chem. Rev.* **2019**, *119*,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

Photochemical α-arylation



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

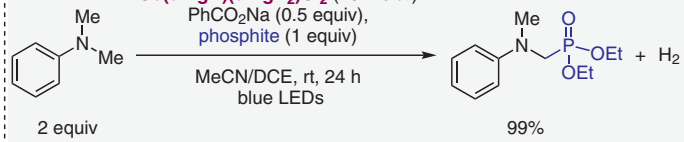
Photochemical α-alkylation of amino acid esters



(20d) Wu, *ACS Catal.* **2015**, *5*, 2391.
See also: (20e) Zhang, *J. Org. Chem.* **2019**, *84*, 3559.

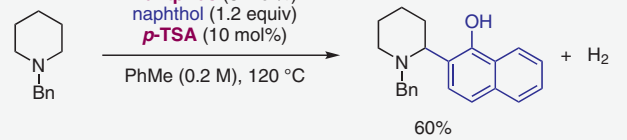
Relative stereochemistry of major diastereomer not established.

Photochemical α-phosphonylation



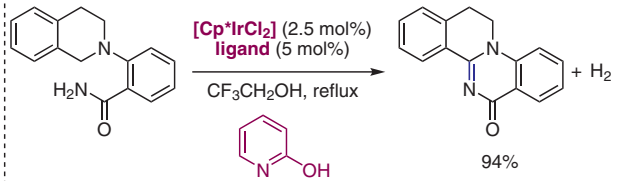
(20f) Lei, *Chem. Commun.* **2018**, *54*, 1659.
See also: (20g) Yang, *Chem. Commun.* **2014**, *50*, 8529.

Thermal cross-coupling



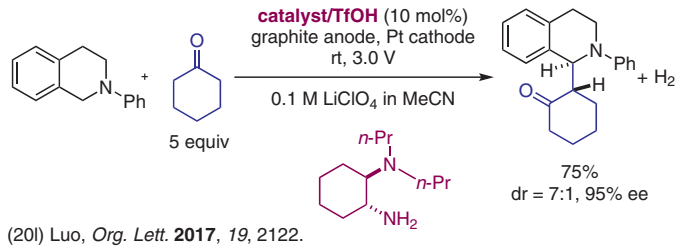
(20h) Zhang, *Org. Lett.* **2020**, *22*, 4781.

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.

Asymmetric electrochemical cross-coupling hydrogen evolution



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

Catalysts

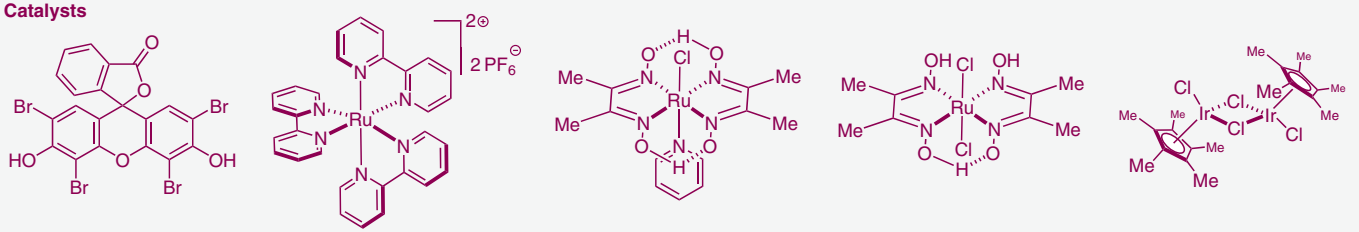


Figure 20 Acceptorless cross-dehydrogenative-coupling (CDC) reactions with hydrogen evolution.[20]

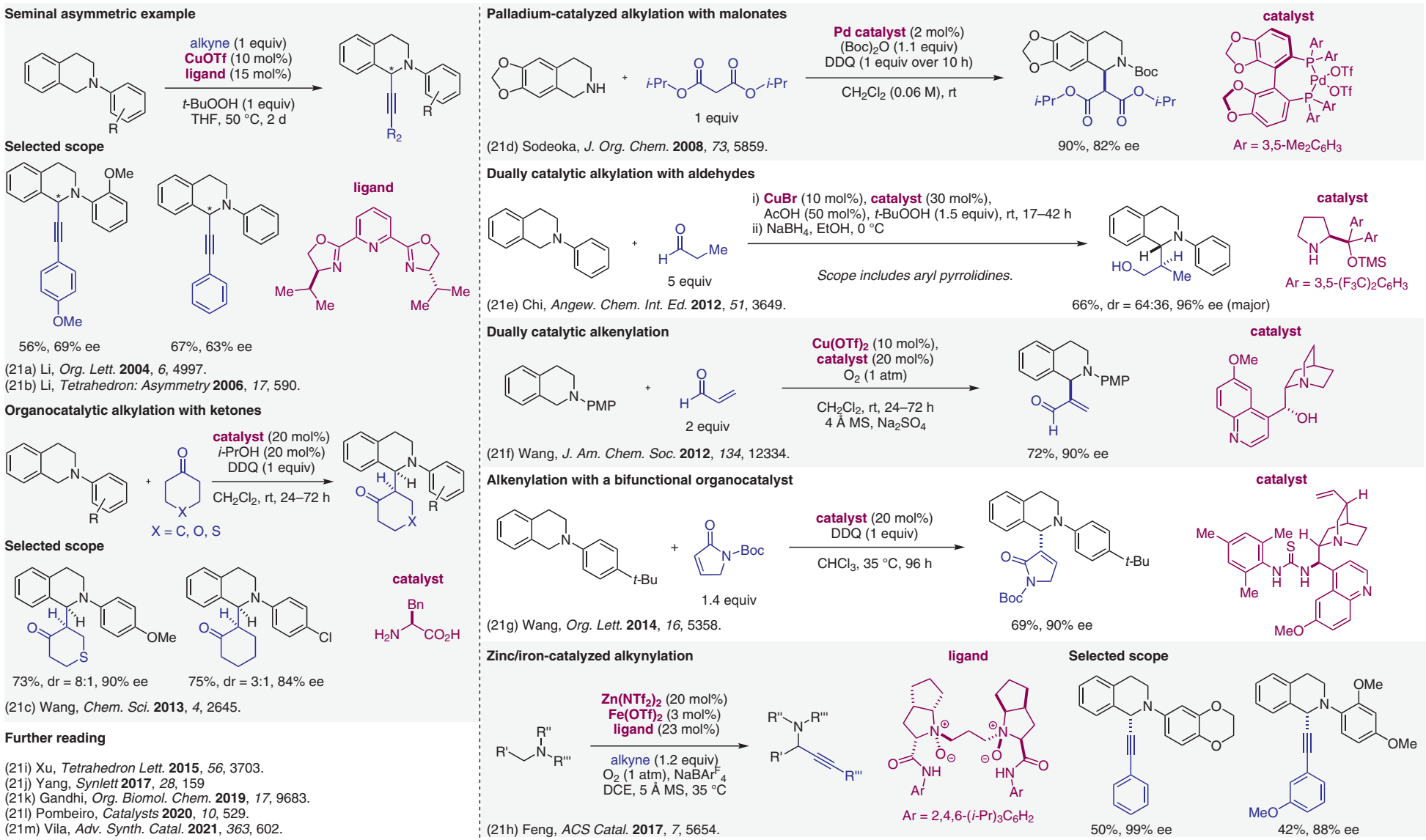
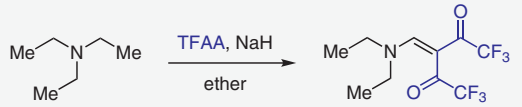


Figure 21 Catalytic enantioselective cross-dehydrogenative-coupling (CDC) reactions.[21]

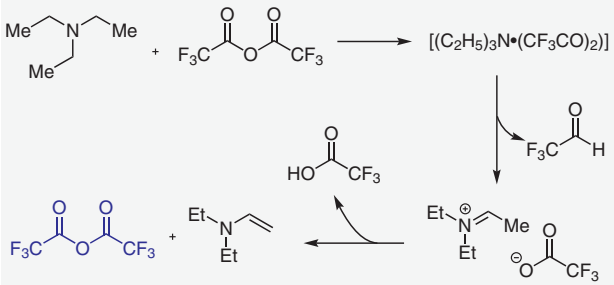
Notable features

- 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



Different mechanisms could account for the formation of the enamine intermediate.

Reaction involves double acylation of the enamine with TFAA.

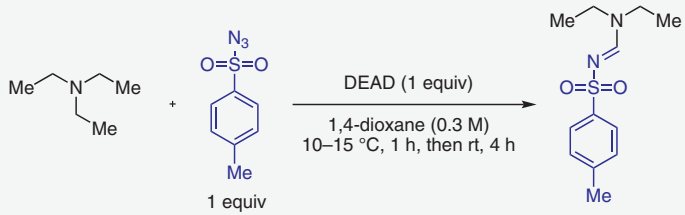
NaH is added to achieve full conversion.

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

Further reading

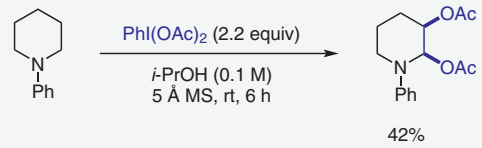
(22k) Archard, *Chem. Eur. J.* **2015**, *21*, 14319
(22l) Zhang, *Synlett* **2017**, *28*, 1630.
(22m) Zhou, *Chem. Commun.* **2017**, *53*, 8770.
(22n) Fan, *Chem. Commun.* **2017**, *53*, 4002.
(22o) Opatz, *Adv. Heterocycl. Chem.* **2018**, *125*, 107.
(22p) Fan, Zhang, *J. Org. Chem.* **2018**, *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



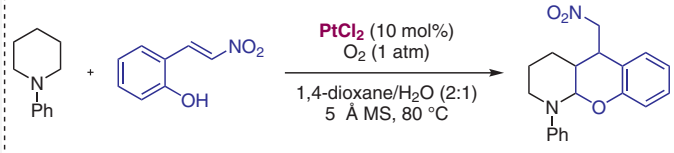
(22b) Weng, *J. Am. Chem. Soc.* **2008**, *130*, 14048.
See also: (22c) Zheng, Wang, *Chem. Commun.* **2009**, *47*, 7372.

α,β-Dioxygenation with DIB



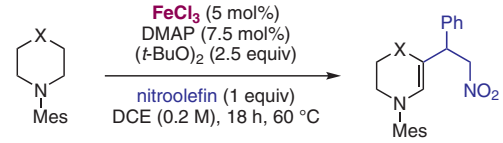
(22d) Liang, *J. Org. Chem.* **2009**, *74*, 7464.

Platinum-catalyzed α,β-difunctionalization



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

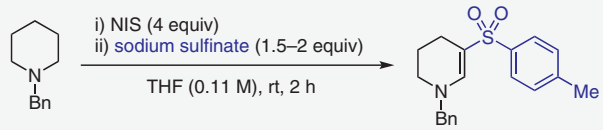
Iron-catalyzed β-alkylation



Applicable to linear amines.

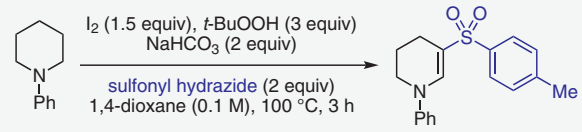
(22f) Kanai, Oisaki, *Org. Lett.* **2013**, *15*, 1918.

Oxidative β-sulfonylation with NIS



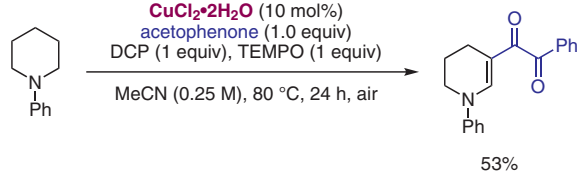
(22g) Talbot, Willis, *Chem. Sci.* **2018**, *9*, 2295.
See also: (22h) Fan, He, *J. Org. Chem.* **2020**, *85*, 15600.

Oxidative β-sulfonylation with iodine

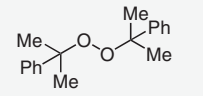


(22i) Xia, Gu, *Eur. J. Org. Chem.* **2021**, 701.

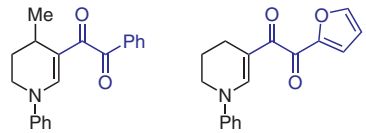
Complex reaction cascade leading to α-keto-enaminones



dicumyl peroxide (DCP)



Selected scope



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

Figure 22 Oxidative β-functionalization.[22]

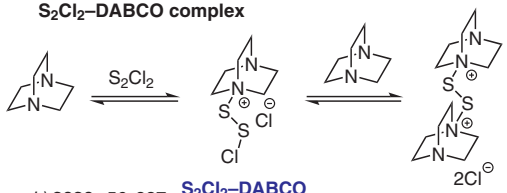
Notable features

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

Reviews

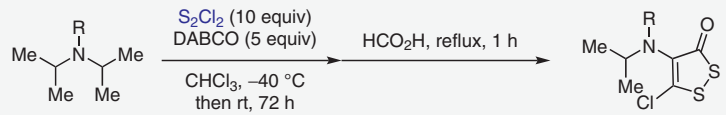
(23a) Rakitin, Rees, *Chem. Rev.* **2004**, *104*, 2617.
(23b) Rakitin, *Chem. Heterocycl. Compd. (Engl. Transl.)* **2020**, *56*, 837.

S_2Cl_2–DABCO complex



S_2Cl_2–DABCO

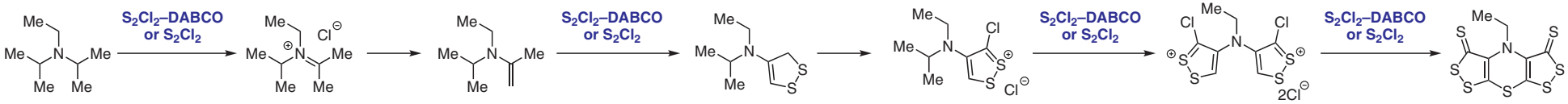
Synthesis of 1,2-dithiol rings



R = CH_2Ph, 80%
$CH_2CH_2CO_2Et$, 94%
CH_2CH_2CN, 91%
$CH_2CH_2N_3$, 77%

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

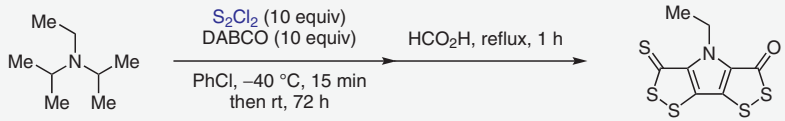
From Hünig's base to bis([1,2]dithiolo)[1,4]thiazine



40%

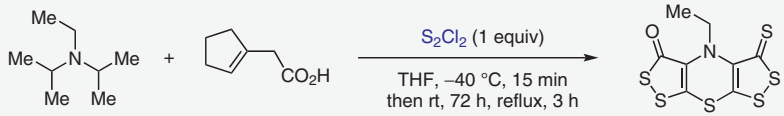
(23c) Rees, Rakitin,Torroba, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 281.

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



25%

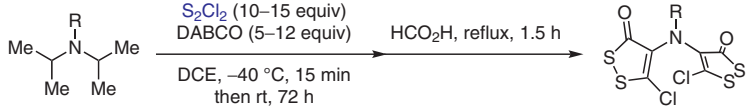
(23d) Rakitin, Rees, Torroba, *Chem. Commun.* **1997**, 879.



0.2 equiv
42%

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

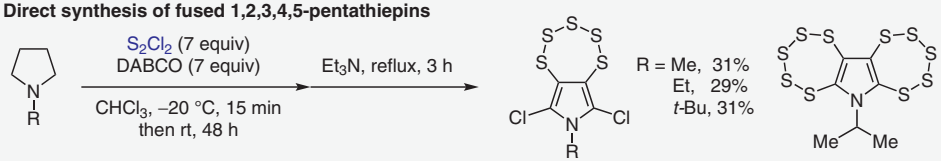
Synthesis of *N,N*-bis(5-chloro-3-oxo[1,2]dithiol-4-yl)amines



R = Et, 19%
$PhCH_2$, 15%
$PhSCH_2CH_2$, 15%
$PhthCH_2CH_2$, 20%

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

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

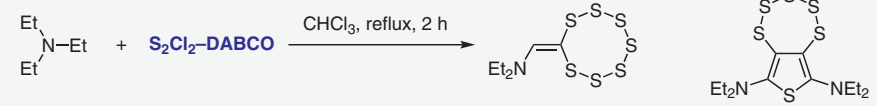


R = Me, 31%
Et, 29%
t-Bu, 31%

31%

(23i) Rakitin, Rees, *Org. Biomol. Chem.* **2005**, *3*, 3496.
See also: (23j) Rakitin, *Russ. Chem. Bull., Int. Ed.* **2006**, *55*, 2081.

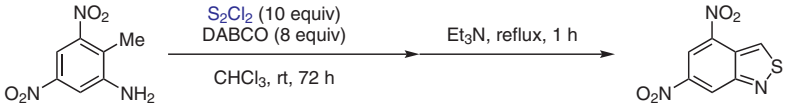
Conversion of Et_3N into a heptathiocane and a thienopentathiepin



0.5 equiv
10%
23%

(23k) Rakitin, Rees, *Org. Lett.* **2003**, *5*, 1939.

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



90%

(23l) Shevelev, *Mendeleev Commun.* **2010**, *20*, 353.

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

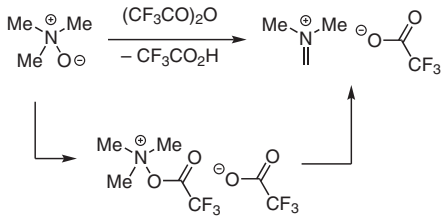
Polonovski–Potier Reaction

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.

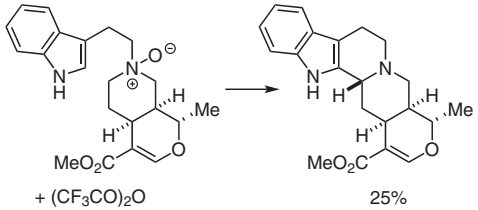
Application to complex natural product synthesis:
(24c) Potier, *J. Am. Chem. Soc.* **1976**, *98*, 7017.
(24d) Fukuyama, *Angew. Chem. Int. Ed.* **2011**, *50*, 4884.

Iminium ion formation



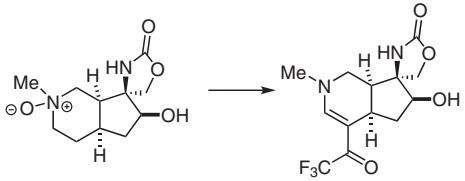
(24e) Potier, *J. Am. Chem. Soc.* **1968**, *90*, 5622.

Application to the Pictet–Spengler reaction



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

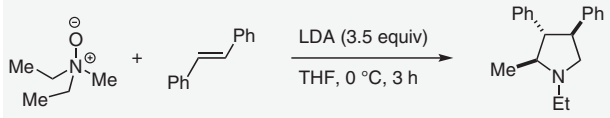
Enamine formation

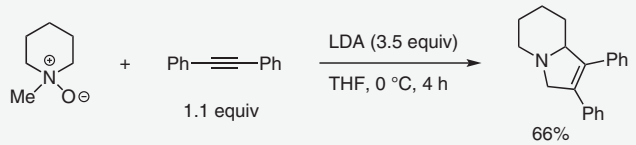


(24g) Kende, *J. Am. Chem. Soc.* **1995**, *117*, 10597.
See also: (24h) Wenkert, *Synth. Commun.* **1973**, *3*, 73.

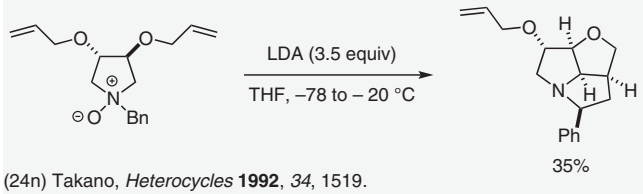
Roussi reaction

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





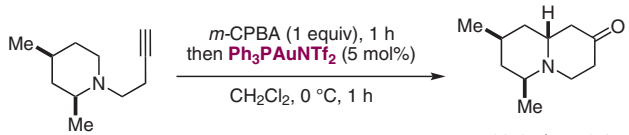
(24i) Roussi, *Chem. Commun.* **1983**, 31. (24j) Roussi, *Heterocycles* **1985**, *23*, 653. (24k) Roussi, *J. Org. Chem.* **1985**, *50*, 2910. (24l) Roussi, *J. Org. Chem.* **1988**, *53*, 3808. See also: (24m) Davoren, *Synlett* **2010**, 2490.



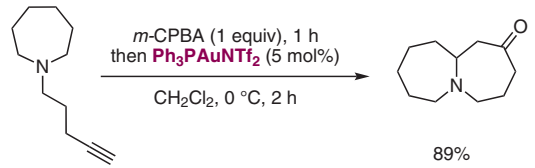
(24n) Takano, *Heterocycles* **1992**, *34*, 1519.
Mechanistic studies: (24o) Williams, *Aust. J. Chem.* **2014**, *67*, 1309.

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

Gold-catalyzed C–H functionalization

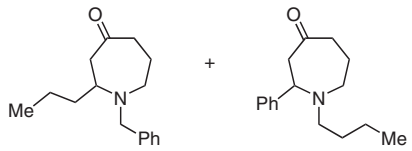


(24q) Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 8394.

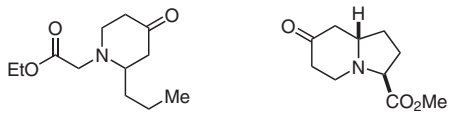


(24r) Zhang, *Chem. Commun.* **2010**, *46*, 3351.

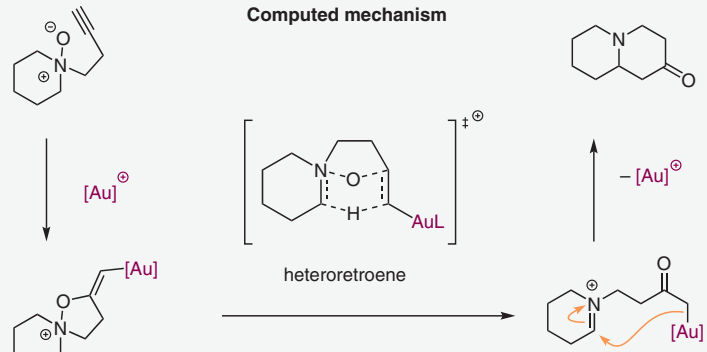
Additional scope



The electronically less activated C–H bond is functionalized preferentially.



Computed mechanism

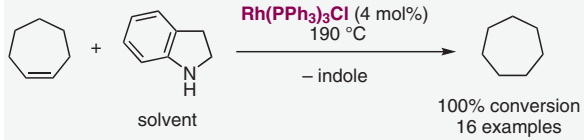


An alternate reaction mechanism involving a 1,6-hydride shift was found to be energetically less favorable.

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

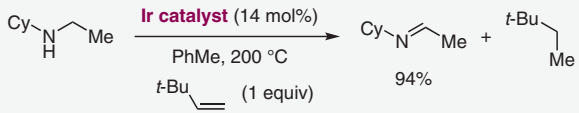
Figure 24 Reactions involving amine *N*-oxides.[24]

Historical precedent

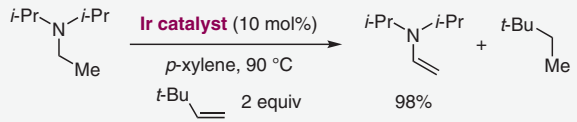


(25a) Nishiguchi, *J. Org. Chem.* **1975**, *40*, 237.
See also: (25b) Otsuka, *J. Chem. Soc., Chem. Commun.* **1979**, 870.
(25c) Murahashi, *J. Chem. Soc., Chem. Commun.* **1985**, 613.

Seminal work



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



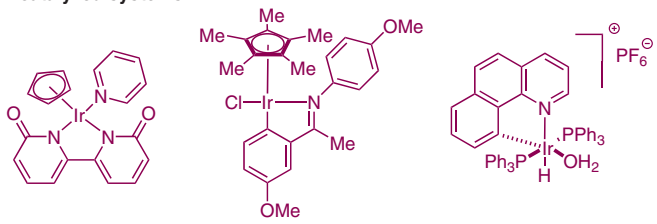
(25e) Knapp, Goldman, *Chem. Commun.* **2003**, 2060.
See also: (25f) Chihara, *J. Catal.* **2005**, *230*, 204.
(25g) Yi, *Organometallics* **2009**, *28*, 947.
(25h) Jensen, *J. Organomet. Chem.* **2009**, *694*, 2854.
(25i) Brayton, *Chem. Commun.* **2014**, *50*, 5987.
(25j) Goldman, *J. Org. Chem.*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

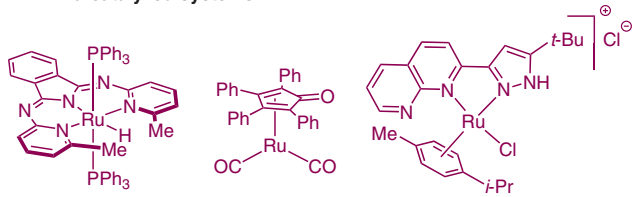
Ir-catalyzed systems



25l, 25m 25n, 25o 25p

(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.

Ru-catalyzed systems

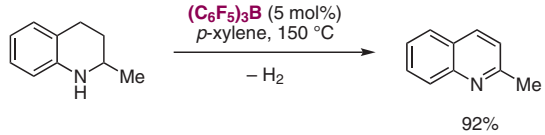


25r, 25s 25t 25u

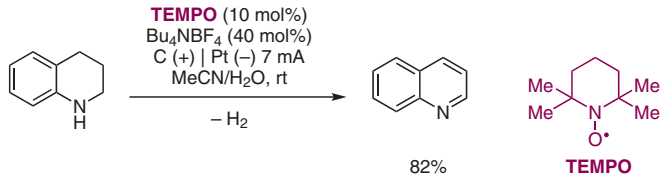
(25r) Szymczak, *J. Am. Chem. Soc.* **2013**, *135*, 16352.
(25s) Paul, Szymczak, *ACS Catal.* **2016**, *6*, 4799.
(25t) Hong, *Adv. Synth. Catal.* **2012**, *354*, 3045.
(25u) Holscher, Bera, *J. Am. Chem. Soc.* **2018**, *140*, 8662.
See also: (25v) Yu, *Organometallics* **2018**, *37*, 584.
(25w)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

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

Acceptorless

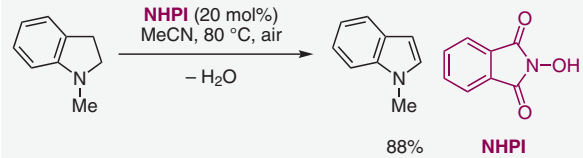


(25x) Kanai, *Angew. Chem. Int. Ed.* **2016**, *55*, 12224.
See also: (25y) Grimme, Paradies, *Angew. Chem. Int. Ed.* **2016**, *55*, 12219.

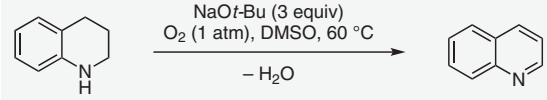


(25z) Lei, *ACS Catal.* **2018**, *8*, 1192.

Aerobic



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



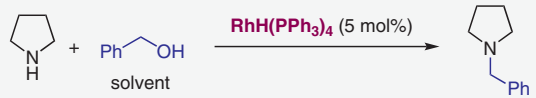
(25ab) Xie, Cai, *J. Org. Chem.* **2020**, *85*, 7501.
See also: (25ac) Song, Wang, *Chem. Eur. J.* **2018**, *24*, 2065.

Figure 25 Dehydrogenation/aromatization.[25]

Notable features

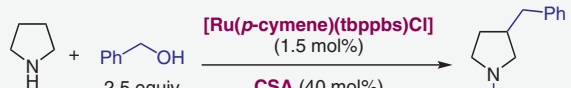
- Powerful tool for the formation of both C–C and C–N bonds.
- No need for prefunctionalizing the amine, alcohol, or aldehyde coupling partners.
- Typically initiates by oxidation of a substrate by the catalyst and ends with reduction of an intermediate to regenerate the catalyst.

Historical precedent

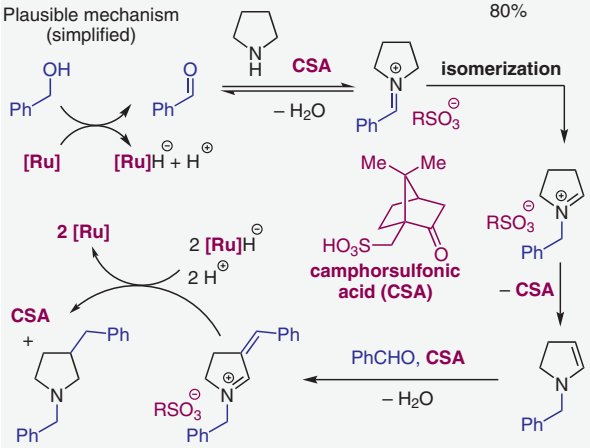


(26a) Grigg, *J. Chem. Soc., Chem. Commun.* **1981**, 611.

Seminal work

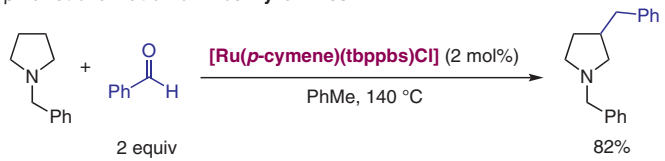


Plausible mechanism (simplified)



(26b) Bruneau, *Adv. Synth. Catal.* **2010**, *352*, 3141.

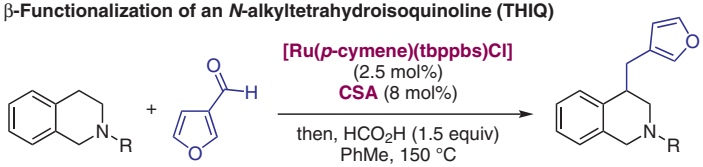
β-Functionalization of *N*-benzyl amines



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.

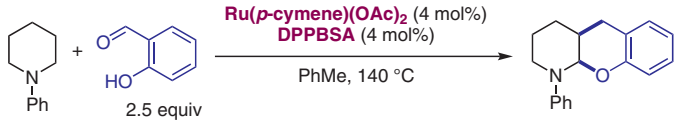
β-Functionalization of an *N*-alkyltetrahydroisoquinoline (THIQ)

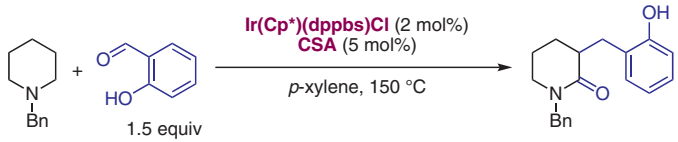


Other aldehydes based on benzofurans, thiofurans, and indoles are also tolerated.

(26d) Bruneau, *J. Org. Chem.* **2012**, *77*, 3674.

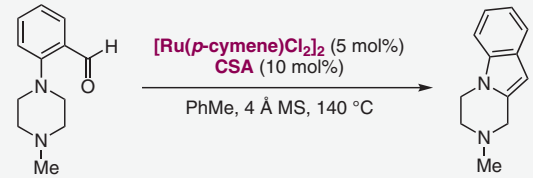
α,β-Difunctionalization of *N*-benzyl amines





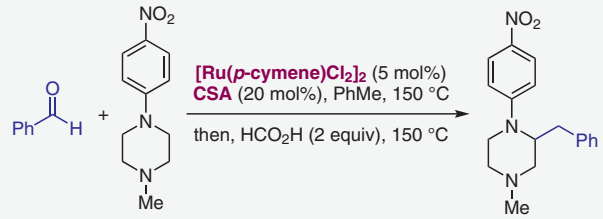
(22k) Bruneau, *Chem. Eur. J.* **2015**, *21*, 14319.

β-Functionalization of piperazines



Aryl substitutents tolerated: F, Cl, Br, CF_3, NO_2.

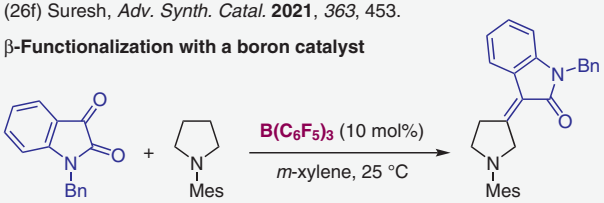
(26e) Suresh, *Chem. Commun.* **2017**, *53*, 10448.



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

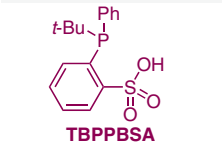
(26f) Suresh, *Adv. Synth. Catal.* **2021**, *363*, 453.

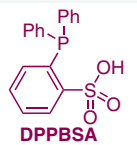
β-Functionalization with a boron catalyst

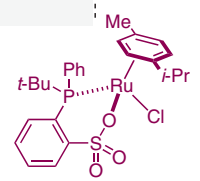


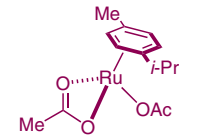
Pyrroles are formed upon heating to 120 °C.

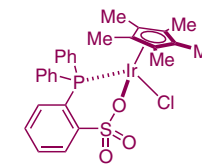
(26g) Yang, Ma, *Org. Lett.* **2020**, *22*, 7797.

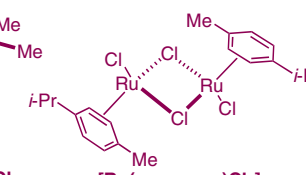












Further reading

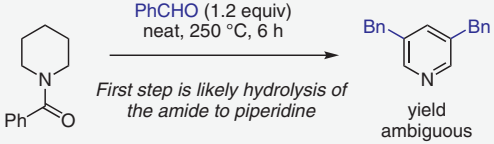
(26h) Bruneau, *Angew. Chem. Int. Ed.* **2012**, *51*, 8876.
(26i) Bruneau, *Green Chem.* **2013**, *15*, 775.
Review on ruthenium-catalyzed hydrogen autotransfer:
(26j) Bruneau, *Top. Organomet. Chem.* **2014**, *48*, 195.
Review on alkylation via hydrogen autotransfer:
(26k) Kempe, *Chem. Rev.* **2019**,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

Figure 26 Hydrogen borrowing.[26]

Notable features

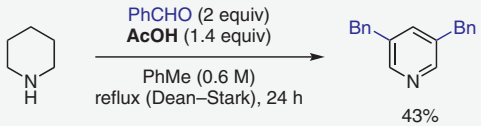
- Simple method for obtaining substituted aromatic heterocycles from their (partially) saturated azacycles.
- Formation of pyrroles from 3-pyrroline or pyrrolidine, and indoles from indoline, are redox-neutral. One equivalent of aldehyde serves as oxidant in the formation of pyridines from piperidine,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

Seminal discovery



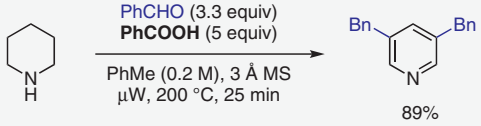
(27a) Rügheimer, *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2186.
(27b) Rügheimer, *Ber. Dtsch. Chem. Ges.* **1892**, *25*, 2421.

Improved procedure



(27c) Poirier, *J. Org. Chem.* **1961**, *26*, 4275.

Further optimization

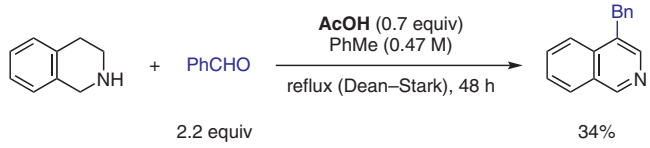


(27d) Seidel, *Tetrahedron Lett.* **2015**, *56*, 3147.

Other selected contributions

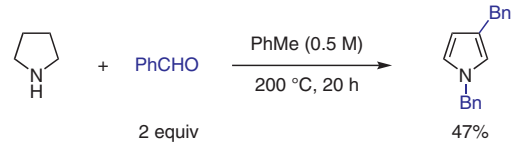
(27e) Burrows, *J. Org. Chem.* **1962**, *27*, 316.
(27f) Sainsbury, *Tetrahedron* **1968**, *24*, 427.
(27g) Dannhardt, *Arch. Pharm.* **1986**, *319*, 977.
(27h) Cook, *Lett. Org. Chem.* **2004**, *1*, 1.
(27i) Toma, *Synth. Commun.* **2009**, *39*, 1871.
(27j) Yu, *Org. Lett.* **2011**, *13*, 6054.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

Isoquinolines from 1,2,3,4-tetrahydroisoquinoline



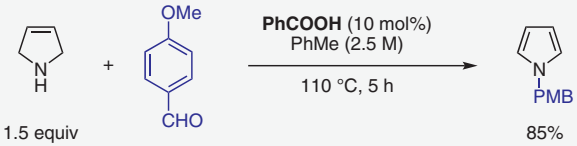
(27l) Burrows, *J. Org. Chem.* **1963**, *28*, 1180.

Pyrroles from pyrrolidine



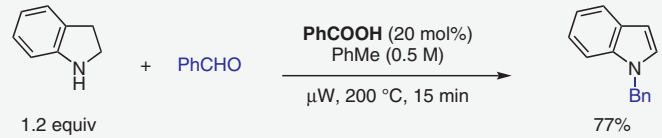
(27m) Oda, *Tetrahedron Lett.* **2007**, *48*, 9159.

Pyrroles from 3-pyrroline



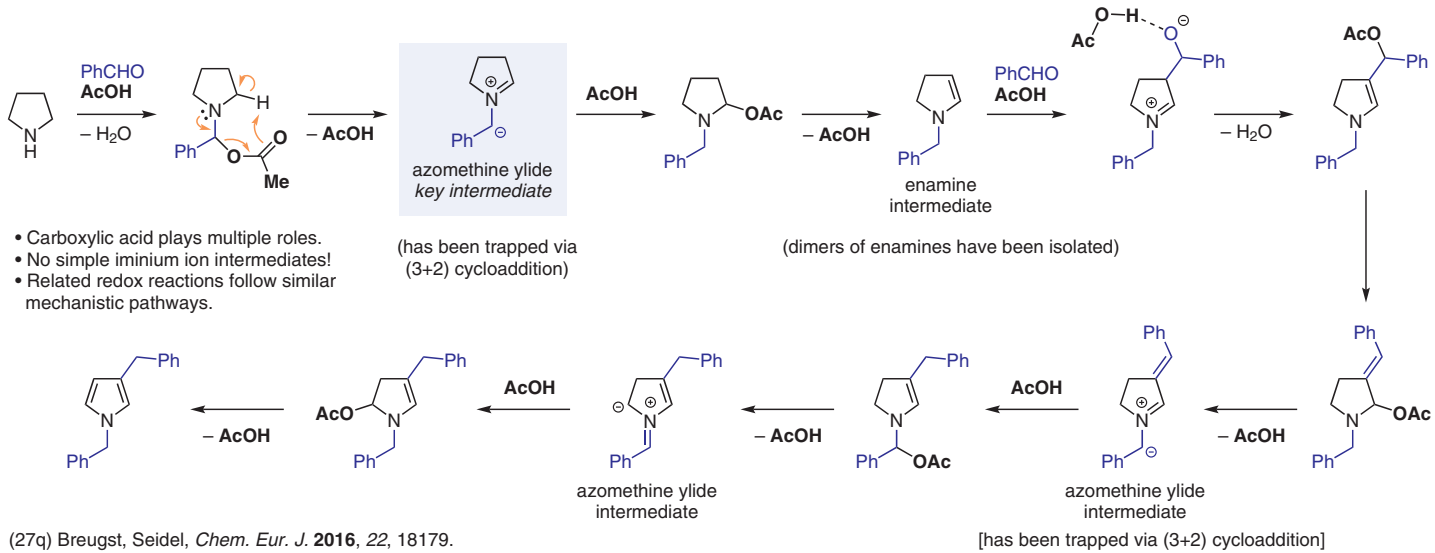
(27n) Tunge, *J. Am. Chem. Soc.* **2009**, *131*, 16626.

Indoles from indoline



(27o) Pan, *Chem. Eur. J.* **2010**, *16*, 13352.
(27p) Seidel, *Org. Lett.* **2011**, *13*, 812.

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



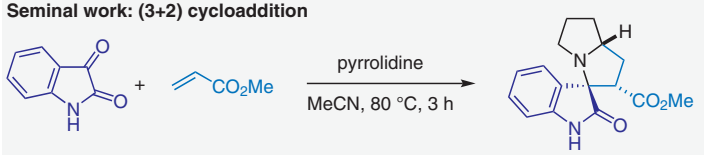
(27q) Breugst, Seidel, *Chem. Eur. J.* **2016**, *22*, 18179.

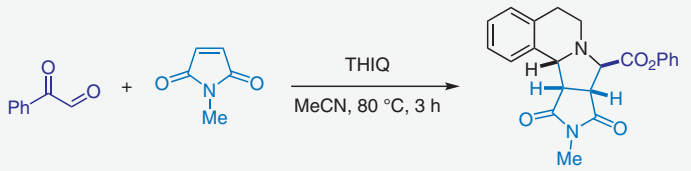
Figure 27 Condensation-based methods involving azomethine ylide intermediates, aromatization.[27]

Notable features

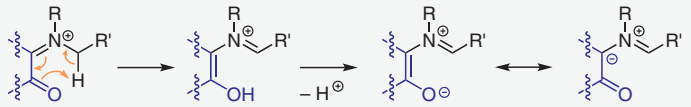
- Azomethine ylides resulting from condensation of a secondary amine with a carbonyl compound undergo pericyclic reactions.
- Redox-neutral method enabling rapid increase of molecular complexity.

Seminal work: (3+2) cycloaddition



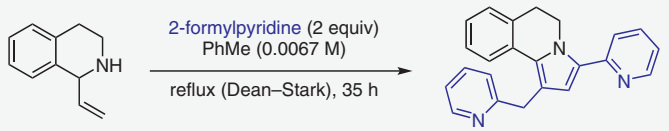


via:



(28a) Grigg, *J. Chem. Soc., Chem. Commun.* **1986**, 602.

Seminal work: 6π-electrocyclization

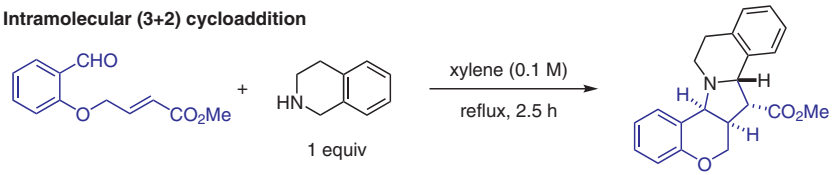


(28b) Grigg, *Tetrahedron* **1990**, *46*, 1599.

Other selected contributions

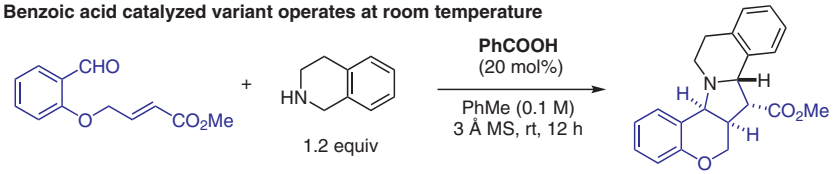
(28j) Risch, *Synthesis* **1996**, 367.
(28k) Miao, *J. Org. Chem.* **2016**, *81*, 11201.
(28l) Wu, *ChemistrySelect* **2017**, *2*, 10762.
(28m) Zanoni, Protti, *Molecules* **2019**, *24*, 1318.

Intramolecular (3+2) cycloaddition



(28c) Grigg, *Tetrahedron* **1990**, *46*, 6449.

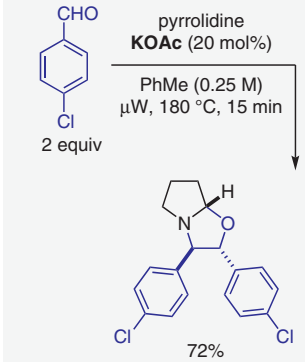
Benzoic acid catalyzed variant operates at room temperature



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

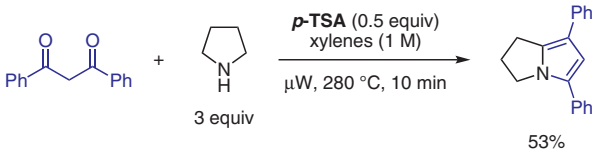
(28d) Seidel, *Org. Lett.* **2014**, *16*, 5910.

Synthesis of bicyclic oxazolidines

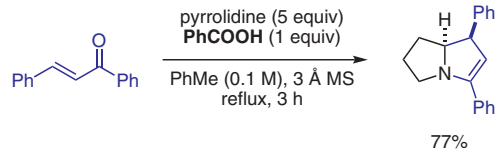


(28e) Hajra, *Chem. Commun.* **2014**, *50*, 2951.

6π-electrocyclizations

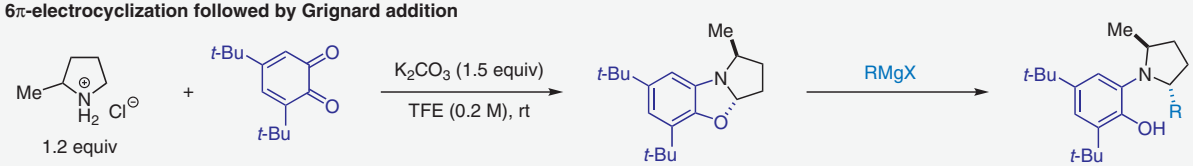


(28f) Seidel, *Tetrahedron Lett.* **2010**, *51*, 2945.



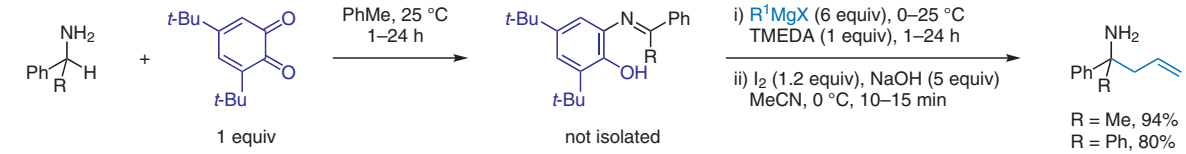
(28g) Seidel, *Chem. Commun.* **2015**, *51*, 10648.

6π-electrocyclization followed by Grignard addition



(28h) Qu, *Org. Lett.* **2015**, *17*, 4758.

Related transformation with primary amines



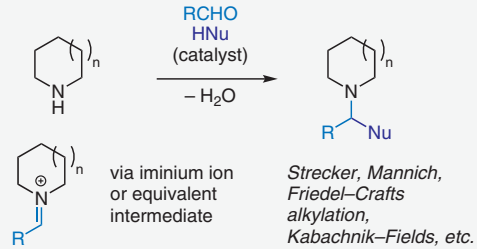
(28i) Dixon, *Chem. Sci.* **2019**, *10*, 3401.

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

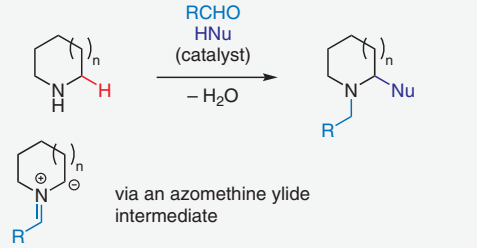
Notable features

- Mirrors classic amine condensation reactions with incorporation of a C–H functionalization step.
- Merges reductive *N*-alkylation with oxidative α-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



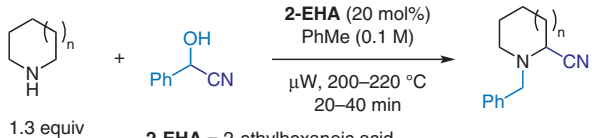
Reviews

(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

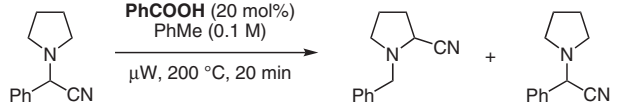


n = 0, 86%, rr = 18:1
n = 1, 61%, rr = 15:1
n = 2, 79%, rr = 11:1

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

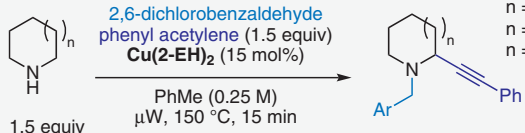
(29a) Seidel, *J. Am. Chem. Soc.* **2012**, *134*, 15305.

Initial observation:
Regioisomers undergo equilibration in the presence of benzoic acid.



84%, rr = 18:1
(thermodynamic equilibrium ratio)
without **PhCOOH**: 91%, rr = 1:5

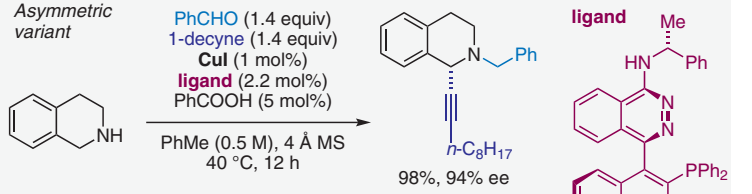
Redox-A3 reaction



n = 0, 81%, rr > 25:1
n = 1, 91%, rr = 7:1
n = 2, 61%, rr = 5:1

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

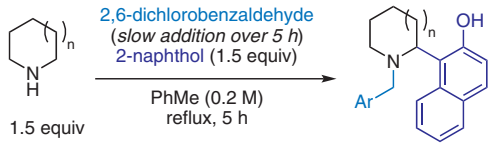
Asymmetric variant



98%, 94% ee

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

Redox-Friedel–Crafts alkylation

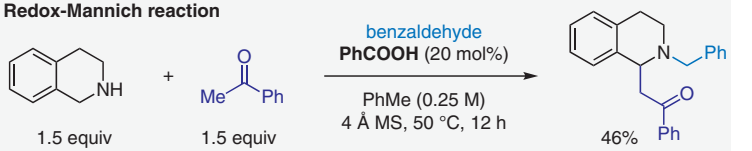


n = 0, 96%, rr > 25:1
n = 1, 16%, rr > 25:1

Other viable nucleophiles: indoles, pyrroles, phenols

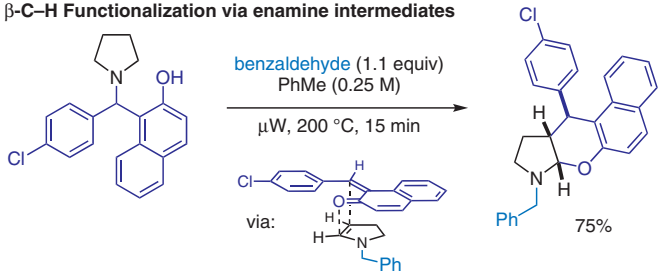
(29f) Seidel, *Org. Lett.* **2014**, *16*, 730.
See also: (29g) Jana, *Asian J. Org. Chem.* **2014**, *3*, 44.

Redox-Mannich reaction



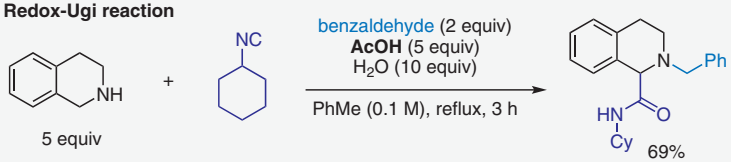
(29k) Seidel, *Org. Lett.* **2014**, *16*, 3158.

β-C–H Functionalization via enamine intermediates



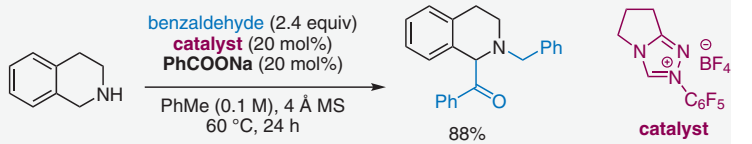
(29h) Seidel, *Angew. Chem. Int. Ed.* **2014**, *53*, 5179. See also:
(29i) Wu, *Org. Lett.* **2016**, *18*, 3526. (29j) Jana, *J. Org. Chem.* **2018**, *83*, 8874.

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



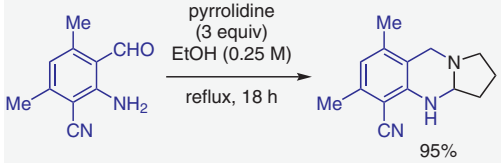
(29o) Wang, *Chin. J. Chem.* **2020**, *38*, 135.

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

Notable features

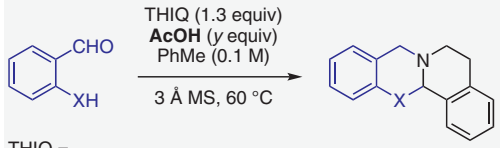
- Powerful method for generating polycyclic amines via redox-neutral ring-annulation of alicyclic amines.
- Azomethine ylides are key intermediates.
- Reactions are often catalyzed/promoted by simple carboxylic acids.
- Water is the only byproduct.

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



THIQ = tetrahydroisoquinoline

X = O, 98%, 3 h (*y* = 1.0)
X = S, 93%, 0.5 h (*y* = 0.1)

(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.

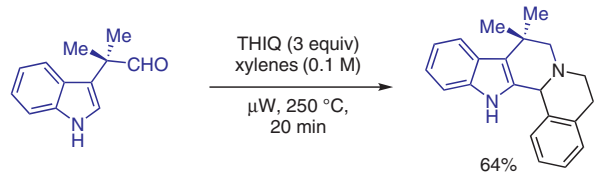
Reviews

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

Other selected contributions

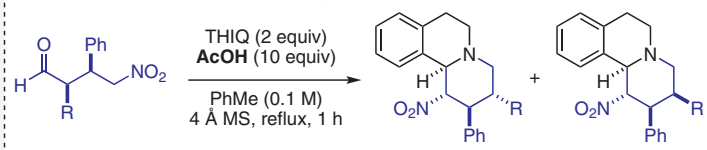
(30s) Seidel, *Org. Lett.* **2017**, *19*, 6424.
(30t) Wu, *Synlett* **2018**, *29*, 1061.
(30u) Chusov, *J. Org. Chem.* **2020**, *85*, 9347.

Redox-Pictet–Spengler reaction



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

Asymmetric redox-annulations of γ-nitroaldehydes

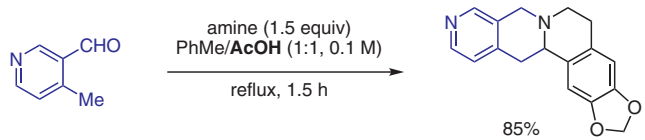


R = Me (96% ee)
R = H (95% ee)

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

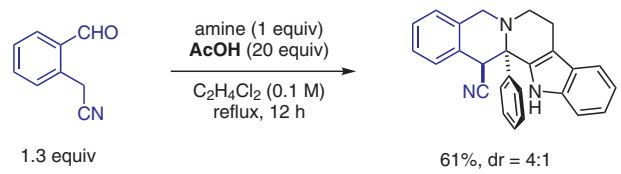
(30k) Breugst, Seidel, *J. Org. Chem.* **2015**, *80*, 9628.

Redox-annulations of heteroaromatic *o*-alkyl aldehydes



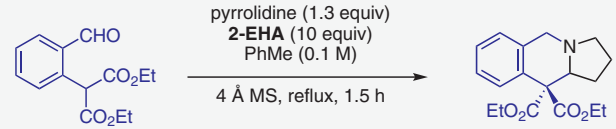
(30m) Seidel, *Org. Lett.* **2017**, *19*, 2841.
See also (30n) Wang, *Adv. Synth. Catal.* **2017**, *359*, 2191.
Catalytic enantioselective variant: (30o) Wang, *Org. Biomol. Chem.* **2017**, *15*, 6474.

Redox-annulations of *o*-cyanomethyl benzaldehydes



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

Redox-annulations of 2-formylaryl malonates

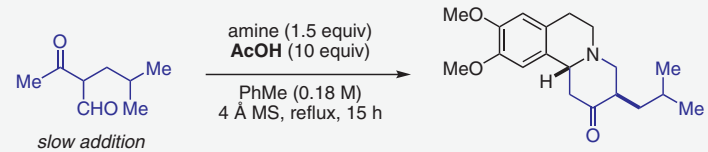


2-EHA = 2-ethylhexanoic acid

76%

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

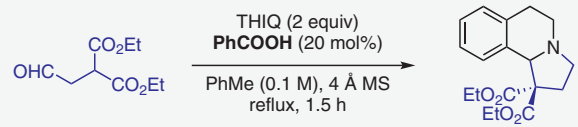
Redox-annulations of β-ketoaldehydes



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

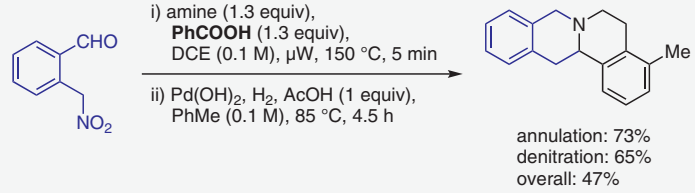
Redox-annulations of 2-(2-oxoethyl)malonates

Formation of 5-membered rings



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

Traceless redox-annulations of *o*-nitromethyl benzaldehyde



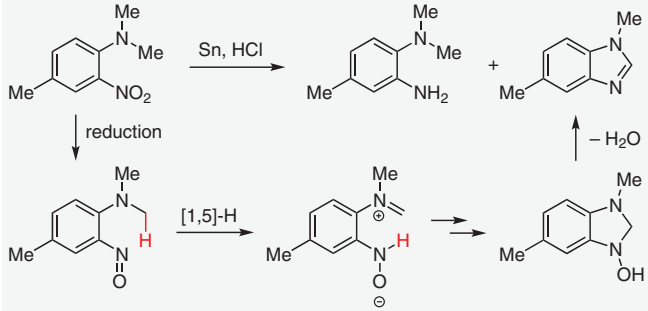
(30r) Seidel, *SynOpen* **2020**, *4*, 123.

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

Notable features

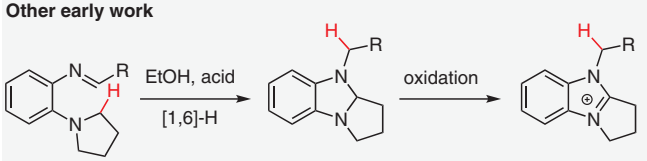
- Redox-neutral method for amine α-C–H bond functionalization involving intramolecular H-transfer followed by cyclization. Can involve oxidation state changes prior to or after the key step.
- Historically categorized under the term "*Tert*-Amino Effect": originally defined as cyclizations of tertiary 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

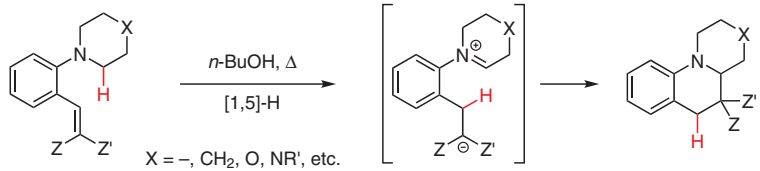


(31c) Meth-Cohn, *Chem. Commun.* **1967**, 1157.
See also: (31d) Volochnyuk, *J. Org. Chem.* **2007**, *72*, 7417.

Reviews

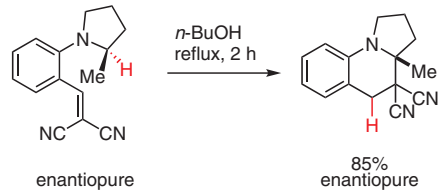
(31q) Meth-Cohn, *Adv. Heterocycl. Chem.* **1972**, *14*, 211.
(31r) Meth-Cohn, *Adv. Heterocycl. Chem.* **1996**, *65*, 1.
(31s) Matyus, *Synthesis* **2006**, 2625.
(31t) Morzherin, *Chem. Heterocycl. Compd. (Engl. Transl.)* **2013**, *49*, 357.

Key contribution



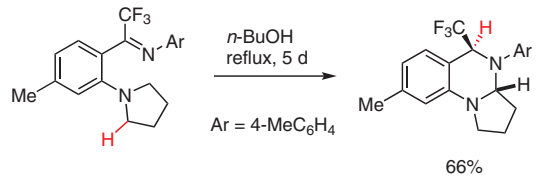
(31e) Reinhoudt, *J. Org. Chem.* **1984**, *49*, 269.
See also: (31f) Reinhoudt, *J. Org. Chem.* **1989**, *54*, 199.

Memory of chirality



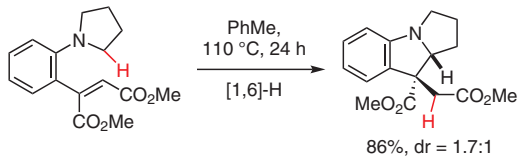
(31g) Reinhoudt, *J. Org. Chem.* **1989**, *54*, 209.

C–N bond formation



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

Formation of a 5-membered ring

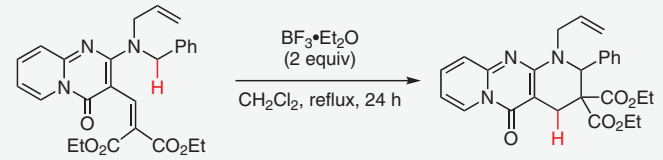


(31e) Reinhoudt, *J. Org. Chem.* **1984**, *49*, 269.
See also: (31j) Reinhoudt, *J. Am. Chem. Soc.* **1983**, *105*, 4775.

Example of higher order H-transfer

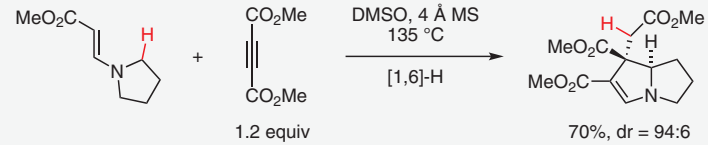
(31n) Matyus, *Synlett* **2008**, 2846.
See also: (31o) Matyus, *Synlett* **2010**, 2109.

Example of a Lewis acid promoted process



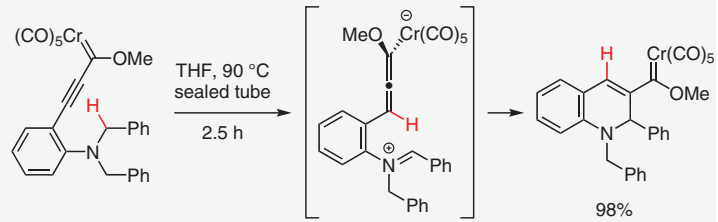
(31i) Noguchi, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3327.

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



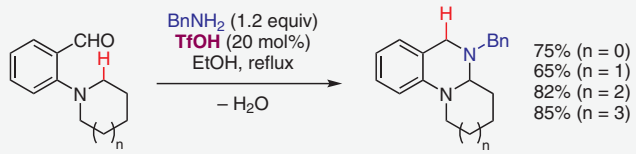
(31p) Barluenga, *Angew. Chem. Int. Ed.* **2008**, *47*, 6594.

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

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.

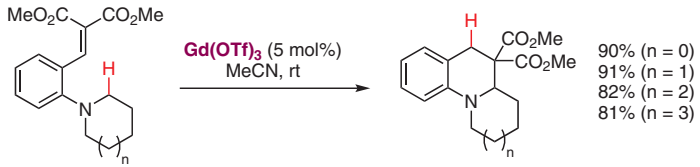
Reviews
(32a) Maulide, *Chem. Eur. J.* **2013**, *19*, 13274.
(32b) Seidel, *Angew. Chem. Int. Ed.* **2014**, *53*, 5010.
(32c) Kim, *Chem. Rec.* **2016**, *16*, 1191.
(32d) Xiao, *Org. Chem. Front.* **2021**, *8*, 1364.

Brønsted acid catalyzed formation of aminals



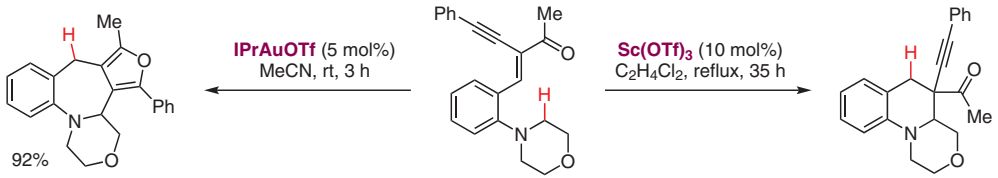
(32e) Seidel, *J. Org. Chem.* **2009**, *74*, 419.
See also (32f) Akiyama, *Chem. Lett.* **2009**, *38*, 524.

Lewis acid catalyzed Reinhoudt reaction



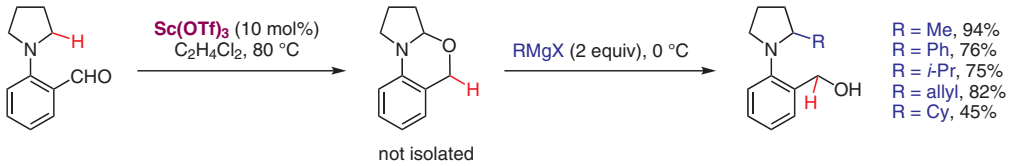
(32g) Seidel, *Org. Lett.* **2009**, *11*, 129.

Divergent reactivity based on the catalyst



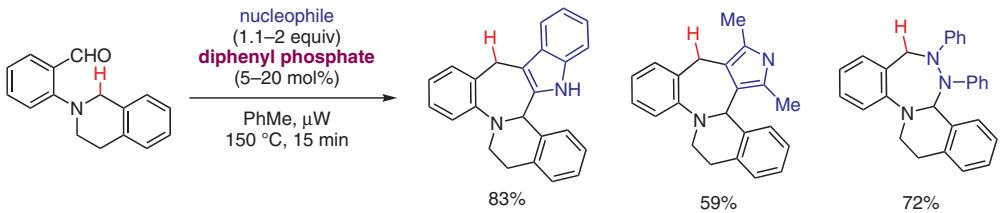
(32h) Zhang, *Chem. Commun.* **2010**, *46*, 6593.

Redox-isomerization/Grignard addition



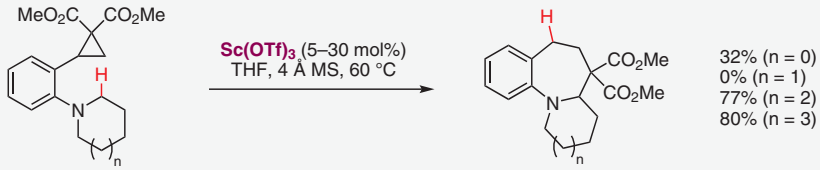
(32i) Maulide, *Angew. Chem. Int. Ed.* **2012**, *51*, 1950.

Annulation with doubly nucleophilic species to access larger rings



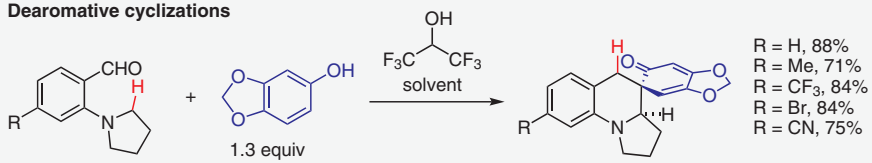
(32j) Seidel, *J. Am. Chem. Soc.* **2011**, *133*, 2100. See also: (32k) Sun, Xu, *Eur. J. Org. Chem.* **2015**, 6727. (32l) Xu, Sun, *J. Org. Chem.* **2015**, *80*, 1155. (32m) Xiao, *Org. Lett.* **2018**, *20*, 138. (32n) Wang, *Chem. Commun.*, **2018**, *54*, 7928. (32o) Wang, Li, *Org. Lett.* **2019**, *21*, 6225. (32p) Xiao, *Org. Lett.* **2019**, *21*, 8904. (32q) Xiao, *J. Org. Chem.* **2019**, *84*, 11839.

Larger rings from donor/acceptor cyclopropanes



(32r) Kim, *Org. Lett.* **2017**, *19*, 1334.

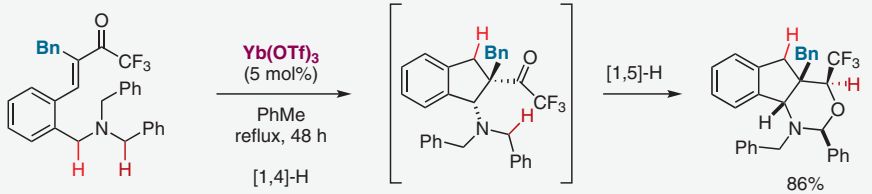
Dearomative cyclizations



Solvent plays a critical role as a weak Brønsted acid/hydrogen bond donor.

(32s) Xiao, *Chem. Sci.* **2018**, *9*, 8253. See also:
(32t) Xiao, *J. Org. Chem.* **2019**, *84*, 1833. (32u) Xiao, *J. Org. Chem.* **2019**, *84*, 13935.

Cascades with two consecutive hydride transfers

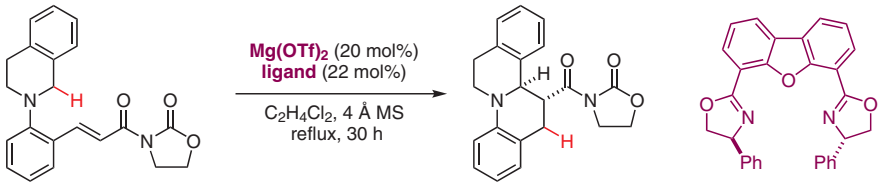


*Divergent reactivity ([1,6]-H/[1,5]-H) is observed when the highlighted **Bn** group is replaced with **H**.*

(32v) Akiyama, *J. Am. Chem. Soc.* **2014**, *136*, 3744.

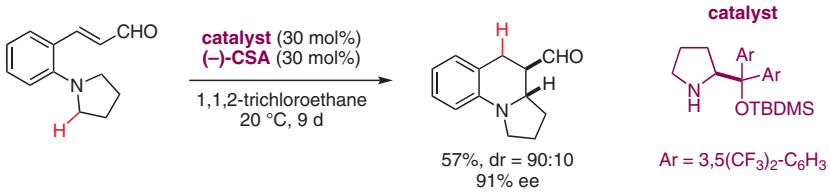
Figure 32 Lewis and Brønsted acid catalyzed internal redox transformations involving [1,*n*]-H transfers.[32]

First highly enantioselective catalytic variant



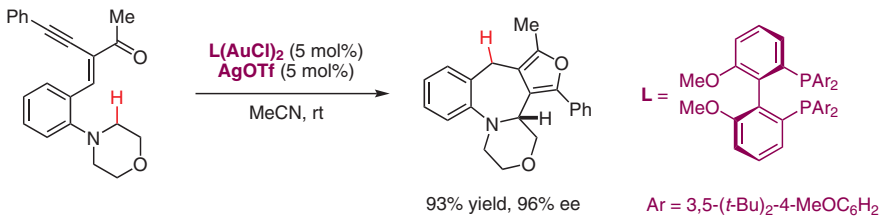
(33a) Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 13226.

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.

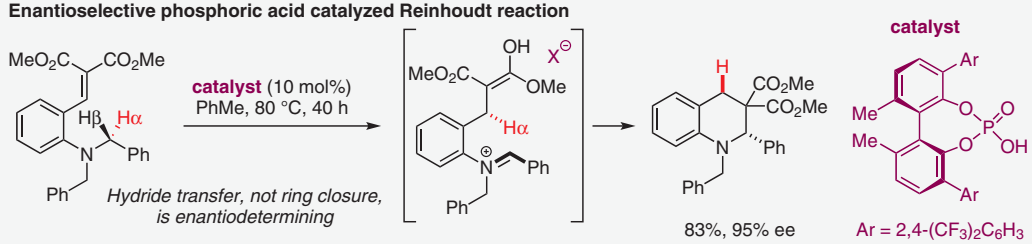
Reviews

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

Additional examples

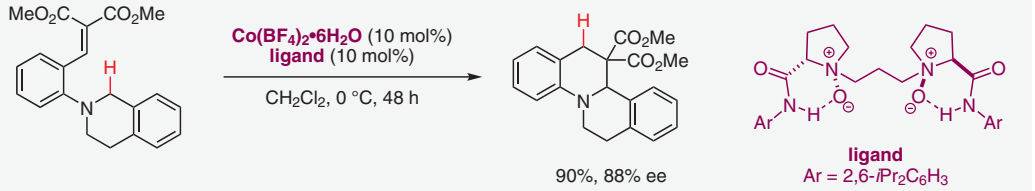
(33n) Feng, *Chem. Eur. J.* **2015**, *21*, 1632.
(33o) Gong, *Chem. Eur. J.* **2013**, *19*, 5232.
(33p) Lin, *Synlett* **2016**, *27*, 546.
(33q) Wen, Xu, *Tetrahedron* **2018**, *74*, 7480.

Enantioselective phosphoric acid catalyzed Reinhoudt reaction



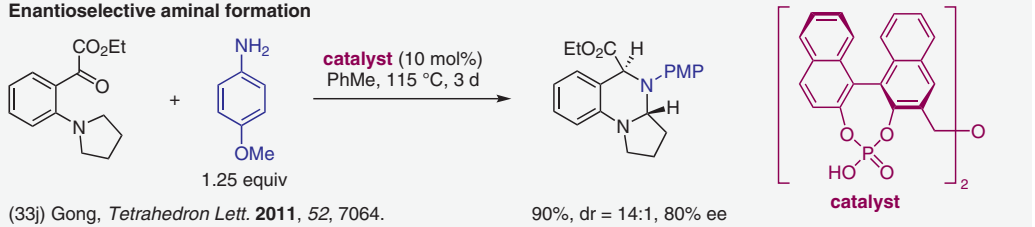
(33g) Akiyama, *J. Am. Chem. Soc.* **2011**, *133*, 6166.

Enantioselective cobalt-catalyzed Reinhoudt reaction



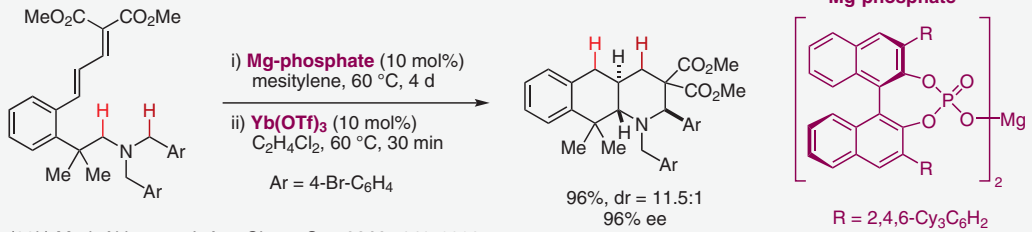
(33h) Feng, *Org. Lett.* **2011**, *13*, 600. See also: (33i) Luo, *Chem. Commun.* **2013**, *49*, 847.

Enantioselective aminal formation



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

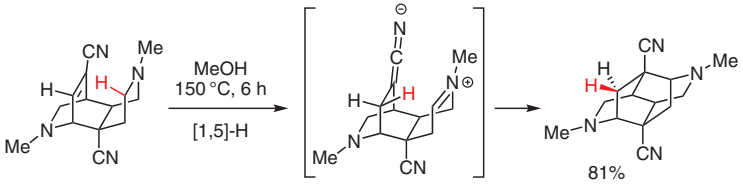
Enantioselective cascades with two consecutive [1,5]-hydride transfers



(33k) Mori, Akiyama, *J. Am. Chem. Soc.* **2018**, *140*, 6203.

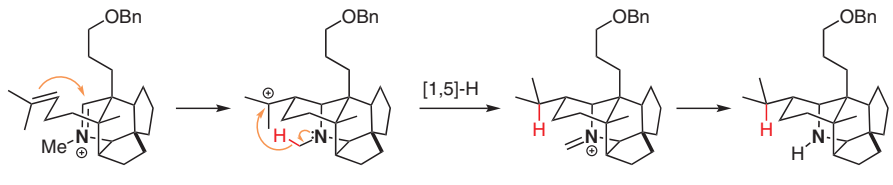
Figure 33 Catalytic enantioselective internal redox transformations involving [1,*n*]-H transfers.[33]

Seminal discovery, formation of a symmetrical diazaditwistane



(34a) Grabowski, *J. Org. Chem.* **1976**, *41*, 3159.

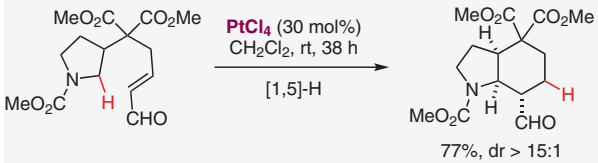
Biomimetic total synthesis of methyl homosecodaphniphyllate, serendipitous discovery and originally proposed mechanism



Per computational analysis, an ene-reaction rather than a stepwise cyclization/hydride transfer process is operative.

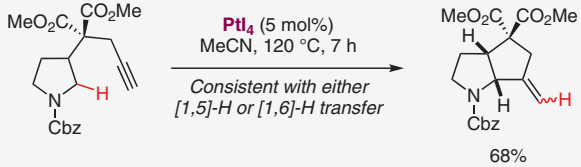
(34b) Heathcock, *J. Org. Chem.* **1992**, *57*, 2544. (34c) Heathcock, *PNAS* **1996**, *93*, 14323. (34d) Tantillo, *Org. Lett.* **2016**, *18*, 4482.

Seminal catalytic example



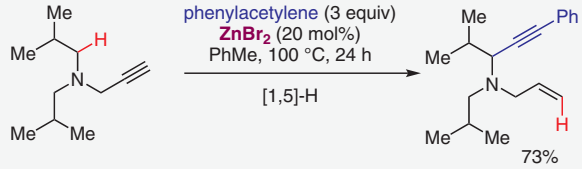
(34e) Sames, *J. Am. Chem. Soc.* **2005**, *127*, 12180.

An alkyne as a hydride acceptor



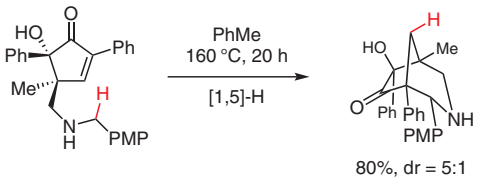
(34f) Sames, *J. Am. Chem. Soc.* **2009**, *131*, 16525.

Intramolecular hydride transfer/external nucleophile



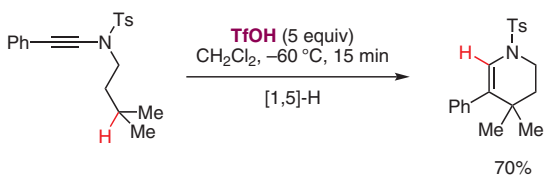
(34g) Nakamura, *J. Am. Chem. Soc.* **2012**, *134*, 2504.
See also: (34h) Ma, *Chem. Sci.* **2019**, *10*, 1796.

Synthesis of bridged bicyclic amines



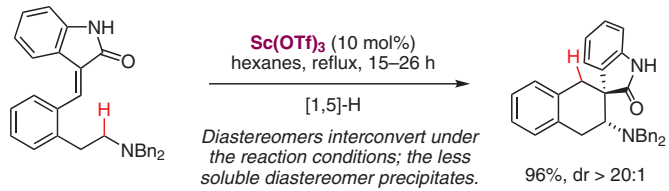
(34i) Frontier, *Org. Lett.* **2016**, *18*, 4896.

Hydride transfer initiating from a remote C–H bond



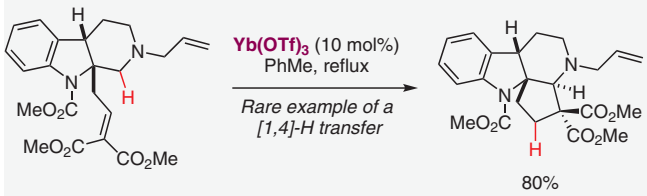
(34j) Evano, *Angew. Chem. Int. Ed.* **2016**, *55*, 4547.

Synthesis of carbacycles



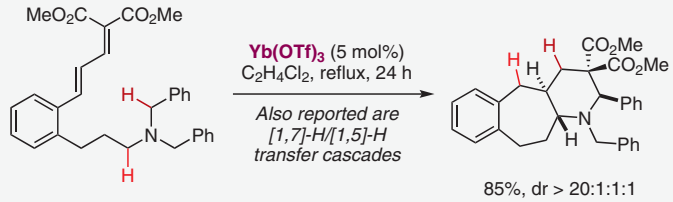
(34k) Mori, *Chem. Lett.* **2018**, *47*, 868.

Alkaloid synthesis



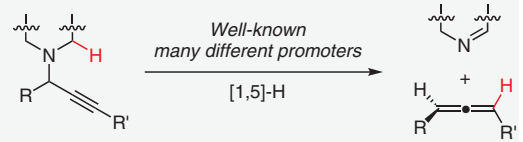
(34l) Anderson, *Angew. Chem. Int. Ed.* **2019**, *58*, 18040.

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



(34m) Mori, *Org. Lett.* **2019**, *21*, 9334. Also see **Figures 32** and **33**.

Synthesis of allenes



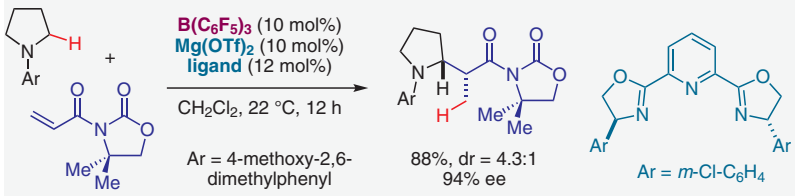
Review: (34n) Ma, *Org. Chem. Front.* **2014**, *1*, 1210.

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

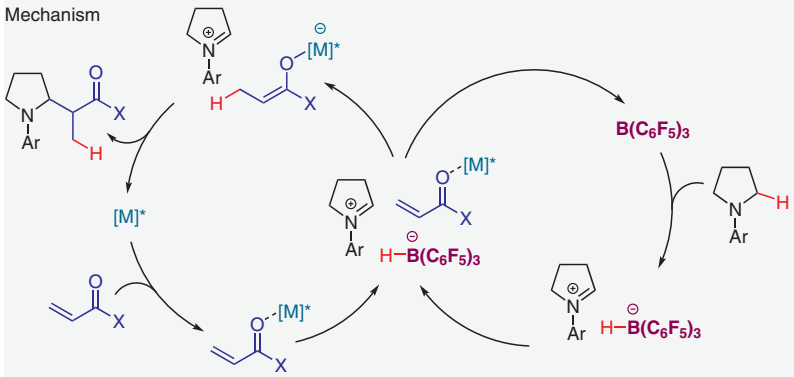
Notable features

- 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

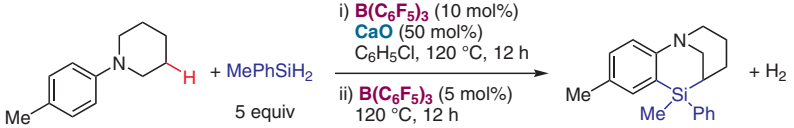


Mechanism



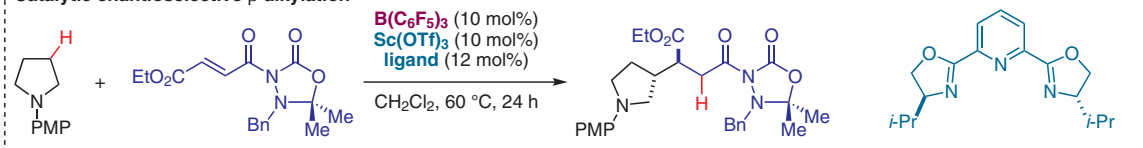
(35a) Wasa, *J. Am. Chem. Soc.* **2018**, *140*, 10593. Seminal work [stoichiometric $B(C_6F_5)_3$]: (35b) Santini, *Eur. J. Inorg. Chem.* **2002**, 3328. (35c) Erker, *Chem. Eur. J.* **2017**, *23*, 4723.

Silylative β-annulation



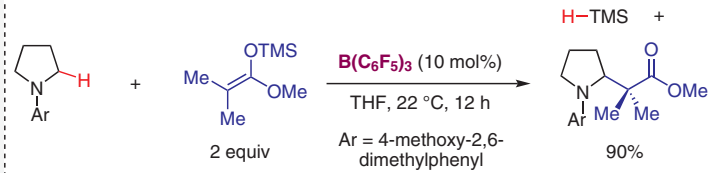
(35d) Chang, *J. Am. Chem. Soc.* **2018**, *140*, 13209.
See also: (35e) Park, Dang, *Org. Chem. Front.* **2020**, *7*, 944.

Catalytic enantioselective β-alkylation



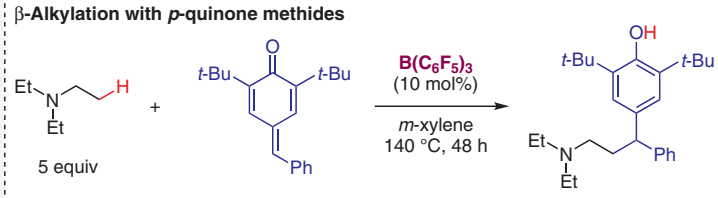
(35f) Wasa, *J. Am. Chem. Soc.* **2021**, *143*, 2441.
Catalytic enantioselective α-alkynylation with alkynylsilanes: (35g) Wasa, *J. Am. Chem. Soc.* **2020**, *142*, 16493.

α-Alkylation with silyl ketene acetals



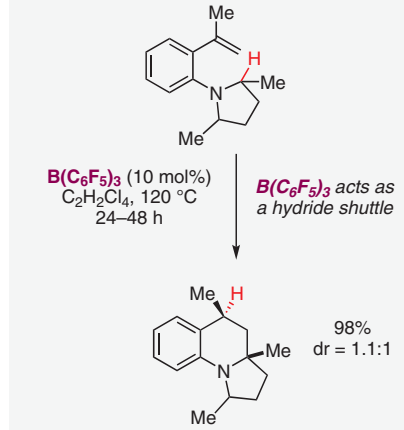
(35h) Wasa, *Org. Lett.* **2019**, *21*, 984.

β-Alkylation with *p*-quinone methides



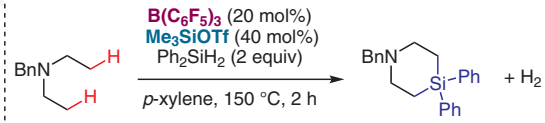
(35i) Yang, Zhao, Ma, *Chem. Commun.* **2019**, *55*, 1217.

Pseudo-intramolecular reaction



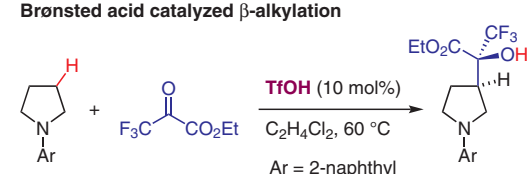
(35j) Paradies, *Chem. Eur. J.* **2018**, *24*, 16287.
See also (35k) Wang, *ACS Catal.* **2019**, *9*, 295.

Silylative ring closure



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

Brønsted acid catalyzed β-alkylation



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

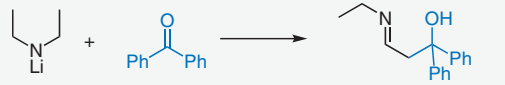
Additional examples: (35n) Wasa, *J. Am. Chem. Soc.* **2019**, *141*, 14570. (35o) Shao, Xiao, *Org. Lett.* **2020**, *22*, 776. (26h) Yang, Ma, *Org. Lett.* **2020**, *22*, 7797. **Reviews**: (35p) Ma, Hou, *Chem. Soc. Rev.* **2021**, *50*, 1945. (35q) Pulis, *Chem. Soc. Rev.* **2021**, *50*, 3720.

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

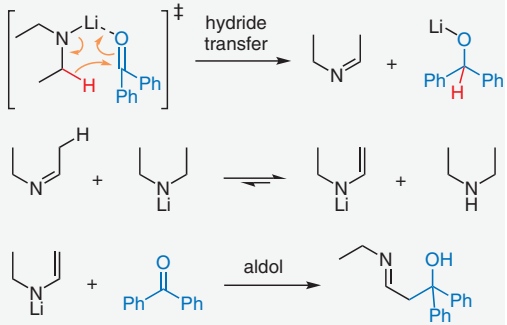
Notable features

- 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

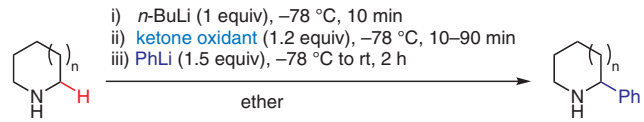


(36b) Wittig, *Chem. Ber.* **1962**, *95*, 2377. See also:
(36c) Wittig, *Liebigs Ann. Chem.* **1971**, *746*, 174.
(36d) Wittig, *Liebigs Ann. Chem.* **1971**, *746*, 185.

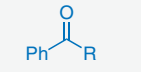
Further reading

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.

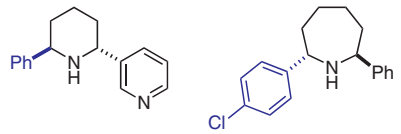
Application to amine α-functionalization (36e) Seidel, *Nat. Chem.* **2018**, *10*, 165.



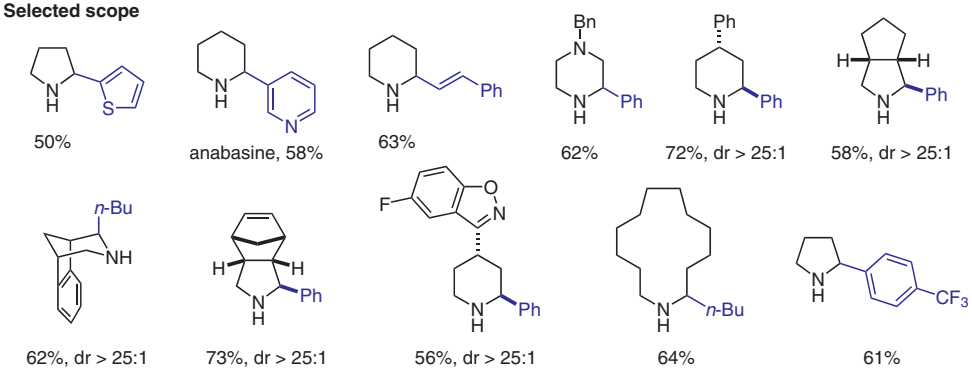
Ketone oxidants:



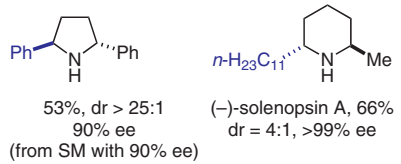
Reactions of α-substituted amines are regioselective for the α'-position:



Selected scope

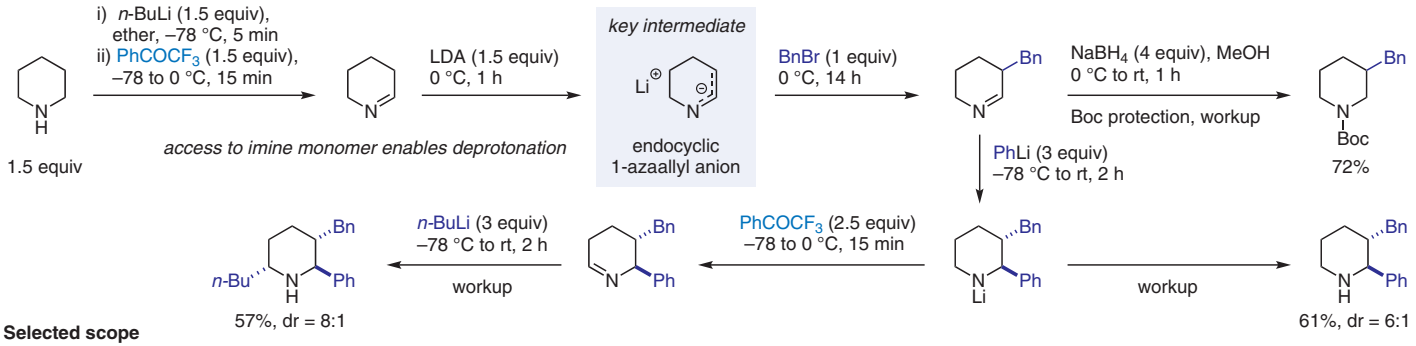


ee of starting material (SM) is maintained:



Other functional groups tolerated:
ArF, ArCl, ArBr, ArOMe, alkyl-$OSiR_3$

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



Selected scope

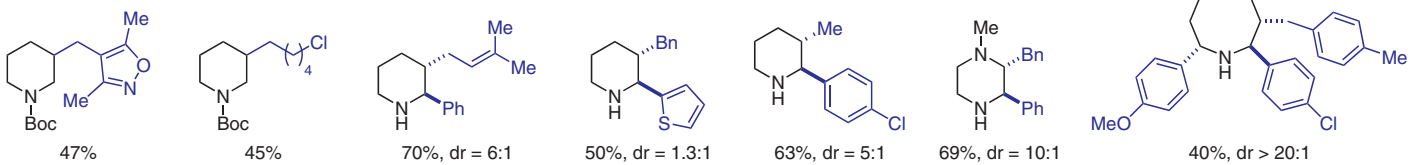
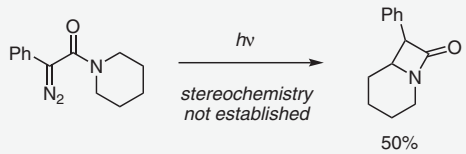


Figure 36 Li-amide-based imine and 1-azaallyl anion generation from unprotected azacycles.[36]

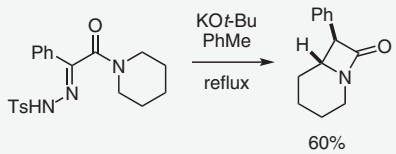
Notable features

- 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.

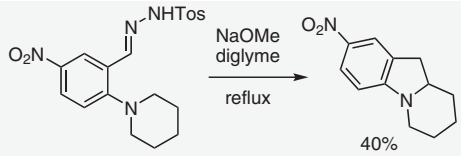
Examples of metal-free, thermal and photochemical reactions



(37a) Corey, *J. Am. Chem. Soc.* **1965**, *87*, 2518. See also: (37b) Hurst, *J. Chem. Soc. C* **1969**, 2093.

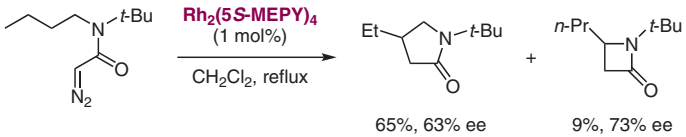


(37c) Winkler, *J. Org. Chem.* **1998**, *63*, 9628.

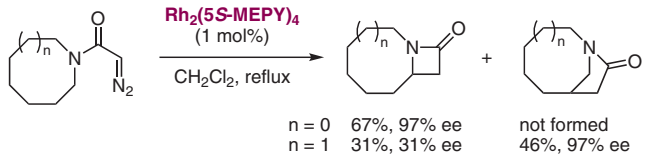


(37d) Garner, *Tetrahedron Lett.* **1968**, *9*, 221. See also: (37e) Kehler, *Synthesis* **2010**, 4287. (37f) Fillion, *Chem. Eur. J.* **2012**, *18*, 68.

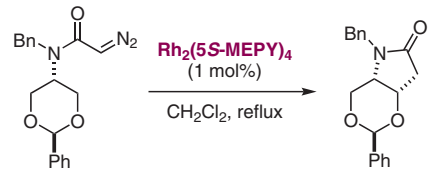
Pioneering catalytic enantioselective intramolecular variants



(37g) Doyle, *Tetrahedron Lett.* **1992**, *33*, 7819. See also: (37h) Doyle, *J. Am. Chem. Soc.* **1993**, *115*, 9968. (37i) Hashimoto, *Synlett* **1994**, 1031.

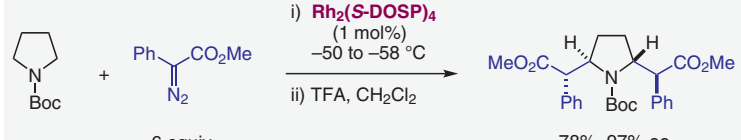


(37j) Doyle, *Synlett* **1995**, 1075.



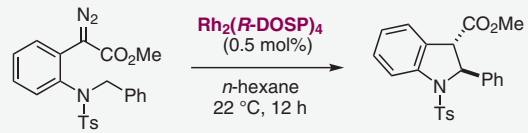
(37k) Doyle, *Adv. Synth. Catal.* **2002**, *344*, 91.

Pioneering catalytic enantioselective intermolecular variants



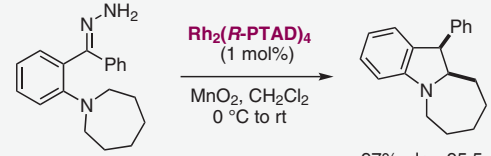
(37l) Davies, *J. Am. Chem. Soc.* **1999**, *121*, 6509. See also: (37m) Winkler, *J. Am. Chem. Soc.* **1999**, *121*, 6511. (37n) Davies, *Org. Lett.* **2001**, *3*, 1773. (37o) Davies, *J. Am. Chem. Soc.* **2003**, *125*, 6462. (37p) Davies, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1799.

Catalytic enantioselective synthesis of indolines



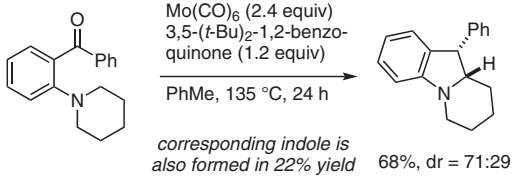
(37q) Wirth, *Eur. J. Org. Chem.* **2017**, 1889.

Simple hydrazones as carbene precursors



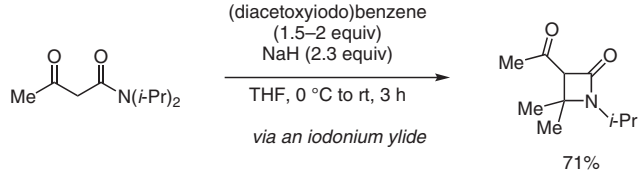
(37r) Shaw, *Angew. Chem. Int. Ed.* **2018**, *57*, 15213.

Deoxygenative cyclization



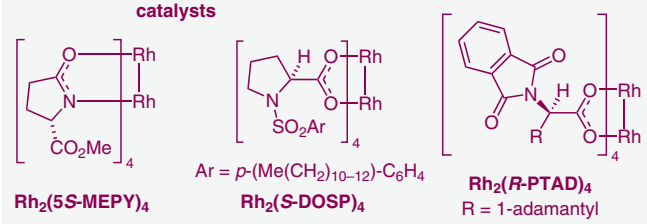
(37s) Asako, Takai, *J. Am. Chem. Soc.* **2019**, *141*, 9832.

Cyclization without pre-functionalization



(37t) Maulide, *Chem. Eur. J.* **2015**, *21*, 1449.

catalysts

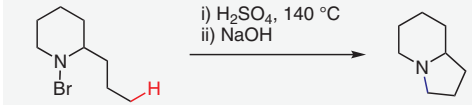


Additional examples: (37u) Doyle, *Tetrahedron Lett.* **1996**, *37*, 1371. (37v) Sulikowski, *Tetrahedron* **1997**, *53*, 16521. (37w) Sulikowski, *Tetrahedron Lett.* **1999**, *40*, 8035. (37x) Compain, *Org. Lett.* **2006**, *8*, 4493. (37y) Compain, *Tetrahedron Lett.* **2007**, *48*, 8531. (37z) 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.[37]

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

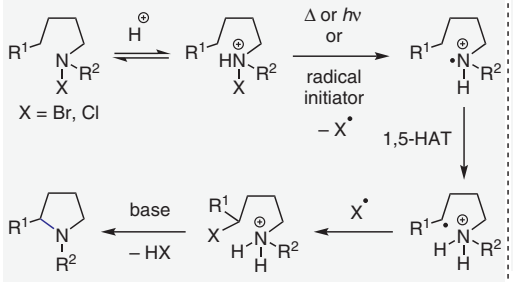
Seminal discovery



(38a) Hofmann, *Chem. Ber.* **1883**, *16*, 558.

(38b) Löffler, Freytag, *Chem. Ber.* **1909**, *42*, 3427.

General proposed mechanism

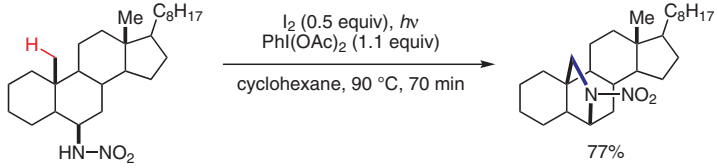


Further reading

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

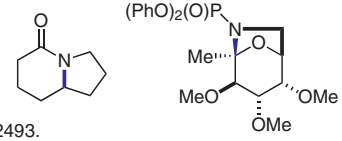


Key features
No preformed *N*-haloamine required as N–I bond is generated in situ.

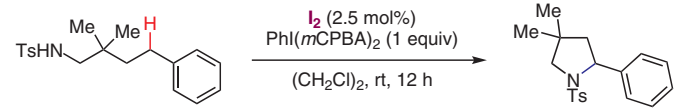
Circumventing harsh reaction conditions by employing electron-deficient protecting groups [e.g., CN, NO_2 and $P(O)(OEt)_2$].

(38c) Suárez, *Tetrahedron Lett.* **1985**, *26*, 2493.
(38d) Suárez, *J. Org. Chem.* **2003**, *68*, 1012.

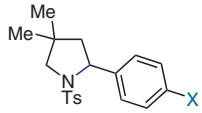
Extension to other systems



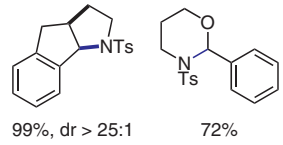
Catalytic HLF cyclization using a hypervalent iodine oxidant



Selected scope

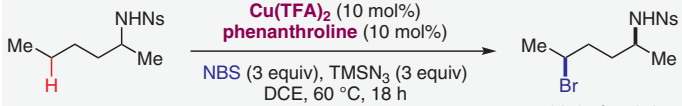


X	% Yield
F	86
Br	82
Me	93
OMe	82
CCPh	77

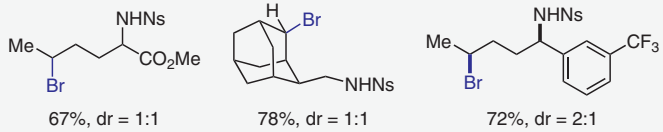


(38e) Muñiz, *Angew. Chem. Int. Ed.* **2015**, *54*, 8287.

δ C–H bromination via an interrupted HLF cyclization

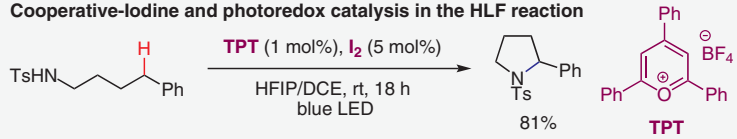


Selected scope

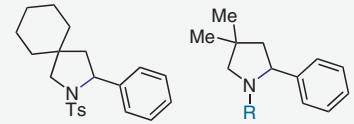


(38f) Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 306.

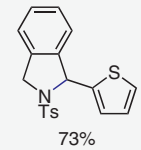
Cooperative-Iodine and photoredox catalysis in the HLF reaction



Selected scope

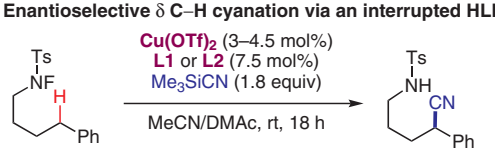


R	% Yield
Ms	92
Ns	60
SES	52
COPh	82
$COCF_3$	70



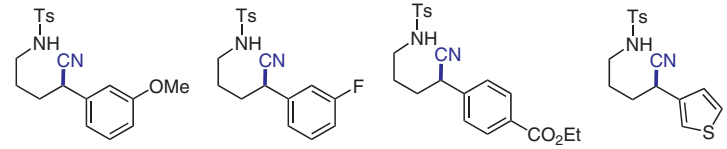
(38g) Reiher, Muñiz, *Angew. Chem. Int. Ed.* **2017**, *56*, 8004.

Enantioselective δ C–H cyanation via an interrupted HLF cyclization

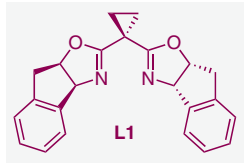


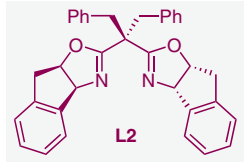
(38h) Nagib, *Chem* **2019**, *5*, 3127.

Selected scope

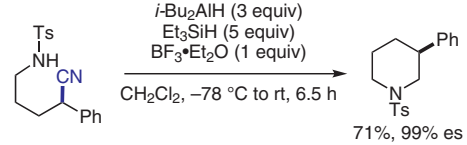


(^**L1** was used, *L2 was used)





Access to chiral β-arylpiperidine motifs



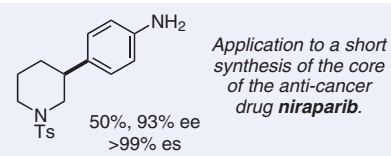
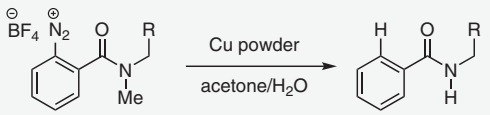


Figure 38 Hofmann–Löffler–Freytag (HLF) reaction.[38]

Notable features

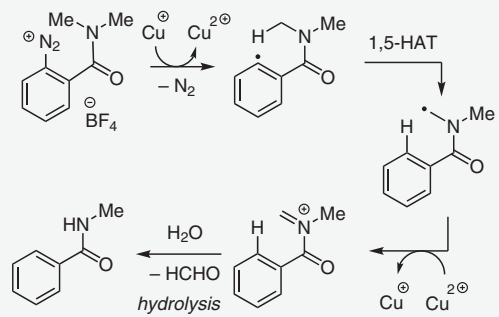
- HAT reactivity dependent on BDE and bond strength.
- Energy difference between C(sp^2) and C(sp^3) radicals favor HAT from an alkyl C–H to an aryl/vinyl C–H.
- HAT mediated by C-centered radicals are rarer than their heteroatom counterparts.

Seminal discovery



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

Proposed mechanism of the Cu(I)-catalyzed process

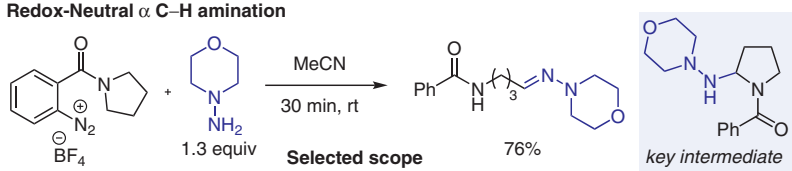


(39b) Cohen, *Tetrahedron* **1966**, *22*, 1527.
See also: (39c) Cohen, *J. Am. Chem. Soc.* **1968**, *90*, 6866.

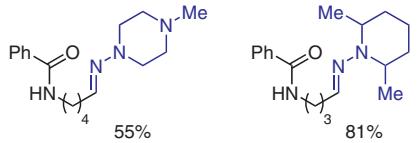
Further reading

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 α C–H amination



Selected scope



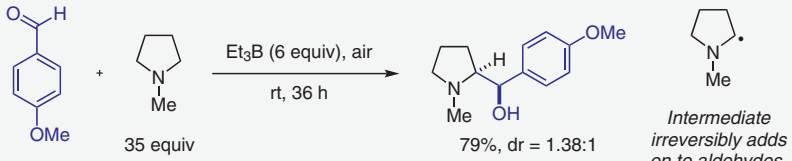
R	% Yield
Me	86
Ph	42

55% 81%

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

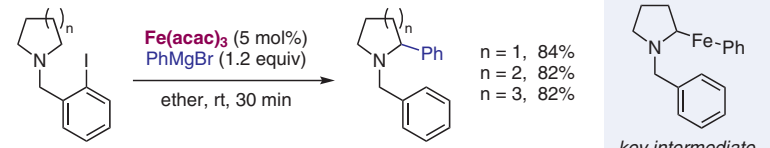
(39d) Maulide, *Org. Lett.* **2016**, *18*, 345.

Radical hydroxylation of C–H bonds

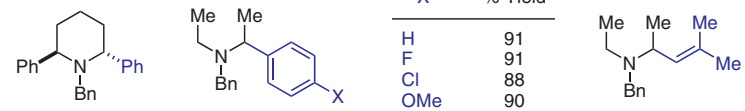


(39i) Yoshimitsu, Nagaoka, *J. Am. Chem. Soc.* **2005**, *127*, 11610.

Iron-catalyzed α-amino arylation



Other substrate scope

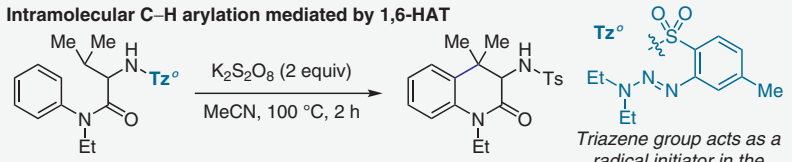


X	% Yield
H	91
F	91
Cl	88
OMe	90

40%, dr = 1.7:1 69%

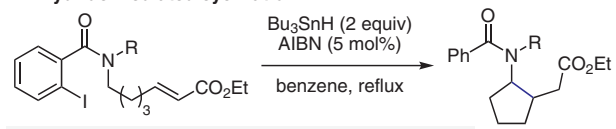
(39j) Nakamura, *J. Am. Chem. Soc.* **2010**, *132*, 5568.

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

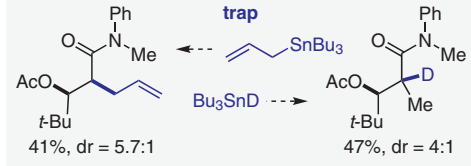


(39k) Fu, *Sci. Rep.* **2016**, *6*, 19931.

Tin hydride mediated cyclization



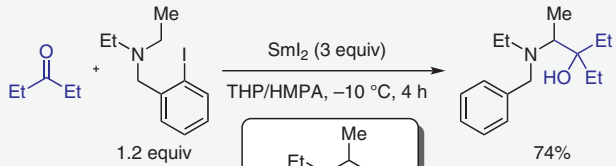
Extension to intermolecular trapping of radicals



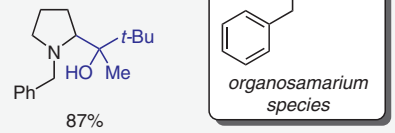
R	% Yield
n-Bu	43
Bn	38
Cy	27

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

Coupling to carbonyls using samarium iodide

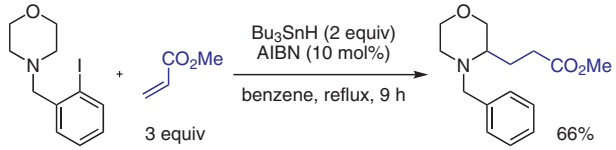


Selected scope

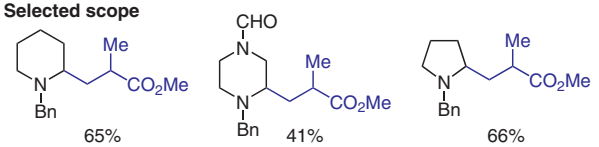


(39g) Ito, *J. Org. Chem.* **1992**, *57*, 793.

Extension to intermolecular α-C–H alkylation



Selected scope



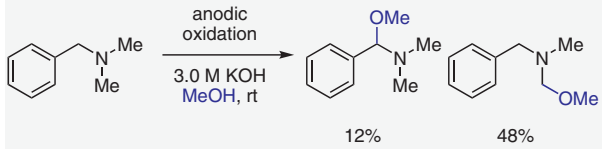
(39h) Undheim, *Tetrahedron* **1994**, *50*, 13697.

Figure 39 Miscellaneous radical-based methods.[39]

Notable features

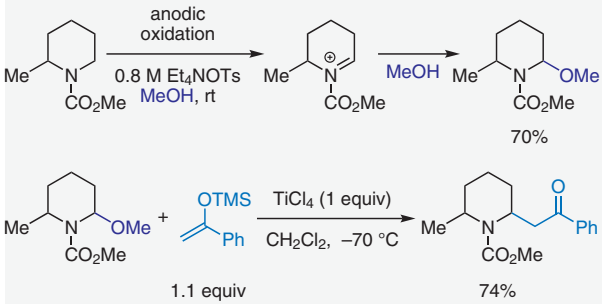
- Obviates the need for chemical oxidants.
- Shono oxidation involves a formal hydride transfer occurring through an electron transfer/proton transfer/electron transfer sequence.
- Electroauxilliaries can be used to direct regioselectivity and lower the oxidation potential, broadening the scope.

Early work



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

Landmark study: Shono oxidation

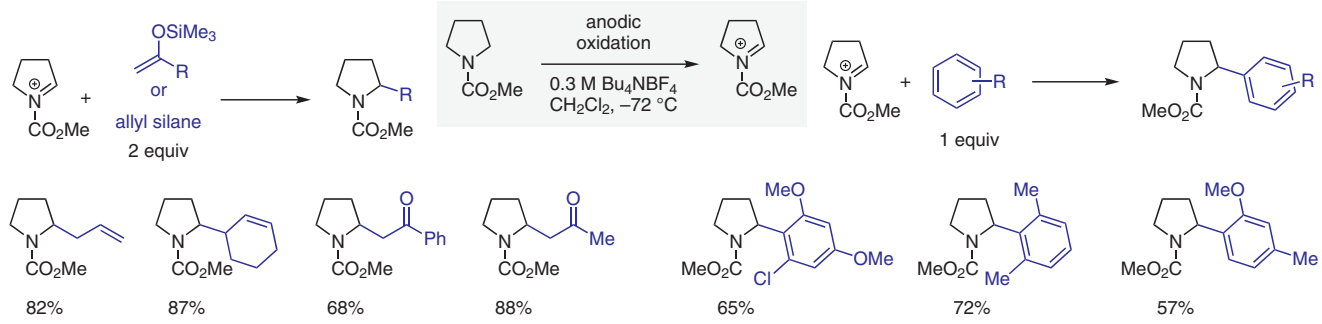


(40b) Shono, *J. Am. Chem. Soc.* **1981**, *103*, 1172.

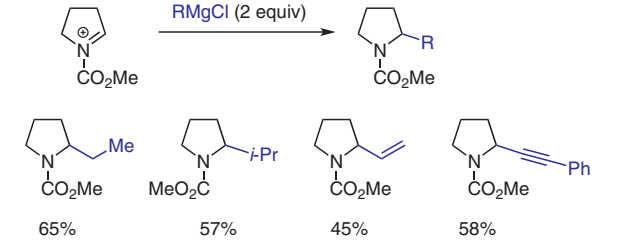
Further reading

'Indirect' cation pool method:
(40h) Yoshida, *J. Am. Chem. Soc.* **2006**, *128*, 7710.
Use of electroauxilliaries to lower potentials and direct oxidation:
(40i) Yoshida, *Tetrahedron Lett.* **1987**, *28*, 6621.
(40j) Yoshida, *Electrochim. Acta* **1997**, *42*, 1995.
Application of electroauxilliaries 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

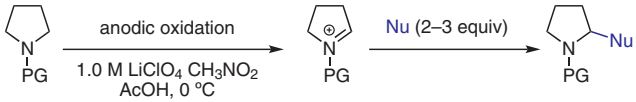


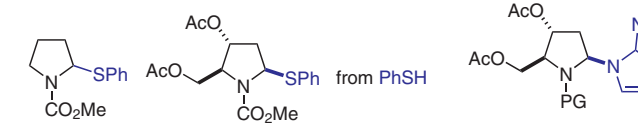
(40c) Yoshida, *J. Am. Chem. Soc.* **1999**, *121*, 9546.



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

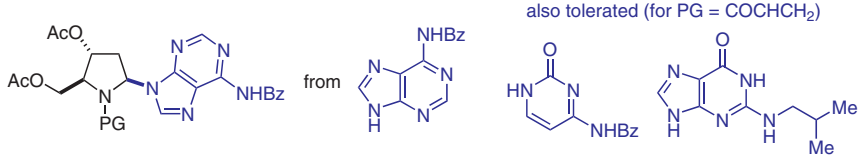
Azanucleoside derivative synthesis





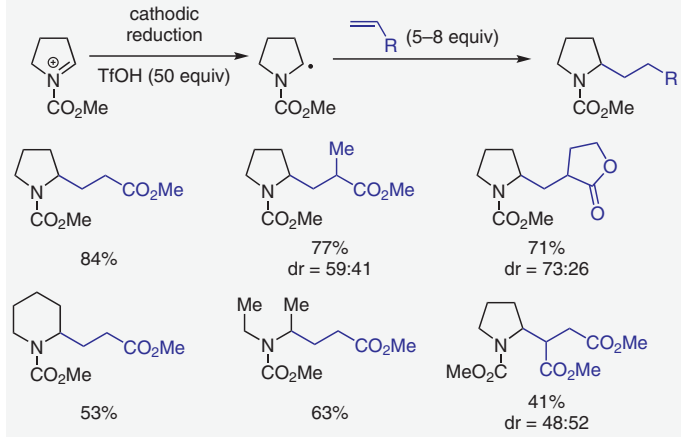
allyl silanes and electron-rich aromatics also tolerated

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



(40g) Chiba, *Angew. Chem. Int. Ed.* **2017**, *56*, 4011

Reduction of a Cation Pool



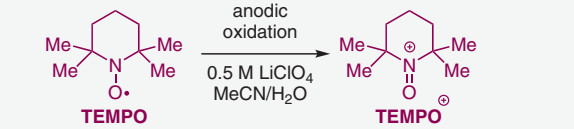
(40e) Yoshida, *J. Am. Chem. Soc.* **2002**, *124*, 30.

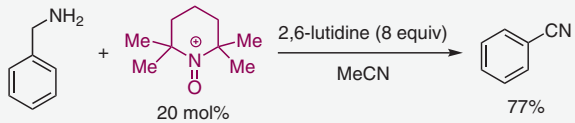
Figure 40 Electrochemical approaches, cation pool method.[40]

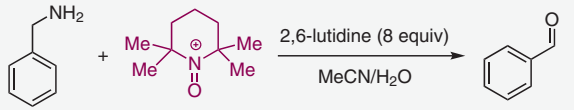
Notable features

- 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

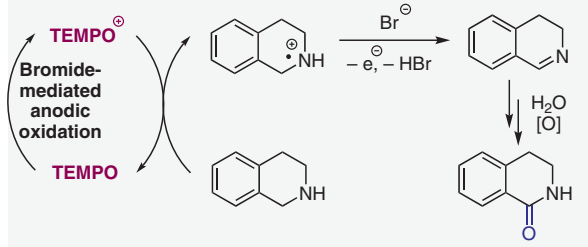






(41a) Semmelhack, *J. Am. Chem. Soc.* **1983**, *105*, 6732.

TEMPO-mediated electrooxidation of THIQ

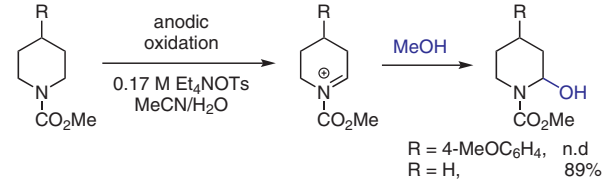


(41b) Little, *Electrochim. Acta* **2013**, *114*, 560.

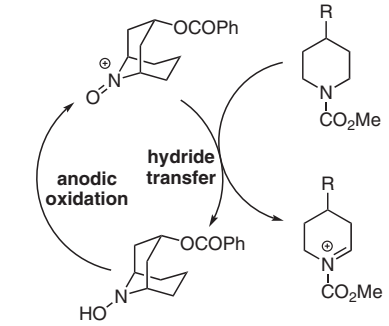
Further reading

(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

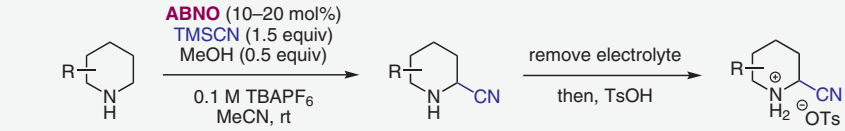


Mechanism

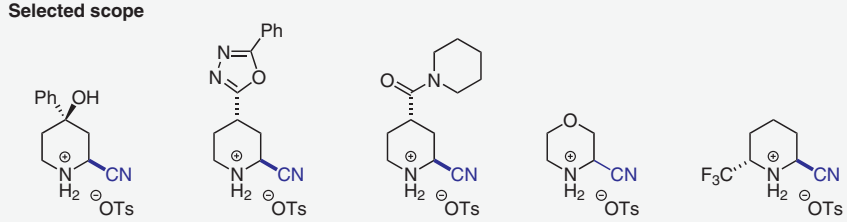


(41c) Stahl, *Angew. Chem. Int. Ed.* **2018**, *57*, 6686.

Application to α-cyanation

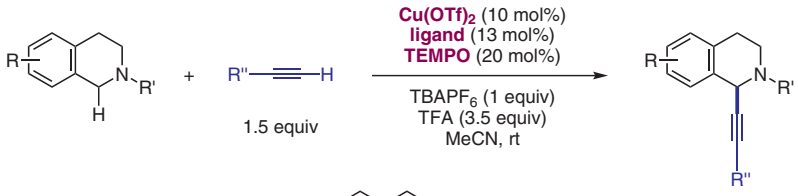


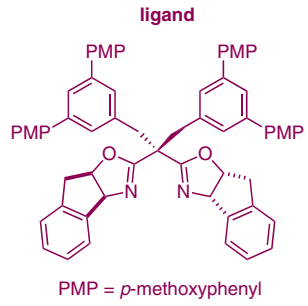
Selected scope



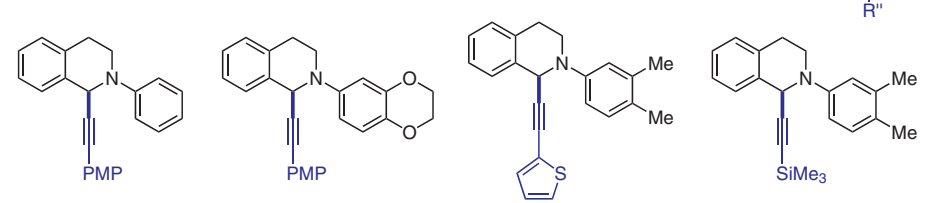
(41d) Stahl, *J. Am. Chem. Soc.* **2018**, *140*, 11227.

Enantioselective alkynation using a dual catalytic system





Selected scope



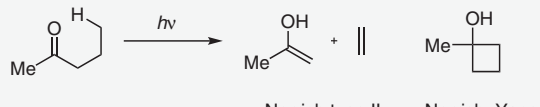
(41e) Mei, *Angew. Chem. Int. Ed.* **2020**, *59*, 15254.

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

Notable features

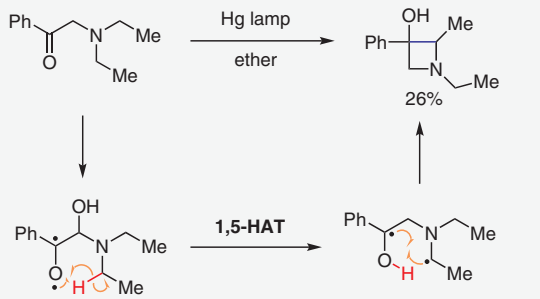
- Intramolecular Hydrogen Atom Transfer (HAT) represents a key step in many photochemical C–H bond functionalizations of amine derivatives.
- Initial products are useful starting materials for further transformations.

Historical precedent: Norrish–Yang cyclization



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

Seminal work

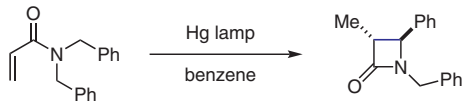


(42c) Clasen, Sealers, *Chem. Commun.* **1966**, 289.
See also: (42d) Cohen, *Chem. Rev.* **1973**, *73*, 141.

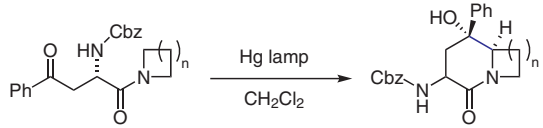
Further reading

Other 1,6-HAT reactions:
(42l) Griesbeck, *Tetrahedron Lett.* **1999**, *40*, 3137.
(42m) Peñéñory, *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

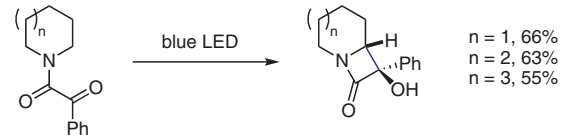


(42e) Aoyama, *Tetrahedron Lett.* **1975**, *16*, 1901.

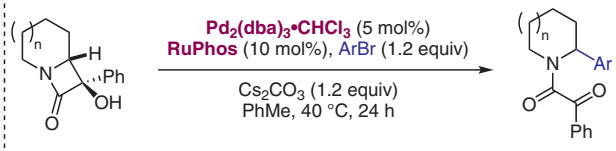


(42f) Wessig, *Tetrahedron: Asymmetry* **1998**, *9*, 4459.

Cyclization of α-ketoamides and subsequent applications

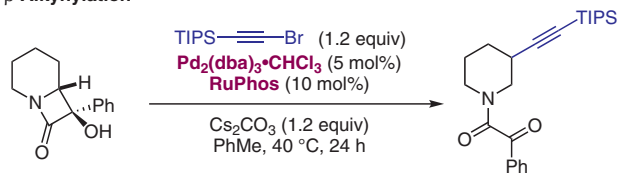


α-Arylation

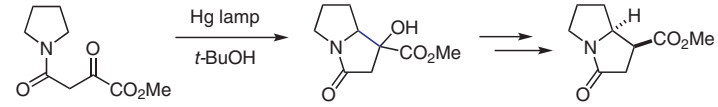


(42j) Sarpong, *ACS Catal.* **2020**, *10*, 2929.

β-Alkynylation

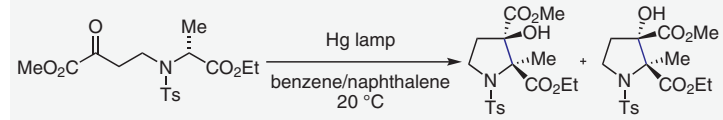


(42j) Sarpong, *ACS Catal.* **2020**, *10*, 2929.



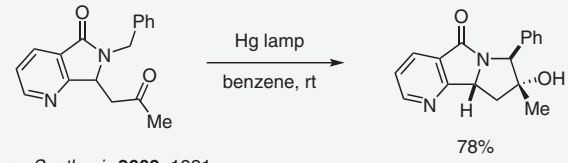
(42g) Gramain, *J. Org. Chem.* **1985**, *50*, 710.

Synthesis of pyrrolidines



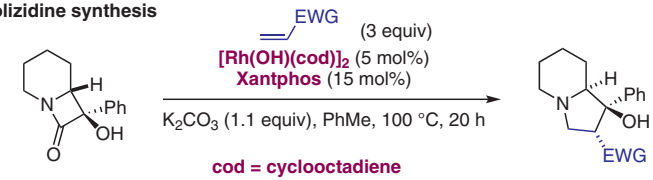
(42h) Giese, *Angew. Chem. Int. Ed.* **1999**, *38*, 2586.

Synthesis of benzopyrrolizidinones



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

Indolizidine synthesis



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

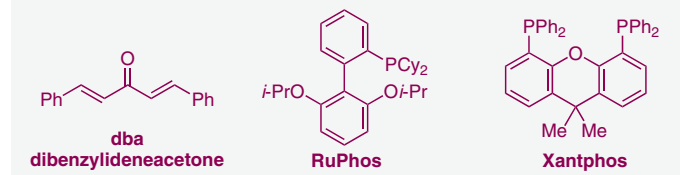
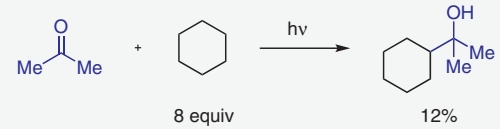


Figure 42 Intramolecular hydrogen atom transfer (HAT).[42]

Notable features

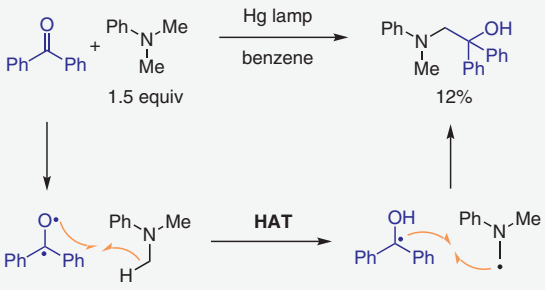
- High redox potentials of certain amine derivatives prevent them from undergoing single-electron transfer (SET) with typical photoredox catalysts. Direct hydrogen atom transfer (HAT) avoids this issue by using a photocatalyst to abstract a hydrogen atom from the substrate, generating the reactive α-amino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

Historical precedent: Intermolecular Yang C–H Functionalization



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

Seminal work

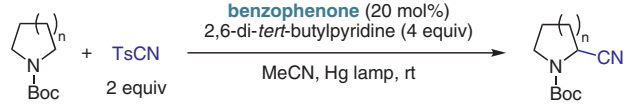


(43a) Davidson, *Chem. Commun.* **1966**, 575.

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 alkynylation:
(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

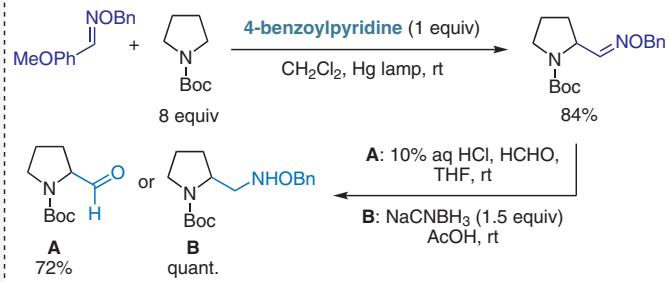


Morpholines and acyclic amines also tolerated.

n = 1, 94%
n = 2, 74%
n = 3, 85%

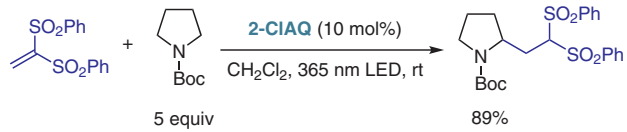
(43b) Inoue, *Synthesis* **2013**, *45*, 874.

Aldoximation and further functionalization



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

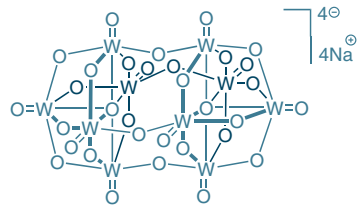
Alkylation



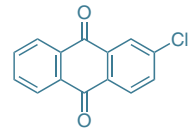
Morpholines and proline esters also tolerated.

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

Direct Hydrogen Atom Transfer agents

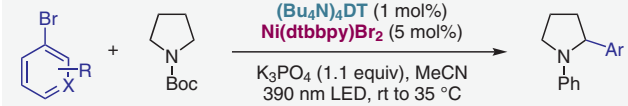


DT = decatungstate anion $W_{10}O_{32}^{4-}$



2-ClAQ
2-chloroanthraquinone

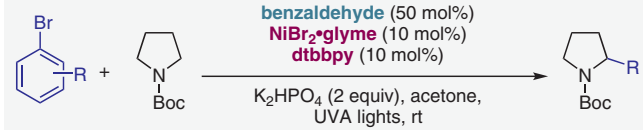
Arylation



X = C, N
5 equiv
For Ar = *m*-F_3C-C_5H_4N, 53%

dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridyl

(43e) MacMillan, *Nature* **2018**, *560*, 70.

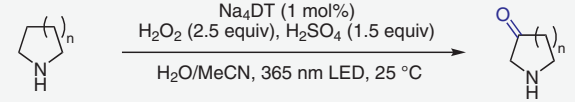


5 equiv
For R = Ph, 80%

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



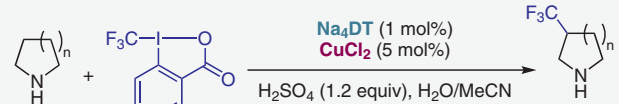
Protonation of the amine deactivates the α C–H bond, allowing HAT to occur at the β- or γ-positions. Selective hydroxylations and iminations also possible.

n = 1, 65%
n = 2, 68%*
n = 3, 58%

* mixture of regioisomers.

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

Trifluoromethylation at distal positions



n = 1, 68%
n = 2, 83%*
n = 3, 56%*

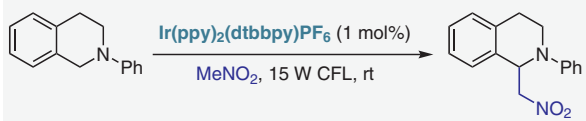
* mixture of regioisomers.

(43h) MacMillan, *Nat. Chem.* **2020** *12*, 459.

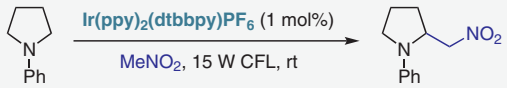
Figure 43 Direct hydrogen atom transfer (HAT).[43]

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

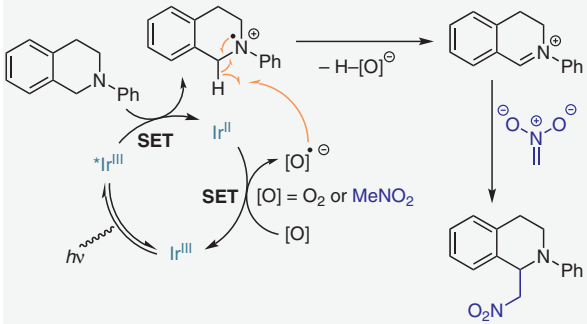


EWG and EDG on aryl groups tolerated 92%



40% conversion
27% yield

Proposed mechanism

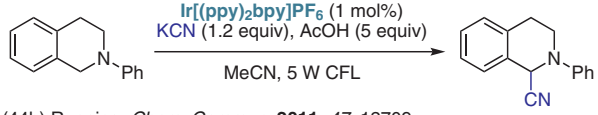


(44a) Stephenson, *J. Am. Chem. Soc.* **2010**, *132*, 1464.

Further reading

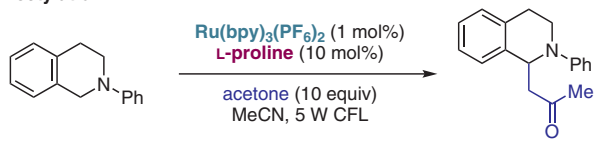
Other enantioselective strategies:
(44n) Kang, *Chem. Commun.* **2017**, *53*, 7665.
(44o) Zhang, *Chem. Commun.* **2017**, *53*, 12536.
Selected examples of redox neutral C–H functionalization of THIQ:
(44p) Pandey, Reiser, *Org. Lett.* **2012**, *14*, 672.
(44q) Nishibayashi, *Chem. Eur. J.* **2012**, *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



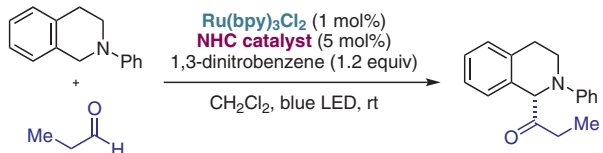
(44b) Rueping, *Chem. Commun.* **2011**, *47*, 12709.
See also: (44c) Stephenson, *Org. Lett.* **2012**, *14*, 94. 94%

Acetylation



(44e) Rueping, *Chem. Commun.* **2011**, *47*, 2360.
See also: (44f) Xia, *Chem. Commun.* **2012**, *48*, 2337. 95%

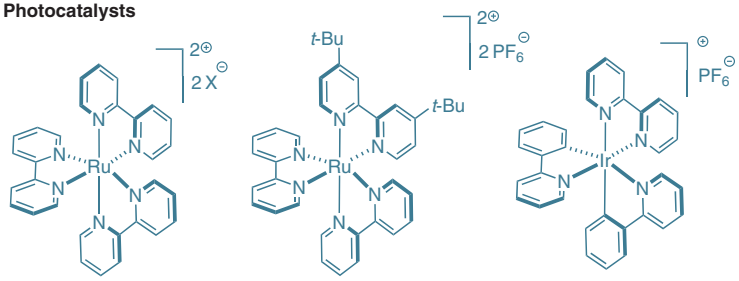
Enantioselective acylation



NHC catalyst

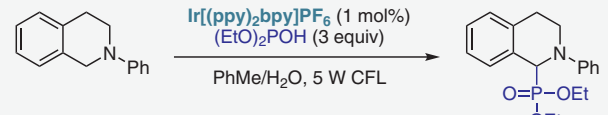
(44h) Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 8094.

Photocatalysts



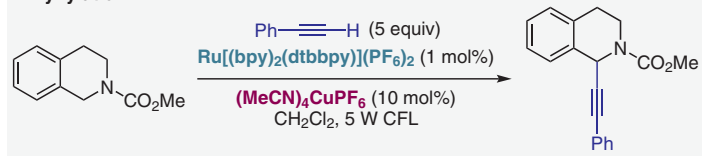
$Ru(bpy)_3X_2$ X = Cl or PF_6 $Ru[(bpy)_2(dtbbpy)](PF_6)_2$ $Ir[(ppy)_2bpy]PF_6$

Phosphonylation



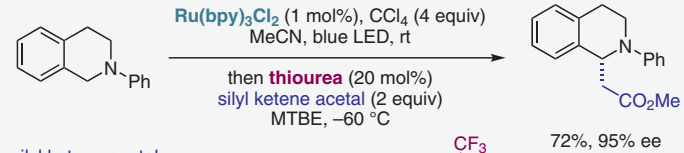
(44d) Rueping, *Chem. Commun.* **2011**, *47*, 8679. 89%

Alkynylation

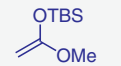


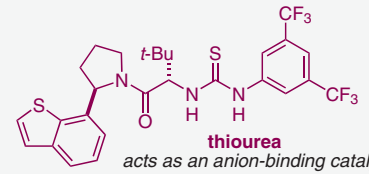
(44g) Rueping, *Chem. Eur. J.* **2012**, *18*, 5170. 88%

Enantioselective synthesis of β-amino esters



silyl ketene acetal

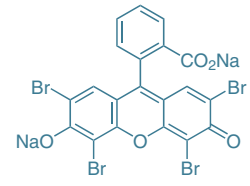




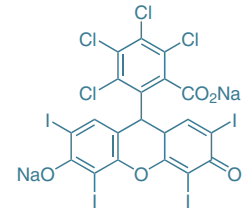
thiourea
acts as an anion-binding catalyst

(44i) Jacobsen, Stephenson, *Chem. Sci.* **2014**, *5*, 112.

Organic-based photocatalysts



eosin Y



Rose Bengal

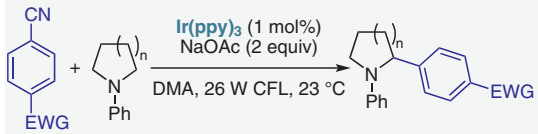
(44j) Tan, *Green Chem.* **2011**, *13*, 2682. (44k) Wu, *Chem. Eur. J.* **2012**, *18*, 620. (44l) Tan, *Green Chem.* **2011**, *13*, 3341. (44m) Fu, *J. Fluorine Chem.* **2012**, *140*, 88.

Figure 44 Photoredox approaches, part I.[44]

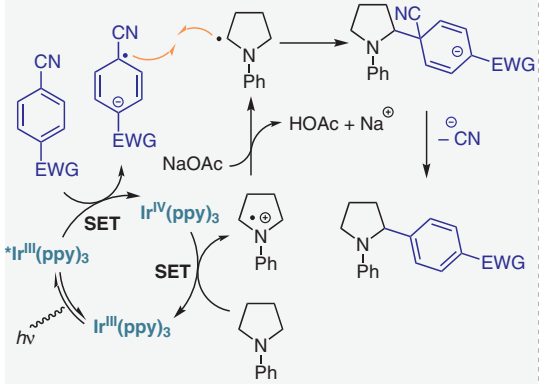
Notable features

- 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

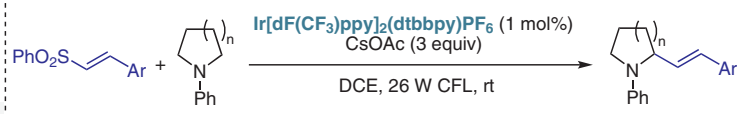


(45a) MacMillan, *Science* **2011**, *334*, 1114.

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.

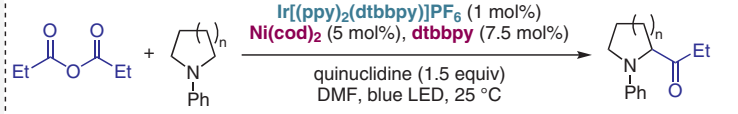
Vinylation



Functional groups on Ar tolerated: Me, F, CO_2Me, CF_3, OMe.

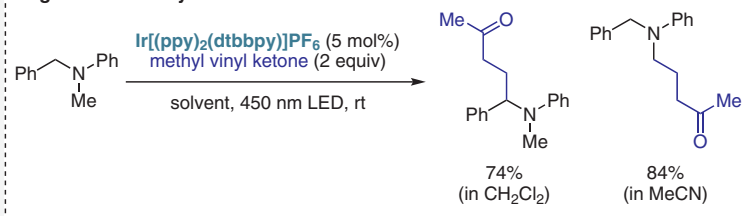
(45b) MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 11602.

Acylation



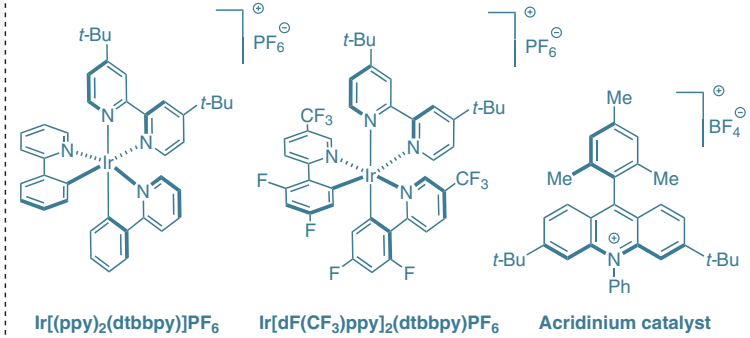
(45c) Doyle, *Angew. Chem. Int. Ed.* **2016**, *55*, 4040.

Regioselective alkylation

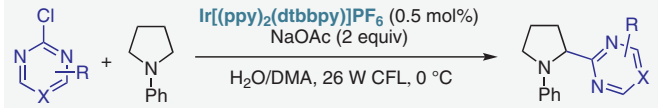


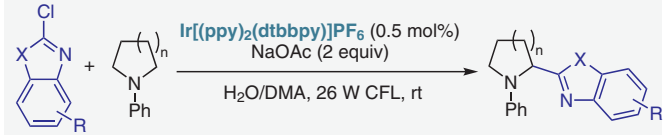
(45d) Liu, Ready, *J. Am. Chem. Soc.* **2020**, *142*, 11972.

Photocatalysts



Heteroarylation

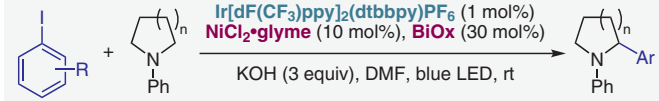




Functional groups on Ar tolerated: Me, F, CO_2Et, CF_3, OMe.

(45e) MacMillan, *Chem. Sci.* **2014**, *5*, 4173.

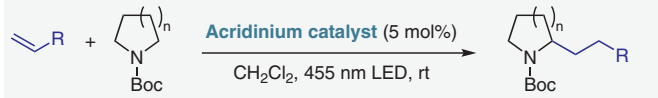
Arylation



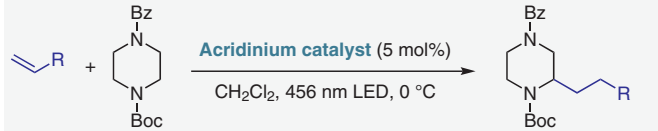
Functional groups on Ar tolerated: CO_2Me, F, CF_3, OMe, indoles.

(45f) Doyle, *Chem. Sci.* **2016**, *7*, 7002.

Regioselective Alkylation of *N*-Boc amines



Functional groups tolerated: CO_2Me, SO_2Ph, CN, CO_2Ph.



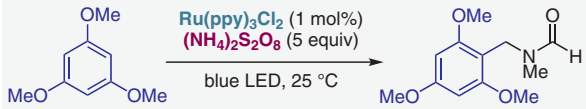
(45g) Nicewicz, *J. Am. Chem. Soc.* **2018**, *140*, 9056.
(45h) Nicewicz, *Org. Lett.* **2020**, *22*, 679.
See also: (45i) Nicewicz, *ACS Catal.* **2021**, *11*, 3153.

Figure 45 Photoredox approaches, part II.[45]

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 α-carbamyl radicals.

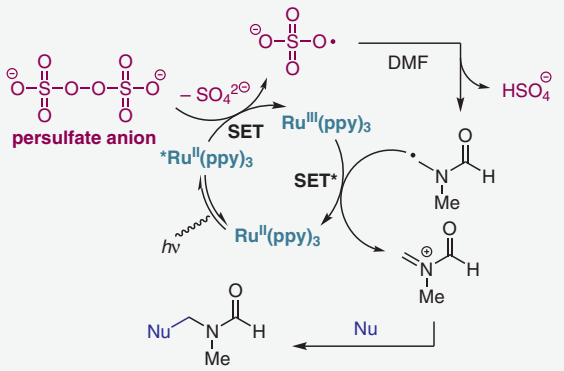
Seminal work



+ DMF (solvent) 89%

75% at 55 °C with no photocatalyst

Proposed mechanism



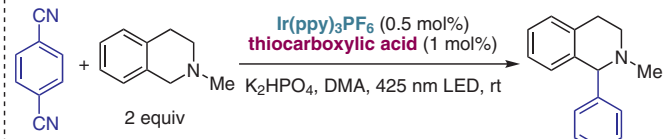
*** Oxidation with persulfate also possible**

(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

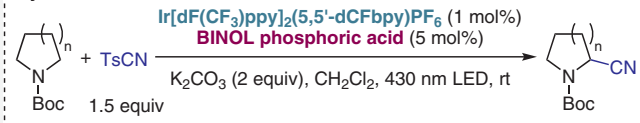


2 equiv 94%

Applicable to other amines with an α-benzylic C–H bond.
Functional groups tolerated: F, Cl, CO_2Me.

(46b) Hamashima, *Chem. Sci.* **2018**, *9*, 8453.
See also: (46c) Hamashima, *ACS Catal.* **2021**, *11*, 82.

Cyanation



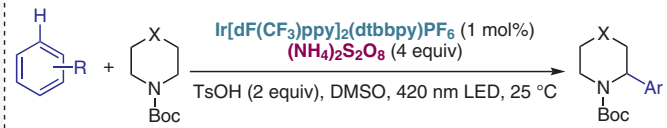
1.5 equiv

n = 1, 95%
n = 2, 77%
n = 3, 85%

Applicable to morpholines, piperazines, THIQ.

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

Cross-dehydrogenative heteroarylation



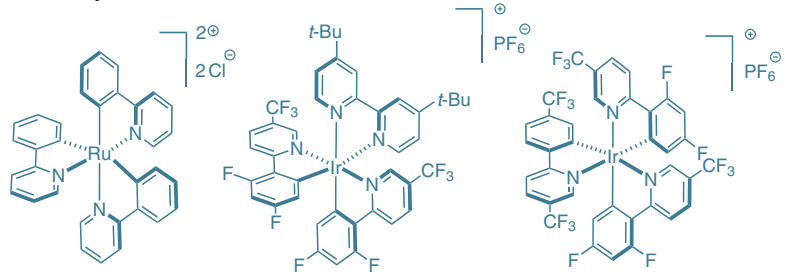
X = C, N, O, S
1.5–3 equiv

For X = O, Ar = pyrimidine 81%

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

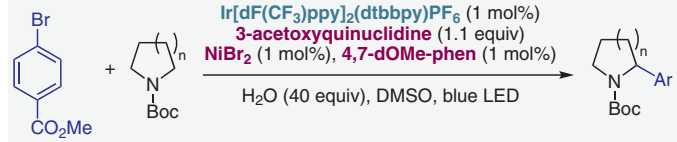
(46e) Grainger, Johnson, *Chem. Sci.* **2019**, *10*, 2264.

Photocatalysts



$Ru(ppy)_3Cl_2$ $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ $Ir[dF(CF_3)ppy]_2(5,5'\text{-}dCFbpy)PF_6$

Arylation



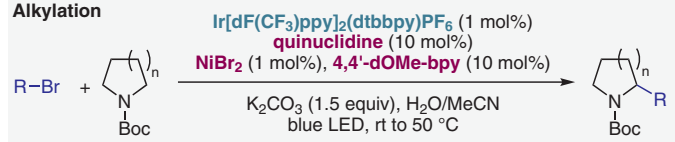
2 equiv

n = 1, 81%
n = 2, 42%
n = 3, 69%

Functional groups on aryl group tolerated: F, CF_3, Me, pyridines, pyridazines.

(46f) MacMillan, *Science* **2016**, *352*, 1304.

Alkylation

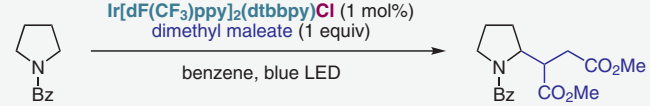


2 equiv

For R = cyclohexyl n = 1, 58%
n = 2, 42%
n = 3, 83%

Functional groups tolerated: CN, CO_2Et, OPh, halides and other alkyl groups.

(46g) MacMillan, *Nature* **2017**, *547*, 79.



96%, dr = 53:47

Chloride is used as the HAT catalyst.

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

Hydrogen Atom Transfer (HAT) catalysts

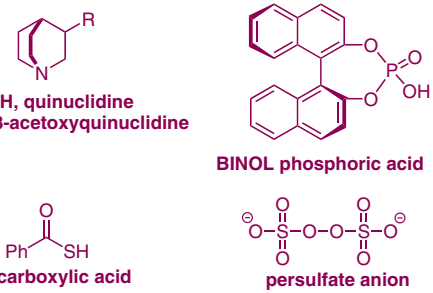
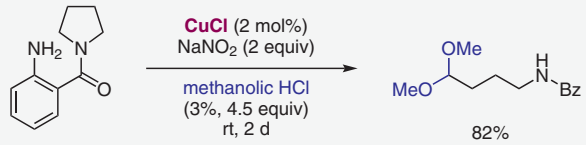


Figure 46 Indirect hydrogen atom transfer (HAT).[46]

Notable features

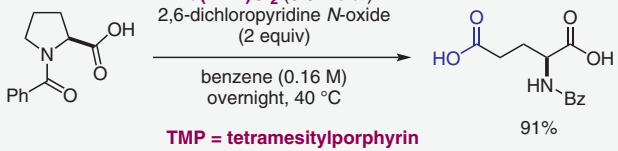
- Different approaches facilitate the ring cleavage of cyclic amines.
- Allows for the rapid formation of highly functionalized linear amines.
- Enables the late-stage modification of peptides.

Early work



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

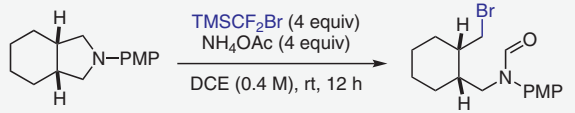
Ruthenium-catalyzed oxidative cleavage of amides



TMP = tetramesitylporphyrin

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

Ring opening with difluorocarbenes



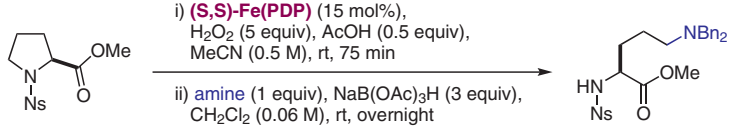
Applicable to late-stage functionalization of biologically active compounds.

(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

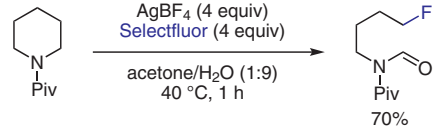


PDP = [*N*,*N*'-bis(2-pyridylmethyl)]-2,2'-bipyrrolidine

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

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

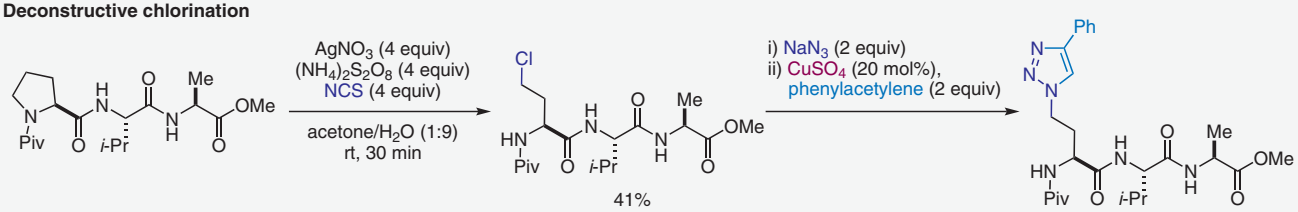
Deconstructive fluorination



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

(47e) Sarpong, *Science* **2018**, *361*, 171.

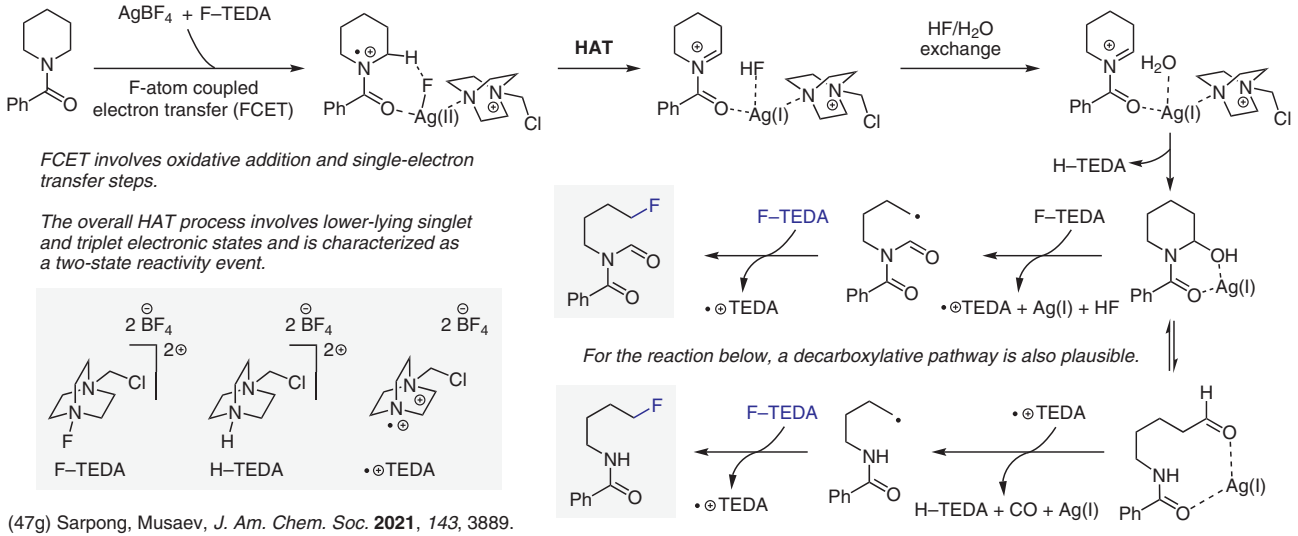
Deconstructive chlorination



NBS is effective in the corresponding bromination.

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

Proposed mechanism using silver (I)



FCET involves oxidative addition and single-electron transfer steps.

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

For the reaction below, a decarboxylative pathway is also plausible.

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

Figure 47 Deconstructive functionalization.[47]

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

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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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