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Recent Advances in Chlorination: Novel Reagents and Methods from the Last Decade

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Conflict of Interest:

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Abstract:

Chlorinated compounds are vital in organic synthesis, impacting nucleophilic substitutions, β -elimination, and C-H acidity. This review highlights recent advances in (hetero)arene chlorination, focusing on novel reagents and methods developed in the past decade. Traditional electrophilic agents like Cl_2 and PCl_5 have been expanded with new chlorinating agents such as Palau'chlor, as well as electrochemical and photochemical techniques. Biocatalyzed chlorination using FAD-dependent halogenases is also explored. Key trends include green chemistry with eco-friendly chlorine sources like NaCl and HCl. Although nucleophilic chlorination remains rare, electrochemical methods show promising, despite equipment limitations. This review emphasizes significant progress in the last decade towards more sustainable and efficient chlorination strategies.

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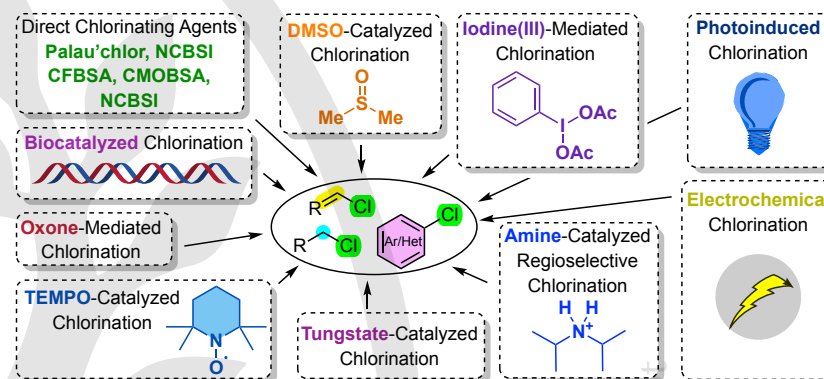
Recent Advances in Chlorination: Novel Reagents and Methods from the Last Decade

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Abstract Chlorinated compounds are vital in organic synthesis, impacting nucleophilic substitutions, β -elimination, and C-H acidity. This review highlights recent advances in (hetero)arene chlorination, focusing on novel reagents and methods developed in the past decade. Traditional electrophilic agents like Cl_2 and PCl_5 have been expanded with new chlorinating agents such as Palau'chlor, as well as electrochemical and photochemical techniques. Biocatalyzed chlorination using FAD-dependent halogenases is also explored. Key trends include green chemistry with eco-friendly chlorine sources like NaCl and HCl. Although nucleophilic chlorination remains rare, electrochemical methods show promising, despite equipment limitations. This review emphasizes significant progress in the last decade towards more sustainable and efficient chlorination strategies.

Key words (Hetero)arene chlorination, electrophilic substitution, nucleophilic chlorination, chlorinating agents, electrochemistry, photocatalysis, biocatalysis, green chemistry.

Chlorinated compounds are pivotal in organic synthesis, playing key roles in reactions such as nucleophilic substitutions, β -eliminations, and increasing C-H acidity. Chlorination significantly alters the physical and chemical properties of organic molecules, making it a valuable tool in drug development and materials science. Most often, chlorine sources act as electrophiles in these transformations.

Traditional electrophilic chlorinating agents like Cl_2 , SO_2Cl_2 , SbCl_5 , PCl_5 , and $t\text{BuOCl}$, though effective, present challenges due to their high toxicity and reactivity. Similarly, widely used reagents such as NCS, DCDMH, TCCA, and PhICl_2 offer poor atom economy and generate excessive waste.

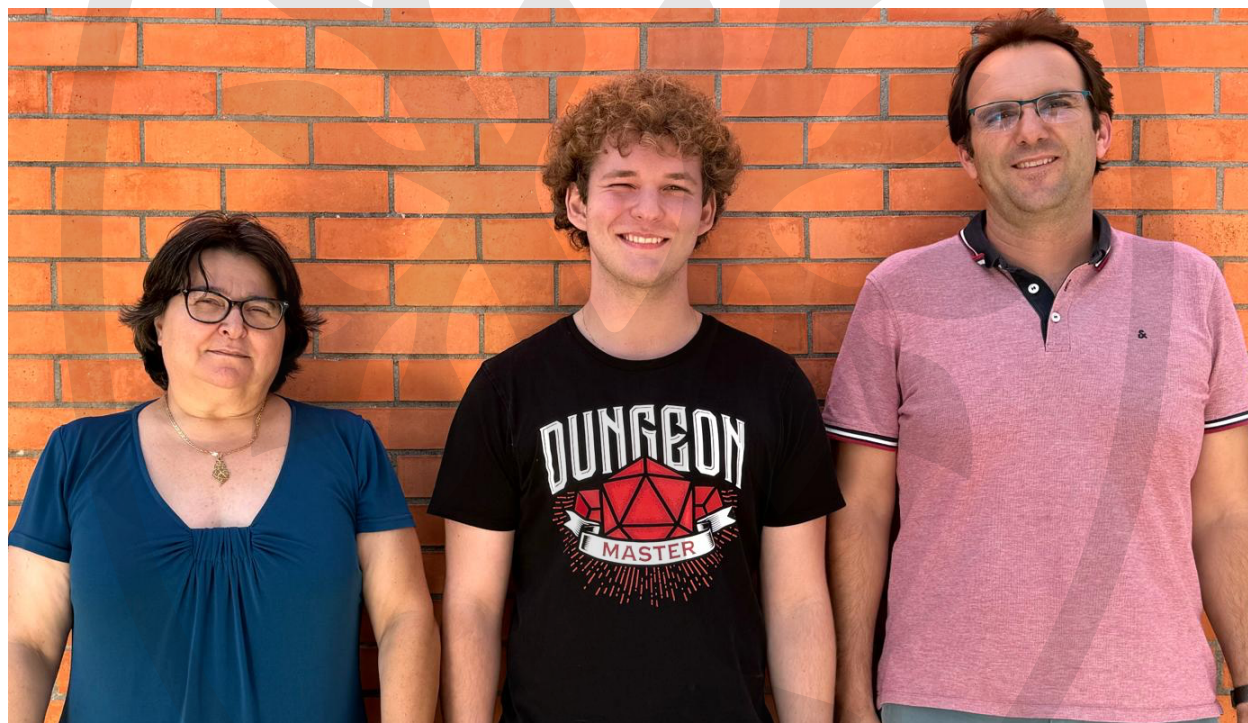
This graphical review highlights key advancements in the chlorination of organic molecules, particularly (hetero)arenes, over the past decade, with a focus on the development of novel chlorinating reagents. The progress in direct chlorinating agents—where the chlorine source is embedded within the reagent's

structure—is emphasized, along with emerging electrochemical and photochemical methods that utilize electrons and photons as reagents. In addition, the review examines new mediators and catalysts that activate established chlorinating agents such as NCS, DCDMH, SO_2Cl_2 , POCl_3 , and TMSCl , thereby broadening the utility of these readily available chlorine sources. The review also explores nature-inspired biocatalyzed chlorination, showcasing recent strides in this area.

Building on Cui's review on oxidative chlorination^{1a} and Verma's review on general C-H chlorination,^{1b} this work shifts the focus toward aromatic chlorination, introducing new direct chlorinating agents, electrochemical methods, and biocatalysis. While there is overlap with previous reviews, this work provides a more expansive and detailed exploration of advanced chlorination techniques.

Each figure in the review presents a novel chlorinating reagent, reaction conditions, substrate scope, and a detailed analysis of mechanisms and catalytic cycles to enhance understanding of these transformations.

Iago Vogel (center) was born in São Paulo, Brazil. He earned his B.Sc. degree in Biochemistry from the University of Aveiro, Portugal, in 2023, where he completed his final project in Organic Chemistry under the mentorship of Professors **Nuno Candeias** (right) and **Diana Pinto** (left). Following this, he entered a Master's program in Chemistry at the same university, where he was awarded the *Novos Talentos Gulbenkian* scholarship. Now in the second year of his Master's, Iago's thesis builds on his undergraduate research, focusing on enhancing the complexity of natural products for medicinal chemistry applications.



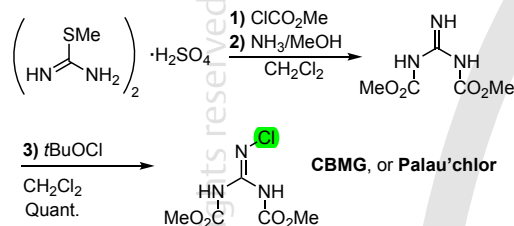
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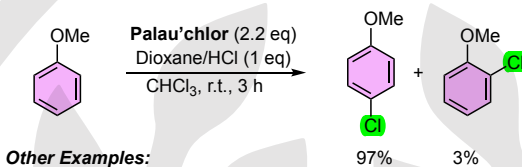
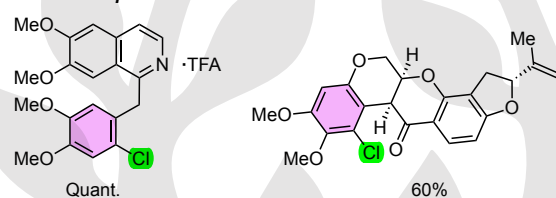
Notable features of Palau'chlor:

- Easily synthesized
- Increased reactivity over conventional chlorinating agents^{1a,e}
- Requires mild conditions

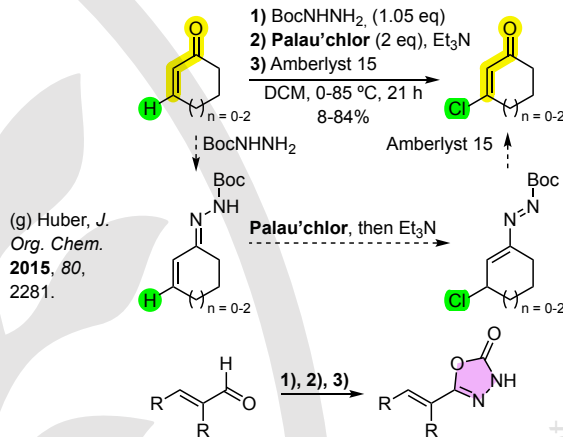
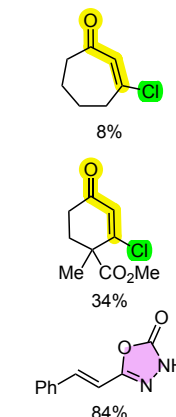
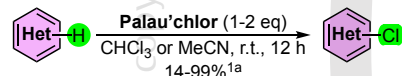
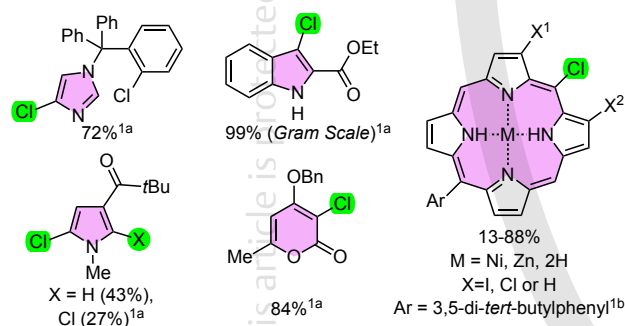
Synthesis of Palau'chlor, developed by Baran and co-workers:



(1c) Baran, *J. Am. Chem. Soc.* **2014**, 136, 6908.

C-H Chlorination of Electron-Rich Arenes**Other Examples:**

(1c) Baran, *J. Am. Chem. Soc.* **2014**, 136, 6908.

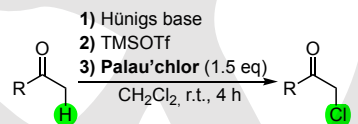
One-pot Selective β -C-H-chlorination of Enones**Selected Examples:****C-H Chlorination of Heteroarenes****Selected Examples:**

(1c) Baran, *J. Am. Chem. Soc.* **2014**, 136, 6908.

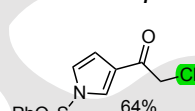
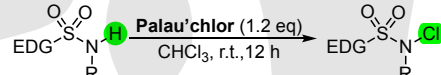
(1d) Osuka, *Angew. Chem. Int. Ed. Engl.* **2015**, 54, 6311.

Further Reading:

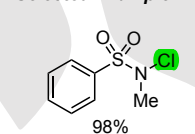
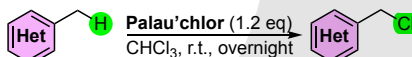
(1e) Osuka, *Chem. Eur. J.* **2015**, 54, 6311.

 α -chlorination of Ketones

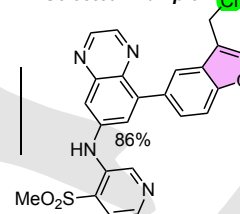
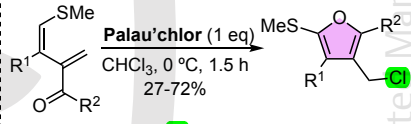
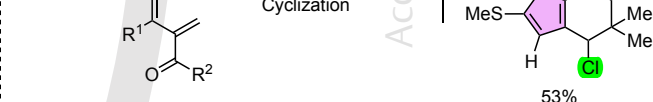
(1c) Baran, *J. Am. Chem. Soc.* **2014**, 136, 6908.

Selected Example:**N-H Chlorination of Electron-Rich Sulfonamides**

(1c) Baran, *J. Am. Chem. Soc.* **2014**, 136, 6908.

Selected Example:**C-H Chlorination of Heteroarene Methyl Groups**

(1f) Boutard, *WO Pat.* 180537A1, 2016.

Selected Example:**Synthesis of Tetrasubstituted Furans****Selected Examples:**

(1h) Magauer, *J. Am. Chem. Soc.* **2021**, 143, 1216.

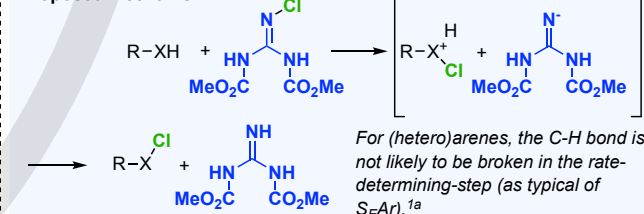
Proposed Mechanism

Figure 1 Diverse applications of Palau'chlor (chlorobis(methoxycarbonyl)guanidine)^{1c-h}

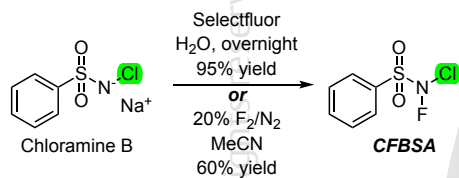
Notable features of CFBSA:

- Highly practical
- Requires mild conditions in the majority of cases
- Little to no fluorination side-reactions
- Comparable reactivity to Palauchlor

Limitation:

- Degrades into benzenesulfonamide in dichloromethane^{2b}

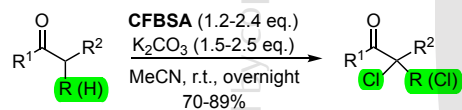
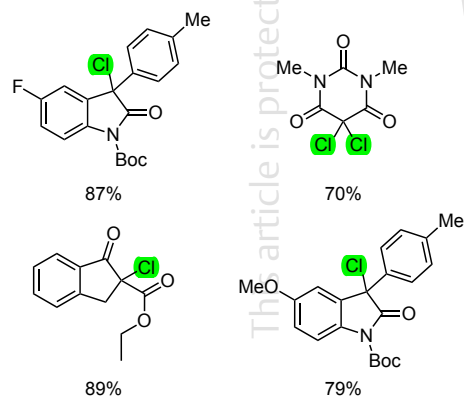
Synthesis of CFBSA, developed by Yang and co-workers



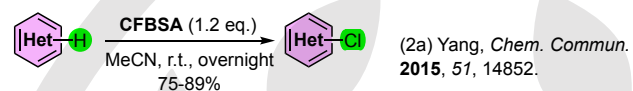
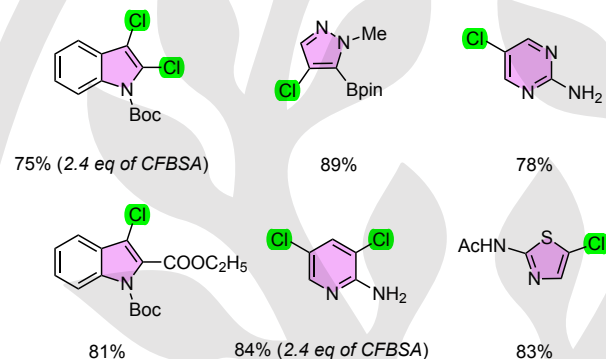
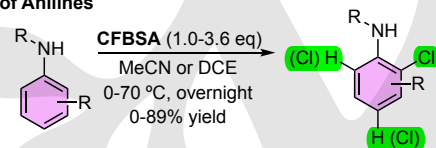
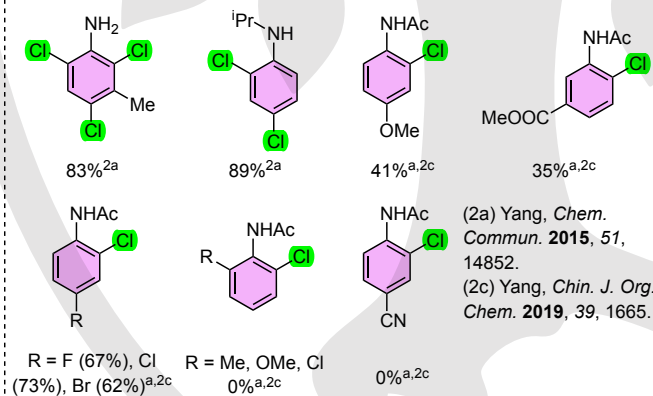
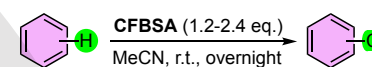
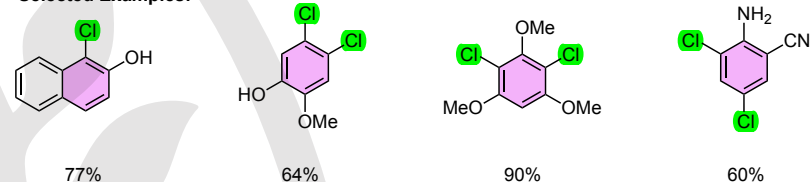
The mechanism follows the same steps of similar electrophilic N-chloro chlorinating agents

(2a) Yang, *Chem. Commun.* **2015**, 51, 14852.

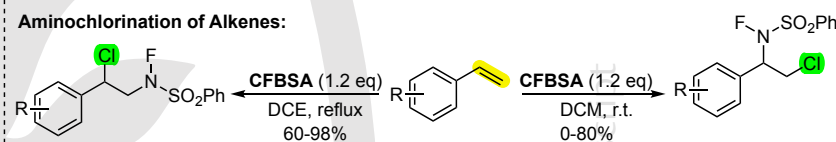
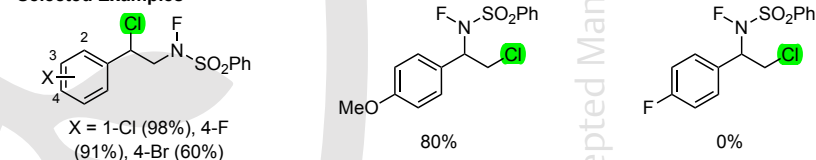
(2b) Yang, *J. Org. Chem.* **2018**, 83, 13103.

Chlorination of Carbonyl Compounds**Selected Examples:**

(2a) Yang, *Chem. Commun.* **2015**, 51, 14852.

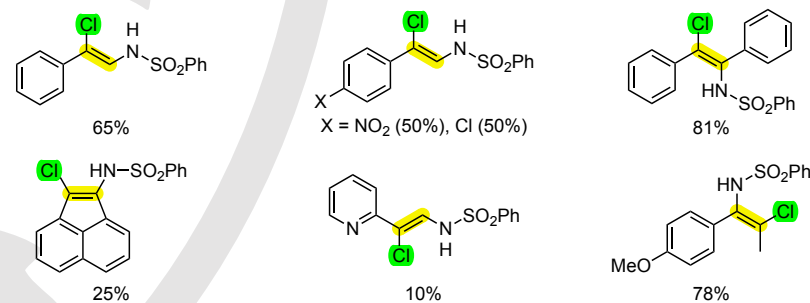
Chlorination of Nitrogen-containing Heteroarenes**Selected Examples:****Chlorination of Anilines****Selected Examples** (^a addition of 10-6 mol% of Pd(AcO)₂ and 0.4 eq of PTSA):**Chlorination of Other Homoarenes****Selected Examples:**

(2a) Yang, *Chem. Commun.* **2015**, 51, 14852.

Aminochlorination of Alkenes:**Selected Examples**

(2d) Yang, *Eur. J. Org. Chem.* **2016**, 4526.

If Et₃N (1.2 eq) is added into the system after the completion of the above reactions, **2-Chloro Enesulfonamides** can be attained. Selected examples illustrated below^{2e}:



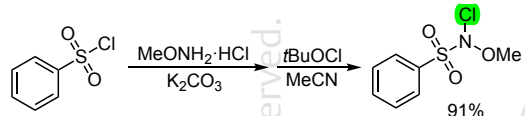
(2e) Yang, *Chin. J. Chem.* **2017**, 35, 1417.

Figure 2 Diverse applications of CFBSA (*N*-chloro-*N*-fluorobenzenesulfonylamine)^{2a-e}

Notable features of CMOBSA:

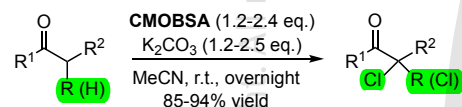
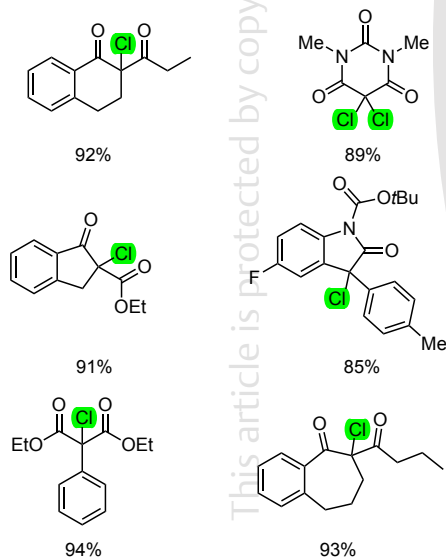
- Highly practical
- Requires mild conditions in the majority of cases
- Little to no fluorination side-reactions
- More economical and reactive than CFBSA

Synthesis of CMOBSA, developed by Yang and co-workers

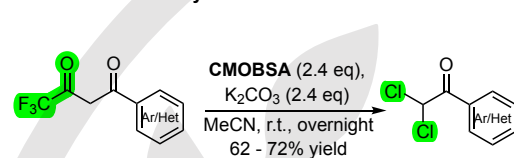


The mechanism follows the same steps of similar electrophilic N-chloro chlorinating agents

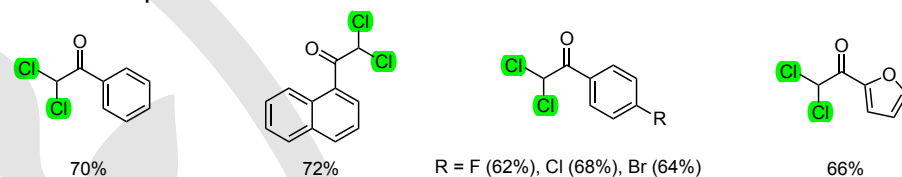
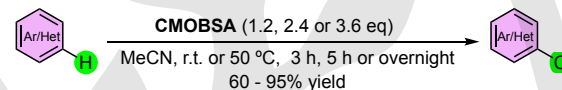
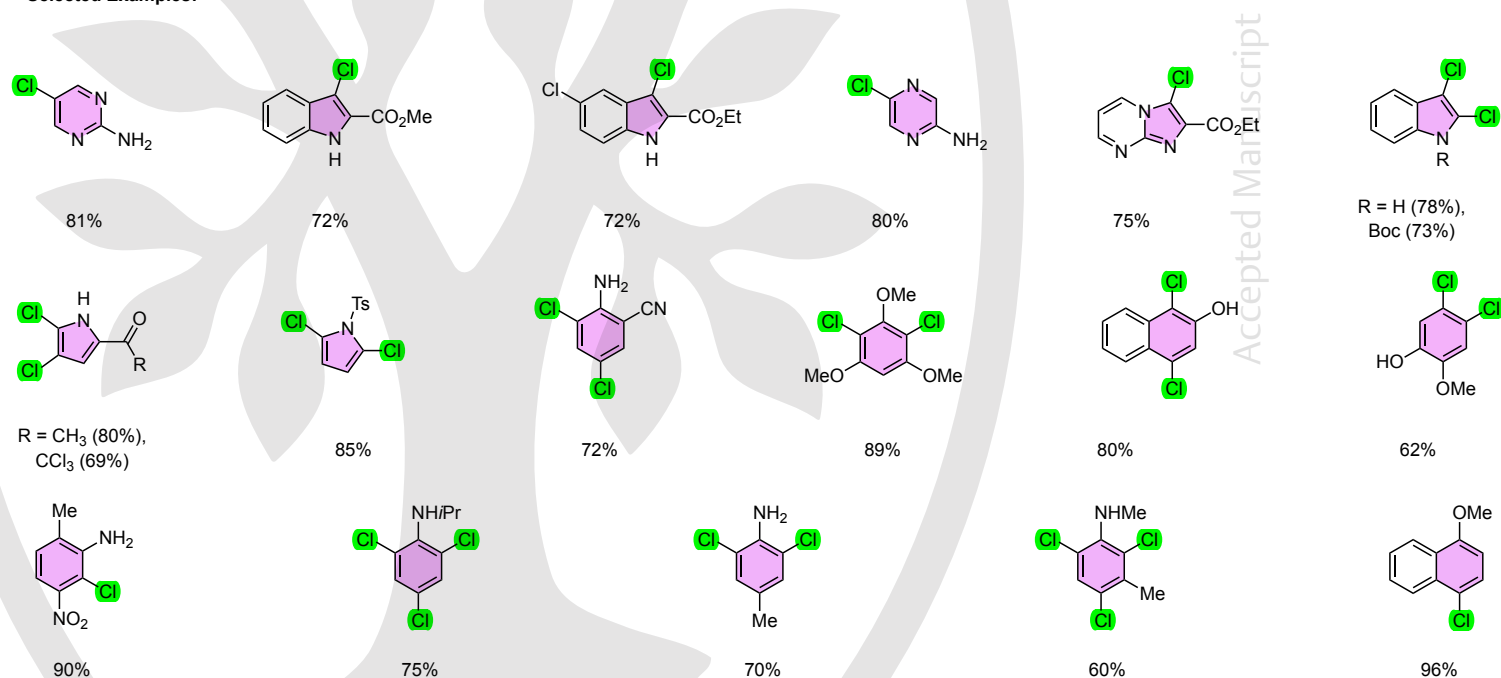
(3) Yang, *Eur. J. Org. Chem.* **2016**, 2016, 5937.

Chlorination of Carbonyl Compounds**Selected Examples**

(3) Yang, *Eur. J. Org. Chem.* **2016**, 2016, 5937.

Chlorination of Benzoyl Trifluoroacetones

(3) Yang, *Eur. J. Org. Chem.* **2016**, 2016, 5937.

Selected Examples:**Chlorination of (Hetero)arenes****Selected Examples:**

(3) Yang, *Eur. J. Org. Chem.* **2016**, 2016, 5937.

Figure 3 Diverse applications of CMOBSA (*N*-Chloro-*N*-Methoxybenzene Sulfonamide)³

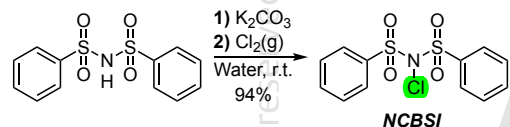
Notable features of NCBSI:

- Very high reactivity
- Can be resynthesized from dechlorinated reaction byproduct
- Requires mild reaction conditions

Current limitations:

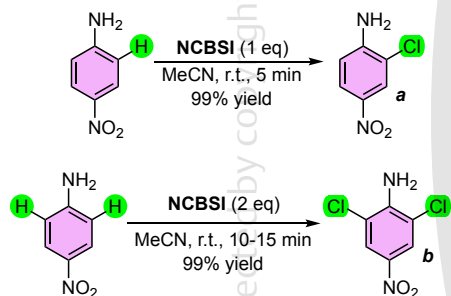
- Not commercially available
- Its synthesis requires the use of Cl₂(g)

Synthesis of NCBSI, developed by Chaturbhuj and co-workers:



The mechanism follows the same steps of similar electrophilic N-chloro chlorinating agents.

(4a) Chaturbhuj, *Tetrahedron Lett.* **2021**, 63, 152689.

Mono and Dichlorination of 4-Nitroaniline

Other solvents are also compatible:

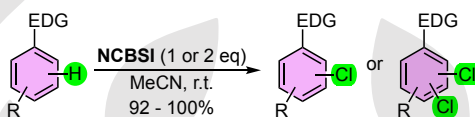
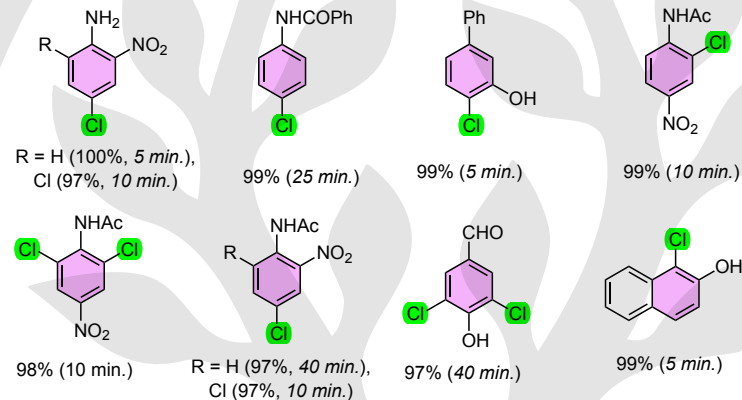
Solvent	T (°C)	t (min.)	Conversion		
			a(%)	b(%)	a(%)
THF		45	100	-	98
Dioxane	10-15	20	100	-	98
CHCl ₃	30-35	3	98	2	96

EtOH/water (1:1) gives **b** as the major product, being **a** generated in only 12%

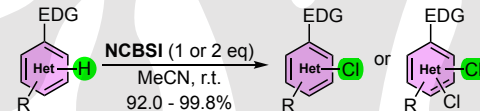
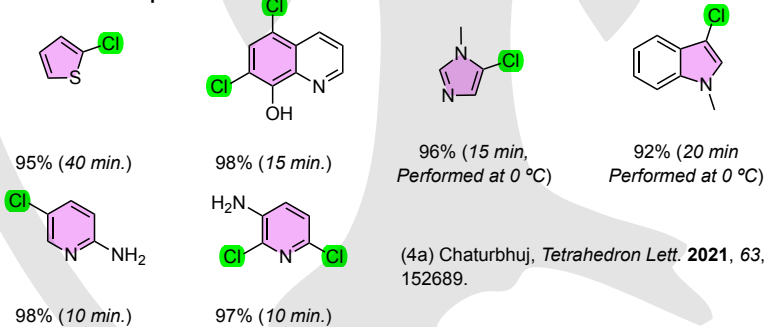
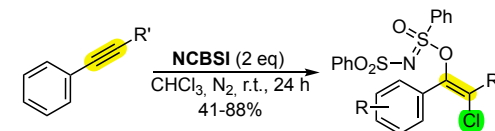
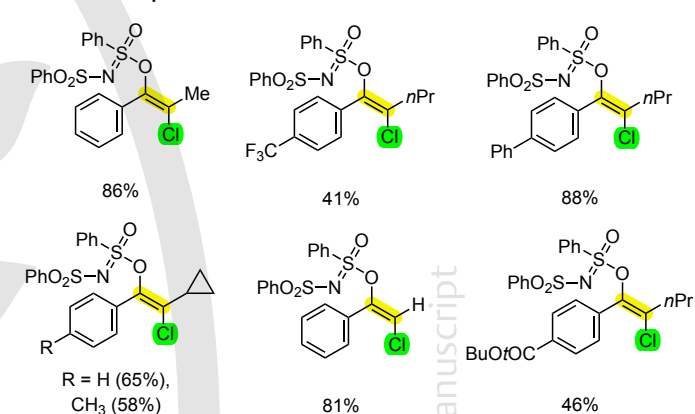
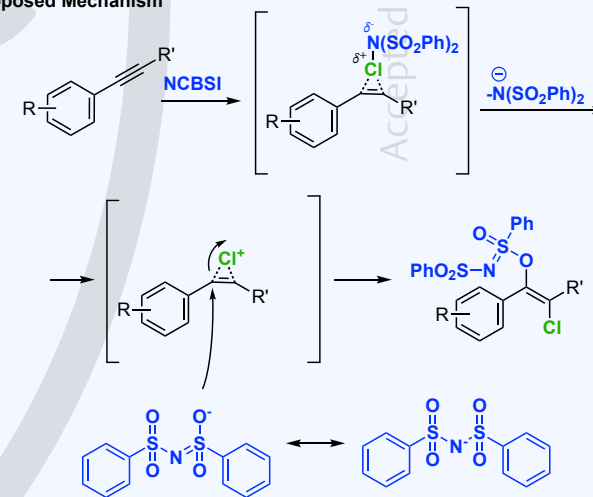
(4a) Chaturbhuj, *Tetrahedron Lett.* **2021**, 63, 152689.

Further Reading:

- (4b) Chaturbhuj, *J. Org. Chem.* **2021**, 86, 12467.
 (4c) Chaturbhuj, *Tetrahedron Lett.* **2021**, 73, 153094.
 (4d) Chaudhari, *Tetrahedron Lett.* **2023**, 123, 154539.

Chlorination of Other Arenes**Selected Examples:**

(4a) Chaturbhuj, *Tetrahedron Lett.* **2021**, 63, 152689.

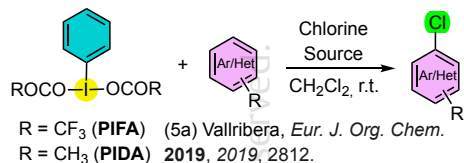
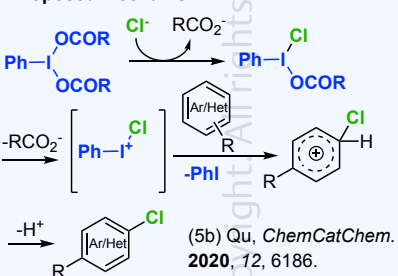
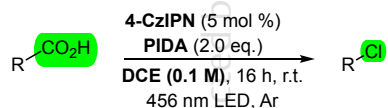
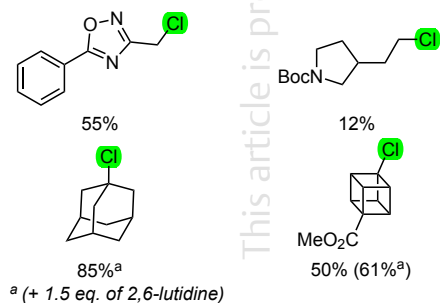
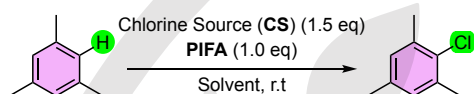
Chlorination of Heteroarenes**Selected Examples:****Anti-oxchlorination of Alkynes****Selected Examples:****Proposed Mechanism**

(4e) Sun, *Molecules* **2023**, 28, 7420.

Figure 4 Chlorination reactions using NCBSI (N-chloro-N-(phenylsulfonyl)benzene sulfonamide) as the chlorinating agent^{4a-e}

Notable features of I(III)-Mediated Chlorination:

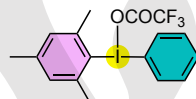
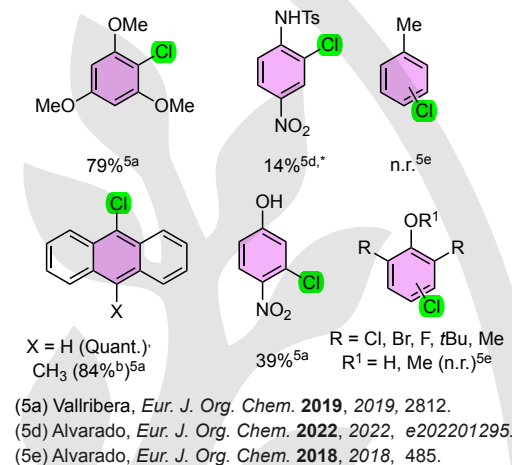
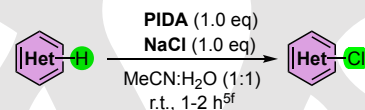
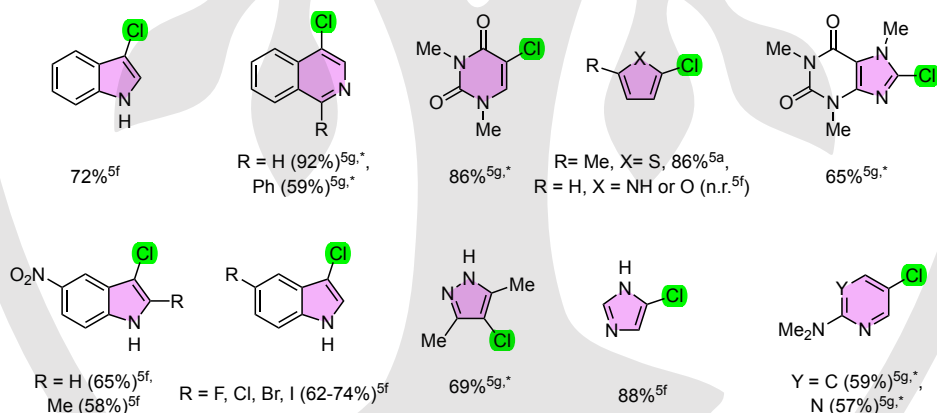
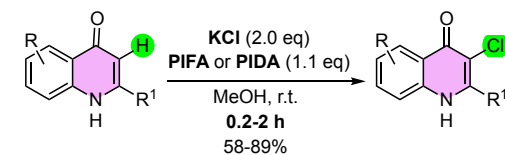
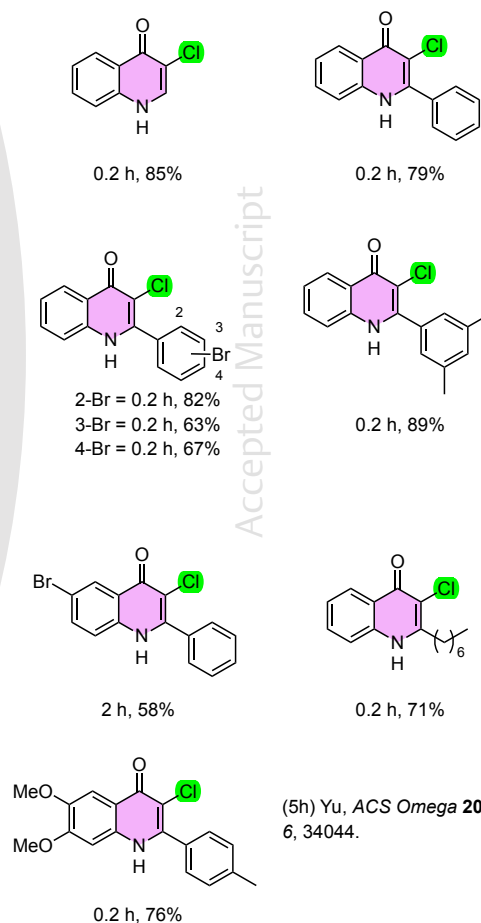
- Environmentally benign
- Similar reactivity to heavy metals
- Requires mild conditions
- Not limited to (hetero)arenes

**Proposed Mechanism****Photoinduced Decarboxylative Chlorination****Selected Examples (see mechanism below):**(5c) Molander, *Green Chem.* **2023**, 25, 560.**Chlorination of Arenes with PIFA**

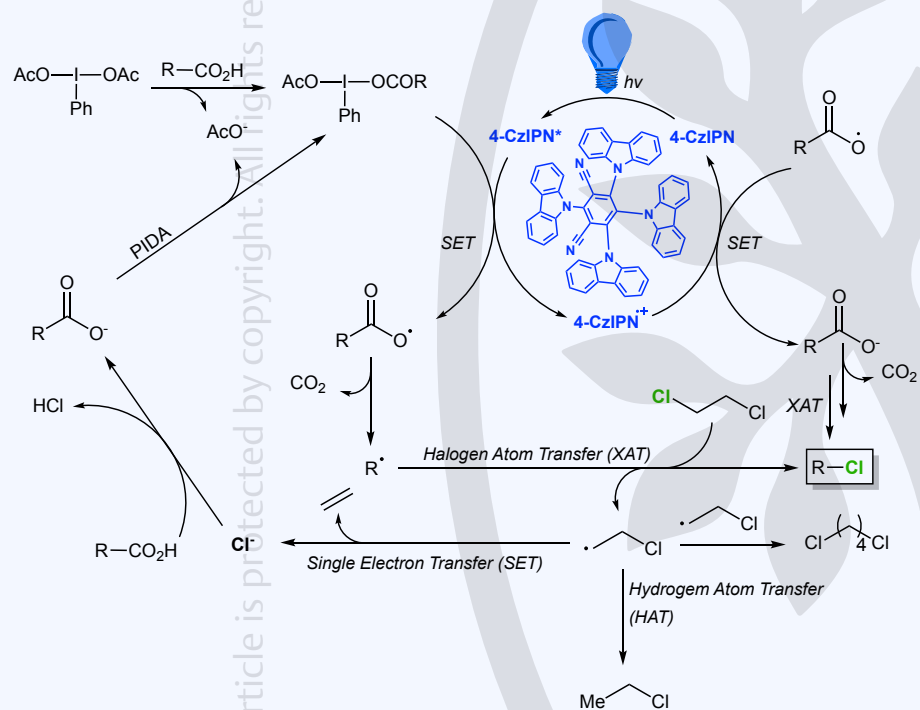
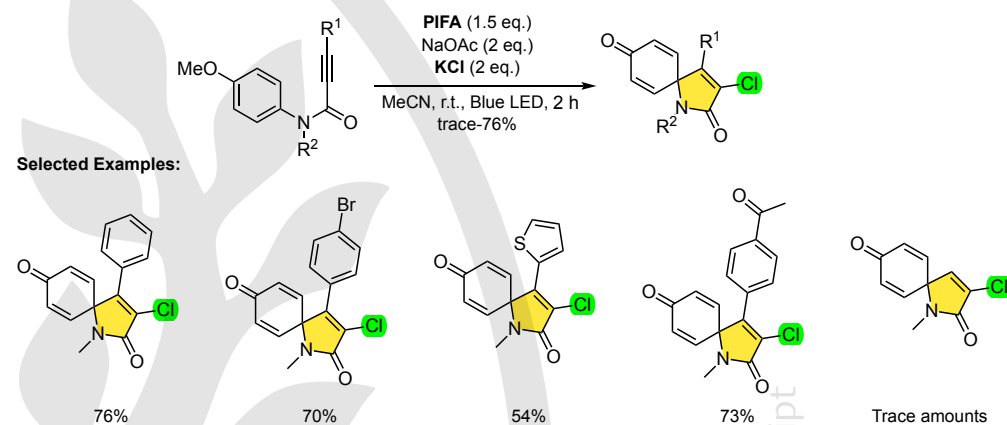
CS	Solv.	Yield
1) NaCl	CH ₂ Cl ₂	55%
2) KCl	CH ₂ Cl ₂	62%
3) TMSCl	CH ₂ Cl ₂	79%
4) KCl	Toluene	10%

Using 2 eq of KCl, 64% yield was achieved. MeCN, MeOH and EtOH are compatible solvents, as well as AlCl₃ as a CS

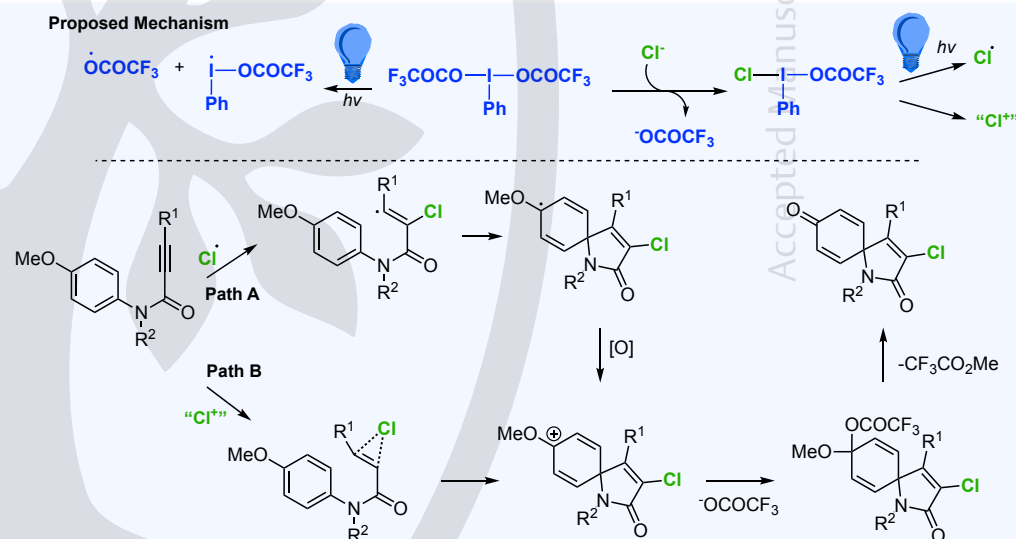
Increasing the temperature slightly (40 °C) leads to the formation of the side product:

**Selected Examples:****Chlorination of Heteroarenes with PIDA****Selected Examples:**(5f) Rao, *New J. Chem.* **2018**, 42, 18889.(5g) Fosu, *Chem* **2019**, 5, 417.**Different conditions were applied***Chlorination of Quinolones with PIFA/PIDA****Selected Examples:****Figure 5 (Part 1)** Recent chlorination methods based on the use of hypervalent iodine reagents PIFA (bis(trifluoroacetoxy)iodo)benzene and PIDA (phenyliodine(III) diacetate) (Part 1)^{5a-h}

Proposed Mechanism for the Photoinduced Decarboxylative Chlorination Using PIDA

(5c) Molander, *Green Chem.* **2023**, 25, 560.Photoinduced Synthesis of Chlorinated Spiro[4,5]trienones of *N*-aryl Alkynamides with PIFA

Proposed Mechanism

(5i) Duan, *Org. Biomol. Chem.* **2020**, 18, 1933.

Further reading:

- (5j) Wang, *Green Chem.* **2018**, 20, 2477.
 (5k) Cariou, *Beilstein J. Org. Chem.* **2018**, 14, 1103.
 (5l) Vallibera, *J. Org. Chem.*, **2020**, 85, 2142.

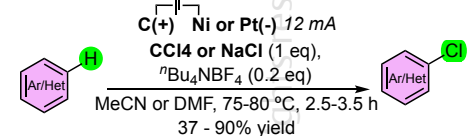
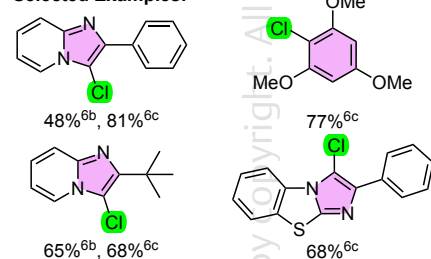
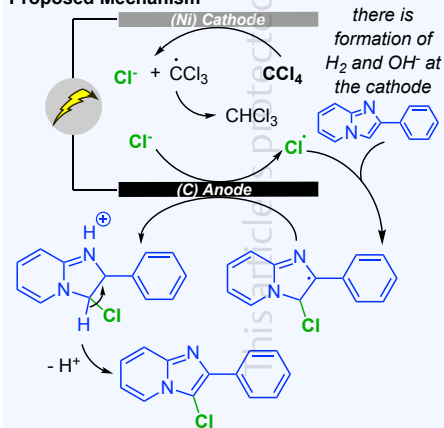
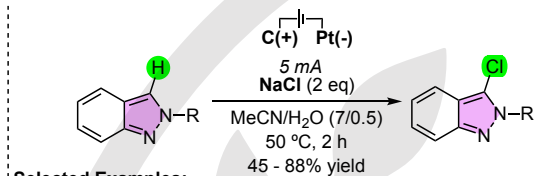
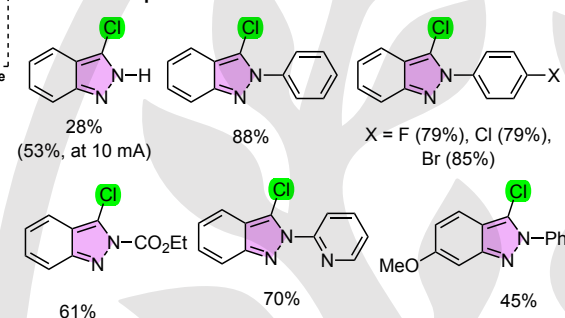
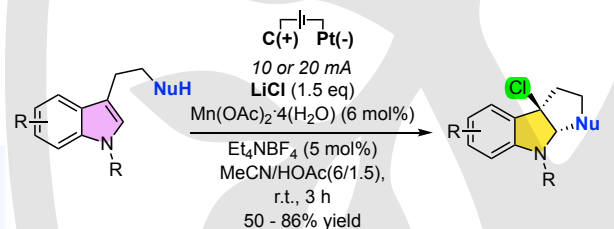
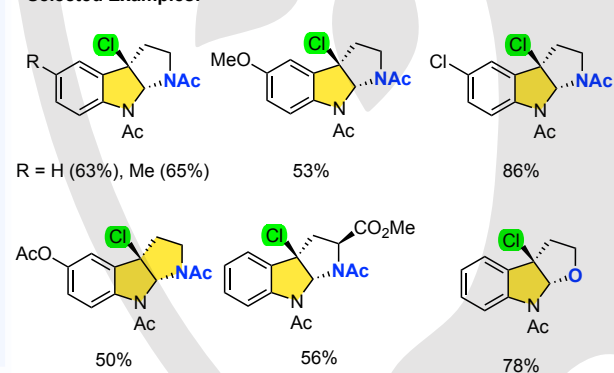
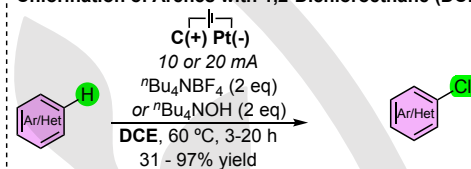
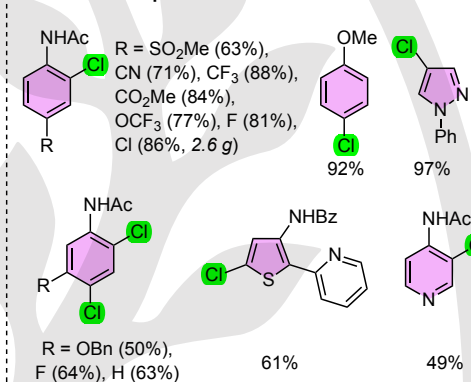
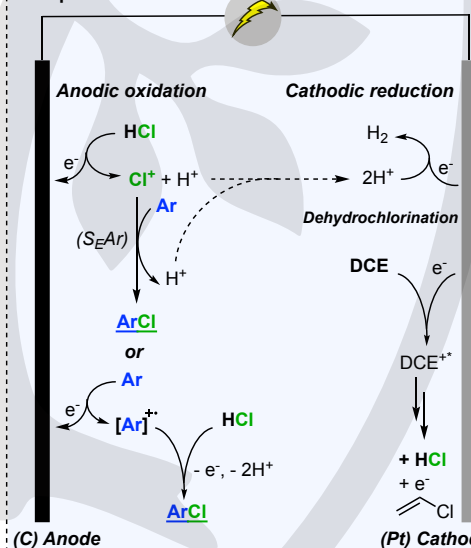
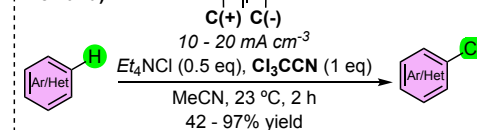
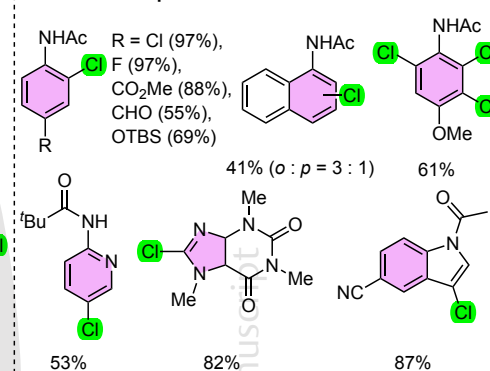
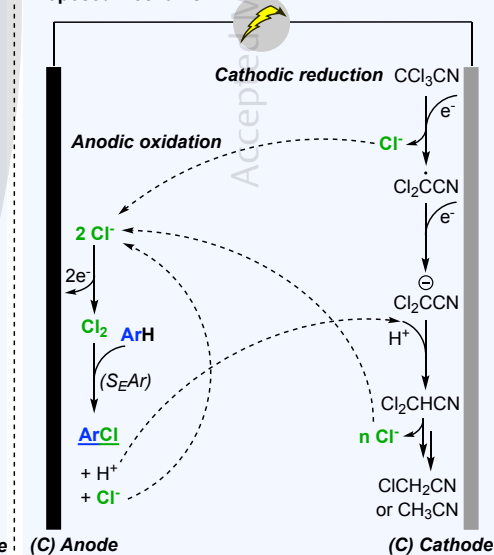
Figure 5 (Part 2) Recent chlorination methods based on the use of hypervalent iodine reagents PIFA (bis(trifluoroacetoxy)iodo)benzene and PIDA (phenyliodine(III) diacetate) (Part 2)^{5c,i,l}

Notable features of Electrochemical Conditions:

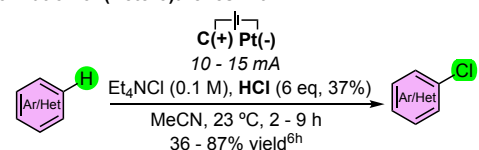
- Usually environmentally friendly
- Exogenous-oxidant/reductant free
- Good functional group tolerance
- Requires mild conditions

Current limitations:

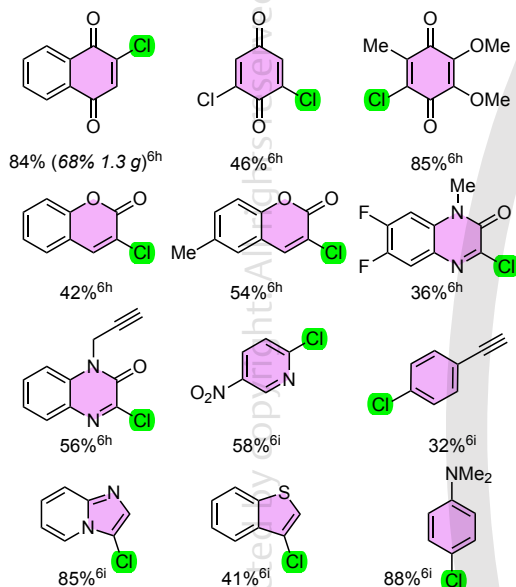
- Can become expensive
- May require a supporting electrolyte
- Use of metal catalysts is limited^{6a}

(6a) Lei, *Nat. Commun.* **2020**, *11*, 802.**Chlorination of Arenes with CCl_4 ^{6b}, NaCl ^{6c,d}, and LiCl ^{6e}****Selected Examples:****Proposed Mechanism**(6b) Lei, *Chin. J. Chem.* **2019**, *37*, 611.(6c) Lei, *iScience* **2019**, *12*, 293.**Selected Examples:**(6d) Shen, *Eur. J. Org. Chem.* **2022**, *2022*, e202200262.**Selected Examples:**(6e) Lei, *Chin. J. Chem.* **2020**, *38*, 1070.**Chlorination of Arenes with 1,2-Dichloroethane (DCE)****Selected Examples:****Proposed Mechanism**(6f) Jiao, *Angew. Chem. Int. Ed.* **2019**, *58*, 4566.**Chlorination of Arenes with Cl_3CCN (Chlorine on Demand)****Selected Examples:****Proposed Mechanism**(6g) Cheng, *Org. Lett.* **2021**, *23*, 3015.**Figure 6 (Part 1)** Electrochlorination of (hetero)arenes^{5a-8}

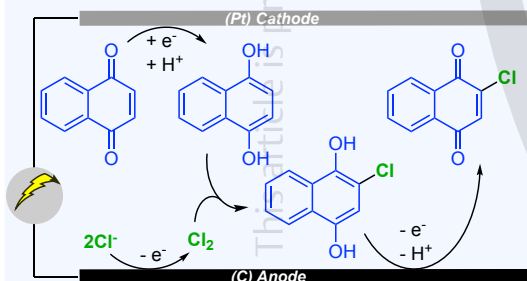
Chlorination of (Hetero)arenes with HCl



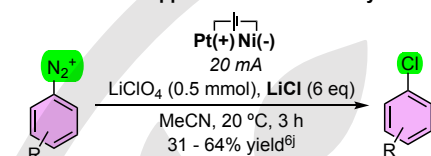
Selected Examples:



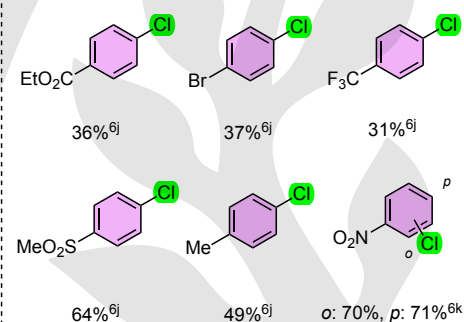
Proposed Mechanism

(6h) Liu, *Tetrahedron Lett.* **2021**, 86, 153514.(6i) Zhou, *ACS Sustainable Chem. Eng.* **2024**, 12, 3289.

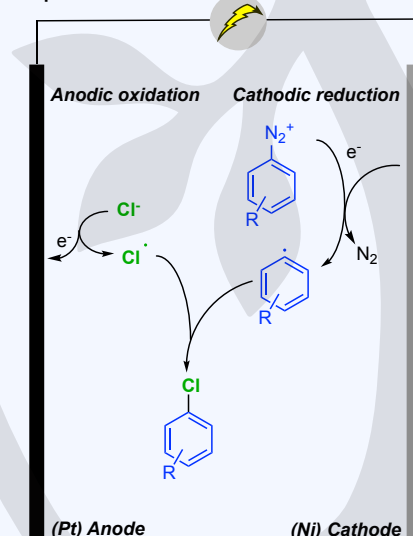
Electrochemical Approach to the Sandmeyer Reaction



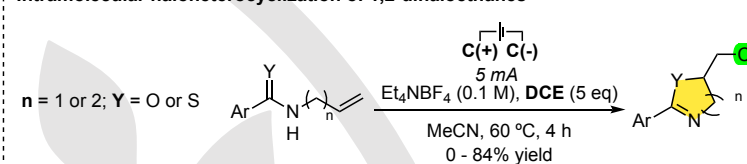
Selected Examples:



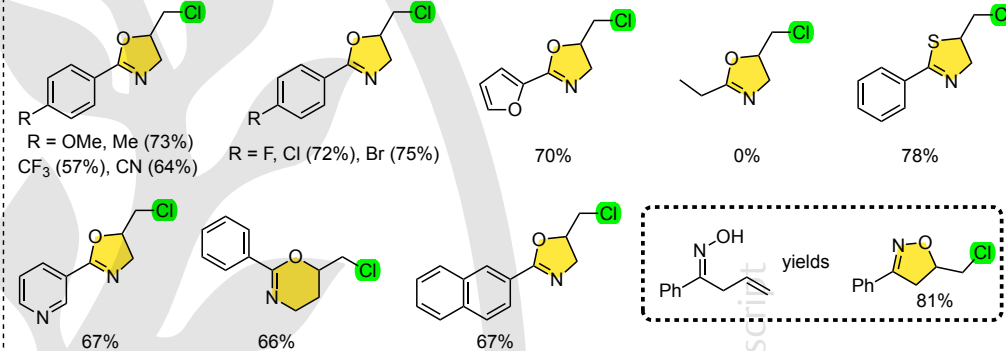
Proposed Mechanism

(6j) Mo, *Chem. Sci.* **2018**, 9, 8731.(6k) Nematollahi, *Org. Lett.* **2020**, 22, 5920.

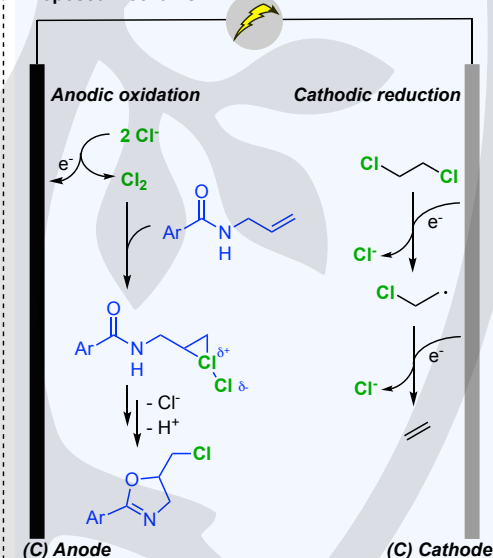
Intramolecular haloheterocyclization of 1,2-dihaloethanes



Selected Examples:



Proposed Mechanism

(6l) Gu, *Tetrahedron Lett.* **2022**, 89, 153602.

Further Reading:

- (6m) Lin, *J. Am. Chem. Soc.* **2017**, 139, 15548.
 (6n) Morrill, *Org. Lett.* **2019**, 21, 9241.
 (6o) Waldvogel and Morandi, *Science* **2021**, 371, 507.
 (6p) Morrill, *Chem. Commun.* **2021**, 57, 12643.
 (6q) McNeil, *Nat. Chem.* **2023**, 15, 222.
 (6r) Zhang, *Tetrahedron Lett.* **2023**, 114, 154244.
 (6s) Cheng, *Chem. Educ.* **2023**, 100, 3008.

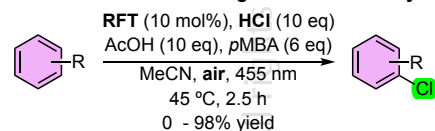
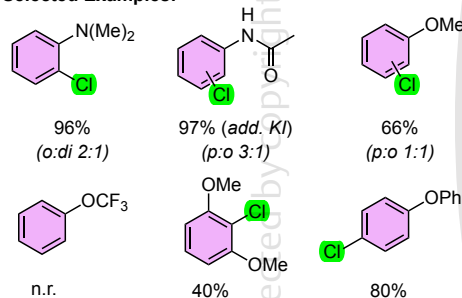
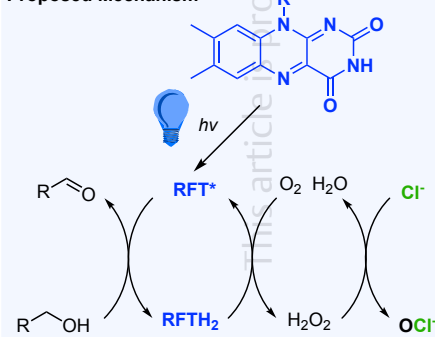
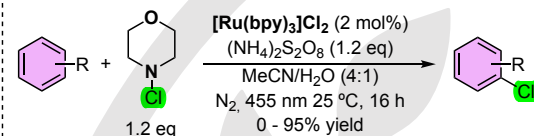
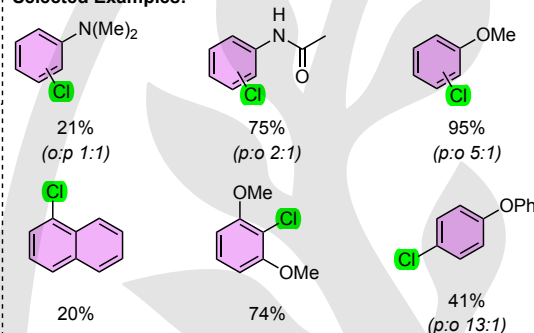
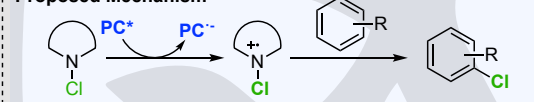
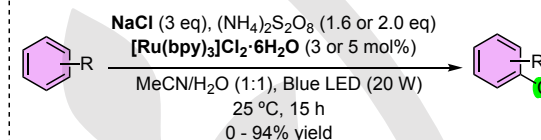
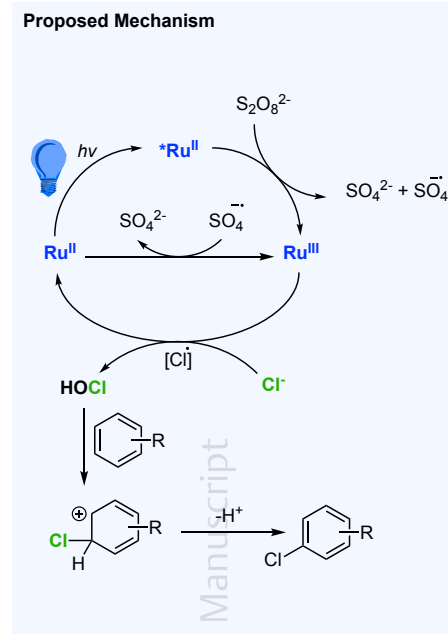
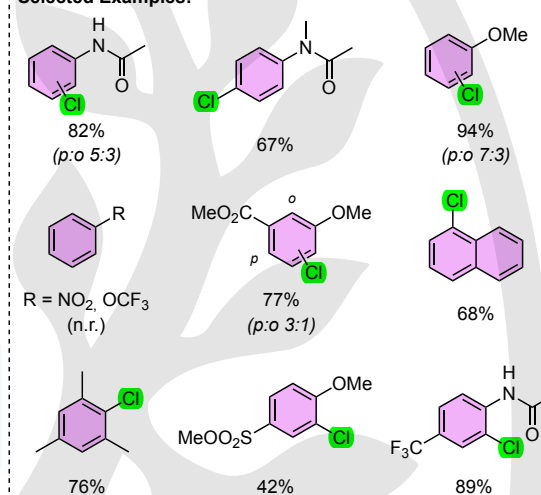
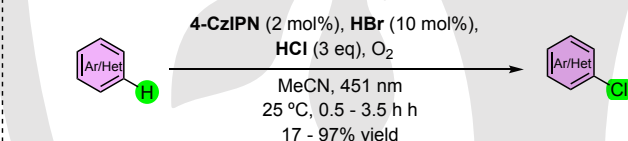
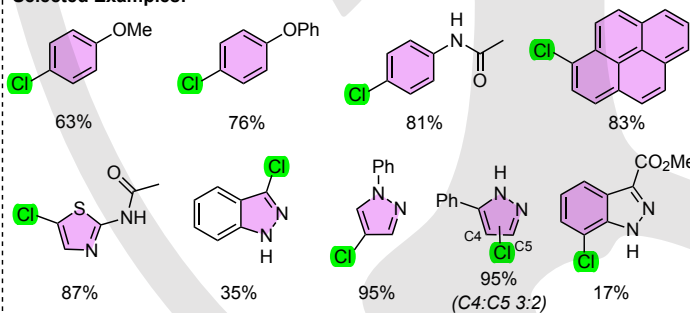
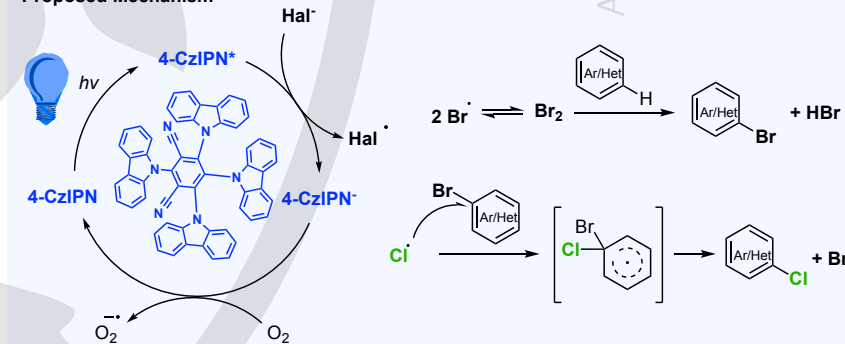
Figure 6 (Part 2) Electrochlorination of (hetero)arenes^{6h-s}

Notable features of Photochemical Conditions:

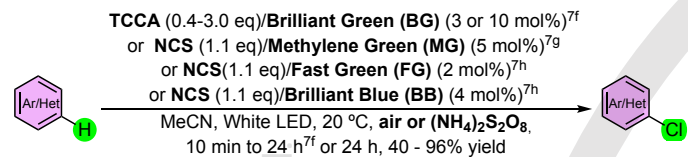
- Offer greener and safer processes
- Access to new chemical space
- Enable rational catalyst design

Current limitations:

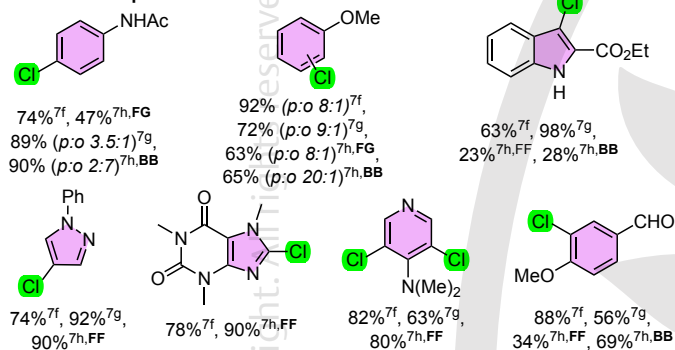
- Difficult to scale up
- Use of expensive setups
- Limited catalyst characterization
- Unclear reaction mechanisms
- Low reproducibility
- Limited Regioselectivity^{7a}

(7a) Noël, *Chem Catal.* **2022**, *2*, 468.**Oxidative Chlorination using Flavin Photocatalysts****Selected Examples:****Proposed Mechanism**(7b) König, *Angew. Chem. Int. Ed.* **2016**, *55*, 5342.**1-Chloromorpholine for the Chlorination of Arenes****Selected Examples:****Proposed Mechanism**(7c) König, *Tetrahedron Lett.* **2016**, *72*, 7821.**Photochlorination of Arenes with NaCl****Selected Examples:**(7d) Hu, *Chem. Sci* **2017**, *8*, 7009.**Photochlorination of (Hetero)arenes through in situ Bromination****Selected Examples:****Proposed Mechanism**(7e) König, *Eur. J. Org. Chem.* **2020**, *10*, 1491.**Figure 7 (Part 1)** Photochlorination of (hetero)arenes^{7a-e}

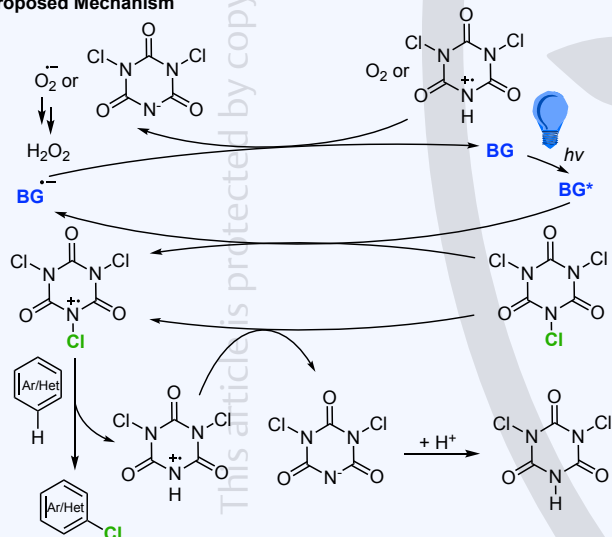
TCCA/NCS Activation Using Organic Dyes for (Hetero)arenes Chlorination:



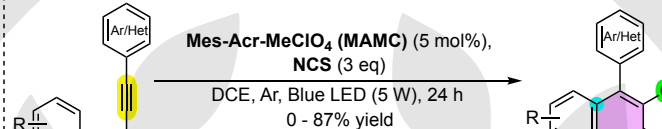
Selected Examples:



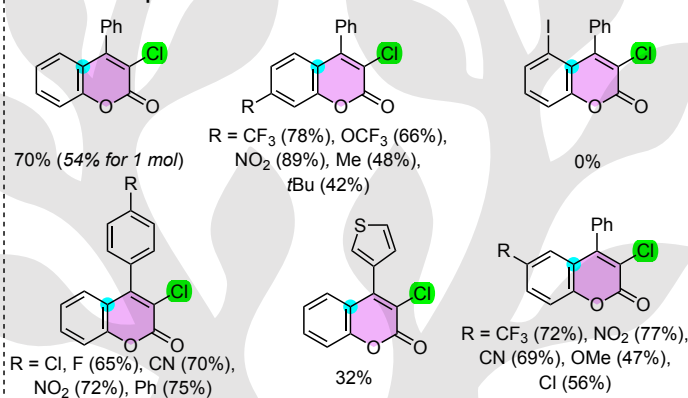
Proposed Mechanism

(7f) Lamar, *Org. Lett.* **2019**, *21*, 4229.(7g) Lamar, *Tetrahedron Lett.* **2019**, *75*, 130498.(7h) Lamar, *ACS Omega* **2020**, *5*, 7693.

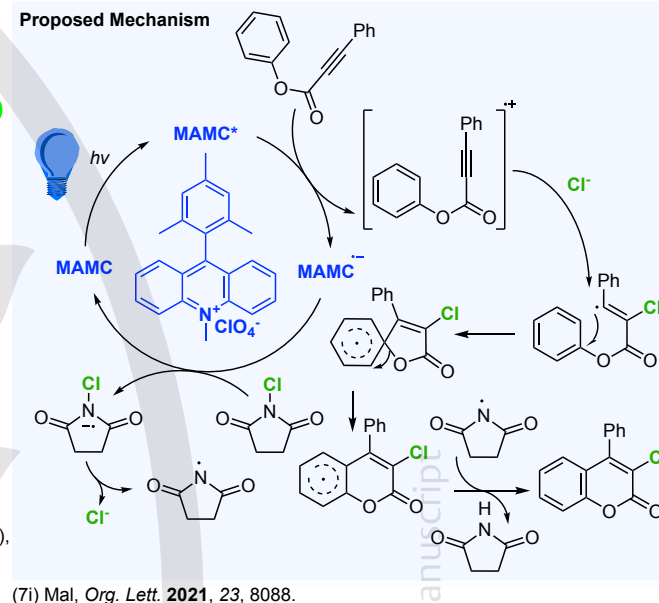
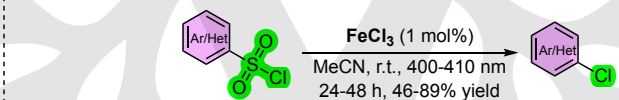
Photochlorinative Cyclization of Aryl Alkynoates into 3-Chlorocoumarins



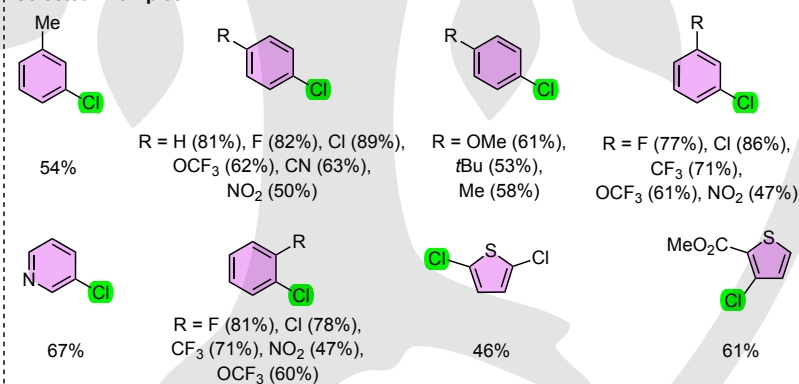
Selected Examples:



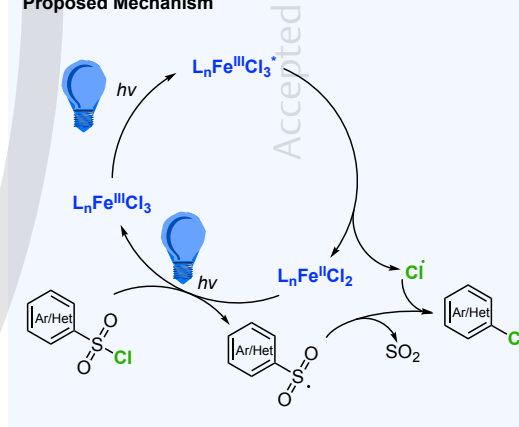
Proposed Mechanism

(7i) Mal, *Org. Lett.* **2021**, *23*, 8088.Photochlorination of Aromatic Sulfonyl Chlorides using FeCl₃

Selected Examples:

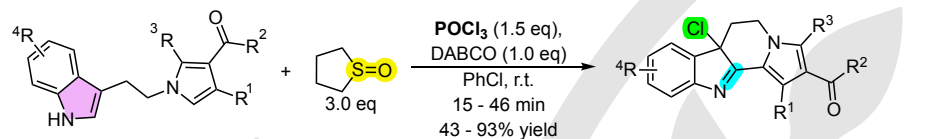
(7j) Dian, *Org. Lett.* **2023**, *25*, 4576.

Proposed Mechanism

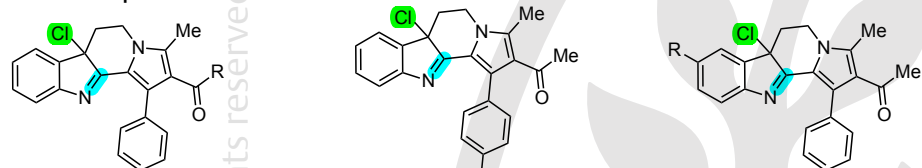


Further Reading:

(7k) Huang, *Org. Biomol. Chem.* **2022**, *20*, 5319.(7l) Zhang, *Mol. Catal.* **2023**, *537*, 112950.(7m) Wu, *J. Org. Chem.* **2020**, *85*, 9080.Figure 7 (Part 2) Photochlorination of (hetero)arenes^{7f–m}

Sulfoxide-Mediated Chlorocyclization of Pyrrole-Tethered Indoles for the Synthesis of Indolizino[8,7-*b*]indoles

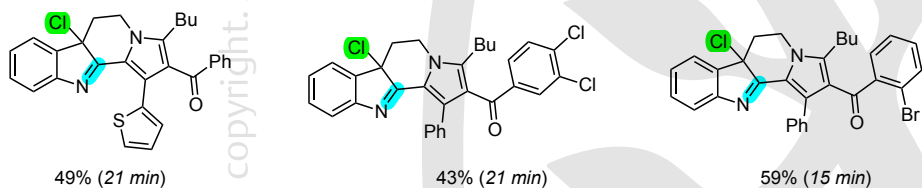
Selected Examples:



R = OMe (93%, 34 min),
Me (65%, 20 min)

R = Cl (85%, 27 min),
Me (57%, 34 min), OMe (61%, 46 min)

R = OMe (62%, 20 min),
Cl (46%, 42 min)

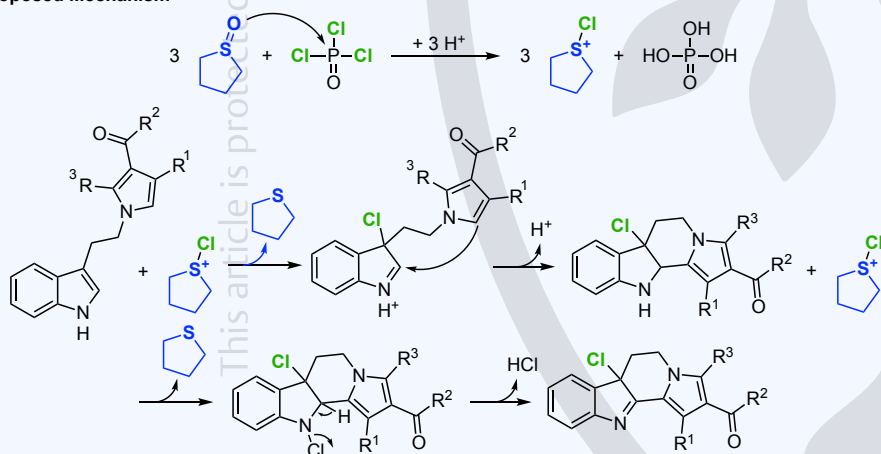


49% (21 min)

43% (21 min)

59% (15 min)

Proposed Mechanism



(8f) Cui, *J. Org. Chem.* **2023**, *88*, 16400.

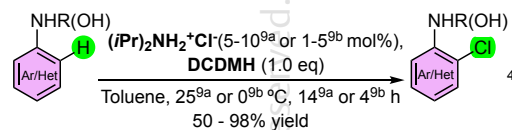
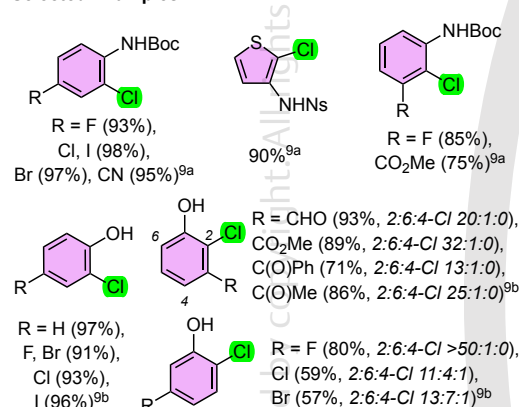
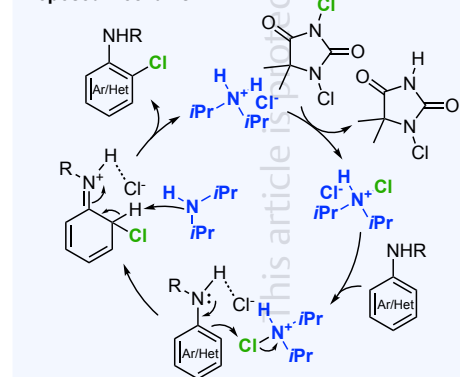
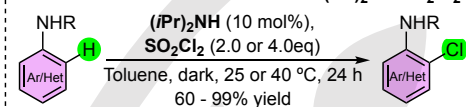
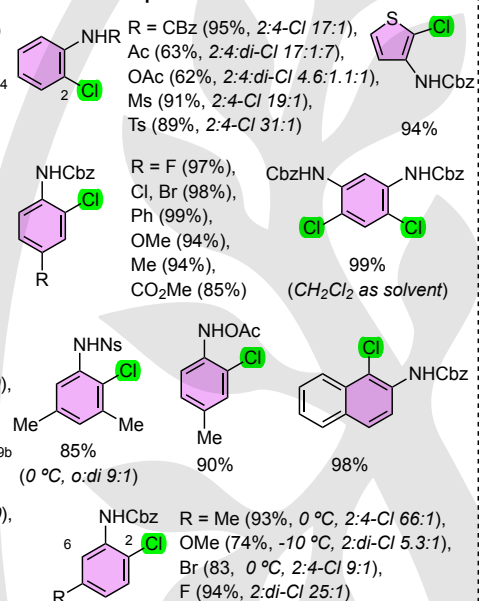
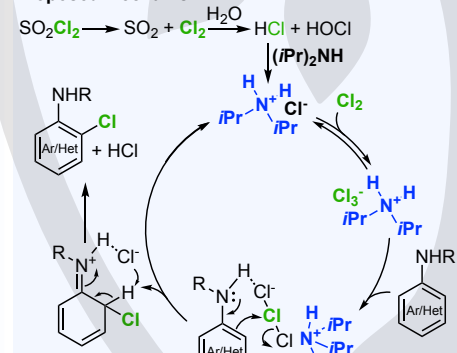
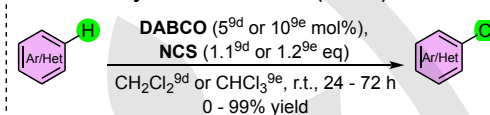
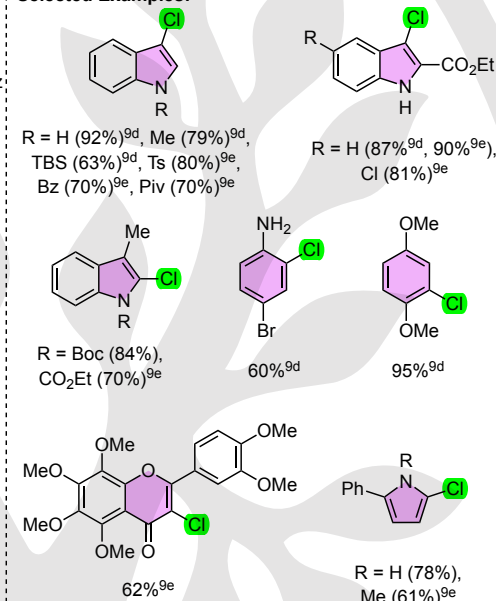
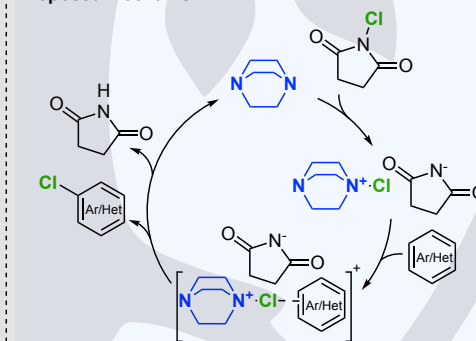
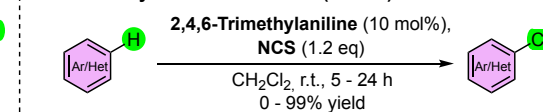
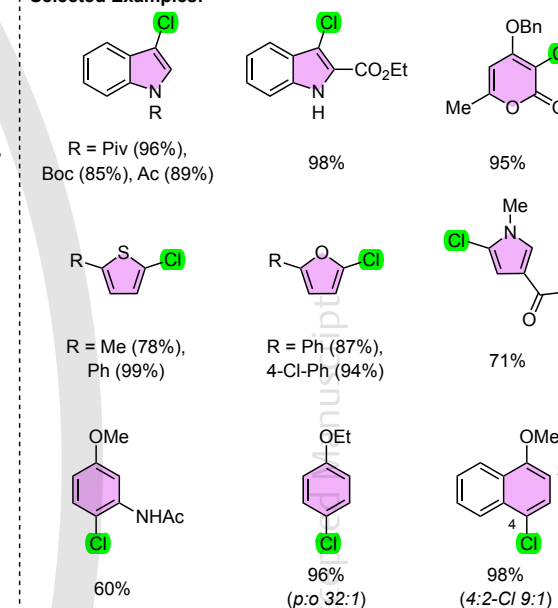
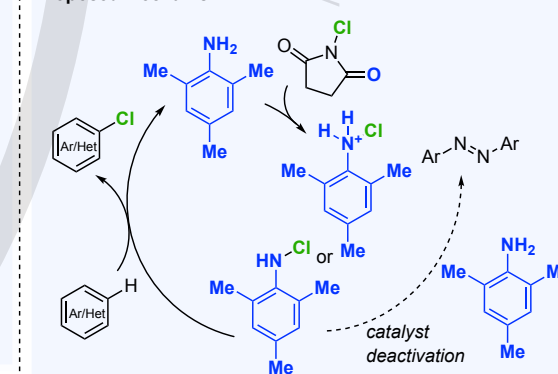
Further Reading:

- (8g) Xu, *Eur. J. Org. Chem.* **2018**, *2018*, 4705.
 (8h) Maddani, *New. J. Chem.* **2019**, *43*, 6563.
 (8i) Duan, *Asian J. Org. Chem.* **2019**, *8*, 479.
 (8j) Liao, *J. Org. Chem.* **2022**, *87*, 15101.

Figure 8 (Part 2) Sulfoxide-mediated chlorination of (hetero)arenes^{8f-j}

Notable features of Amine-Catalyzed Chlorinations:

- Requires mild reaction conditions
- Offers high efficiency and practicality
- High selectivity, in some cases
- Catalyst can be easily prepared and recovered

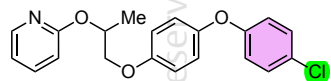
Ortho-Chlorination using $(iPr)_2NH_2^+Cl^-/DCDMH$ **Selected Examples:****Proposed Mechanism**(9a) Yeung, *Angew. Chem. Int. Ed.* **2016**, *55*, 16101.(9b) Yeung, *ACS Catal.* **2018**, *8*, 4033.**Ortho-Chlorination of Anilines with $(iPr)_2NH/SO_2Cl_2$** **Selected Examples:****Proposed Mechanism**(9c) Xiong, *Chem. Commun.* **2022**, *58*, 13325.**DABCO-Catalyzed Chlorination of (Hetero)arenes****Selected Examples:****Proposed Mechanism**(9d) Huang, *RSC Adv.* **2022**, *12*, 7115.(9e) Yang, *Tetrahedron Lett.* **2024**, *136*, 154928.**Aniline-Catalyzed Chlorination of (Hetero)arenes****Selected Examples:****Proposed Mechanism**(9f) Yamamoto, *Chem. Eur. J.* **2015**, *21*, 11976.**Figure 9** Amine-catalyzed chlorination of (hetero)arenes^{9a-f}

Notable features of *Thianthrenium-Aided Chlorination*:

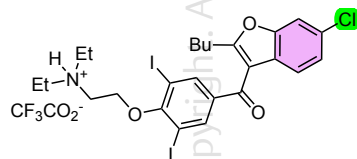
- Offers high selectivity
- Several types of functionalization can be attained
- Compatible with photoredox and transition-metal catalysis

Current limitations:

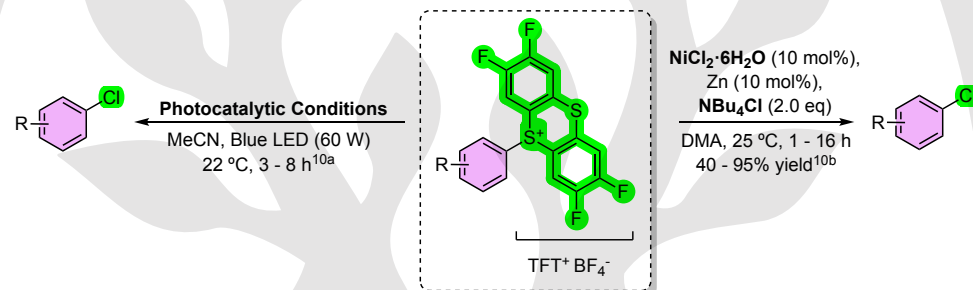
- High cost of starting materials (TFT and TFT S-Oxide)

Selected Examples (conditions shown below):

NBu₄Cl (2.5 eq), CuCl (2.0 eq), **Ru(bpy)₃(PF₆)₂** (2 mol%)
53% yield



LiCl (4.5 eq), Cu(MeCN)₄BF₄ (1.5 eq), CF₃CO₂H (1.1 eq),
Ru(bpy)₃(PF₆)₂ (4 mol%),
50% yield



(10a) Ritter, *Nature* **2019**, 567, 223.

(10b) Ritter, *J. Am. Chem. Soc.* **2023**, 145, 9988.

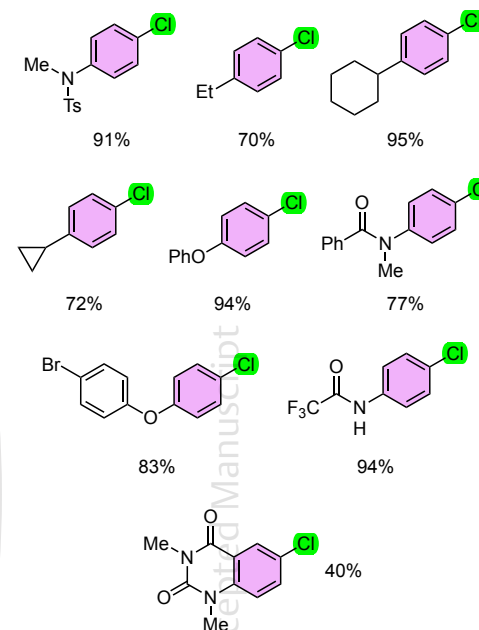
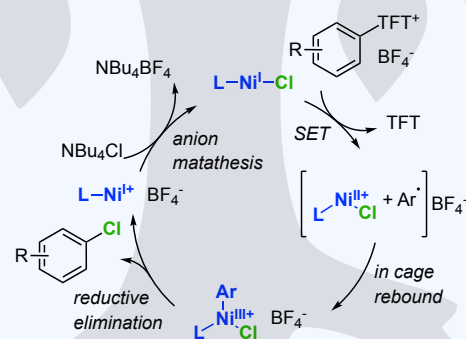
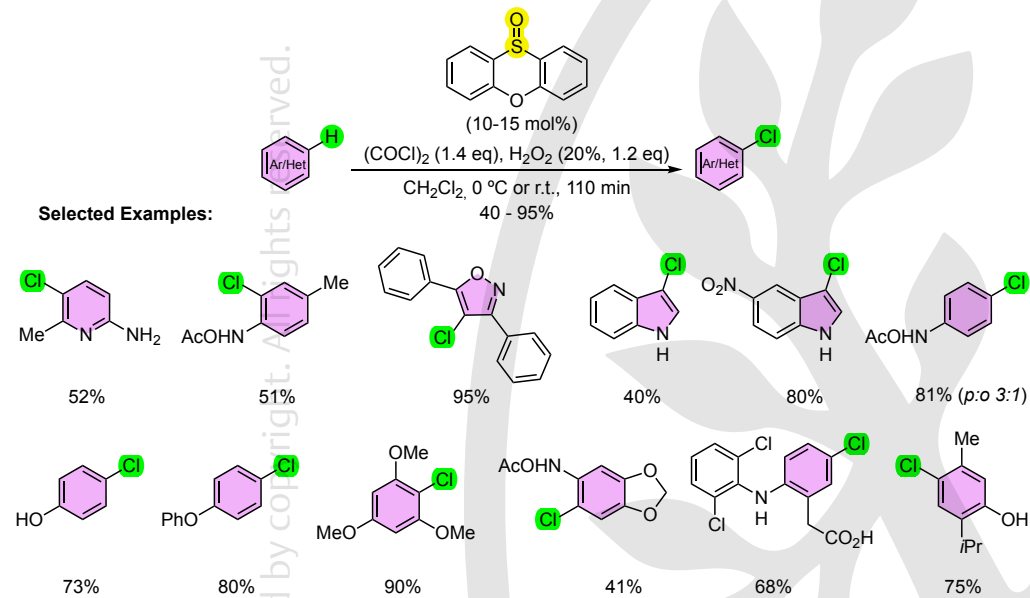
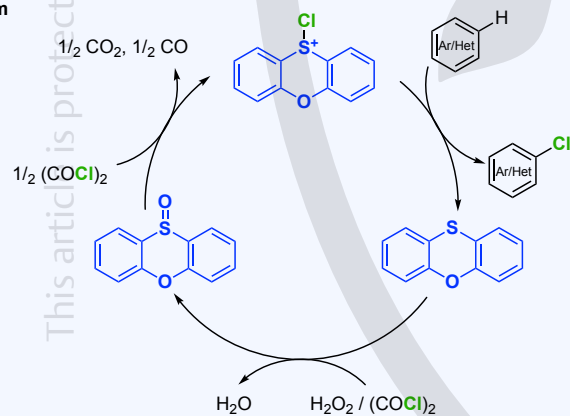
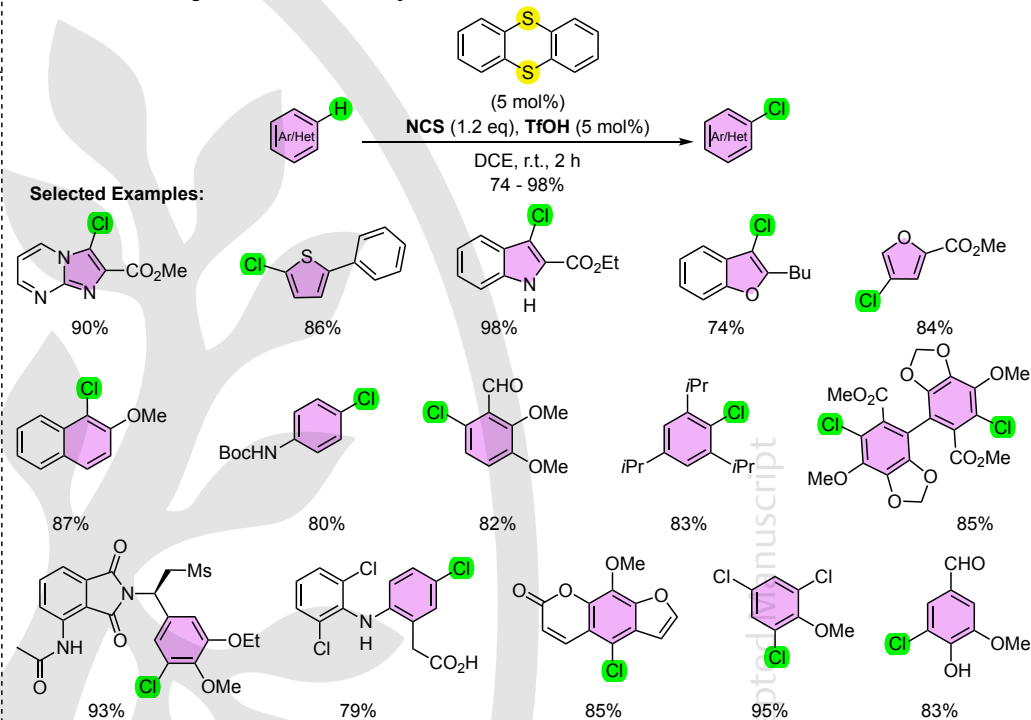
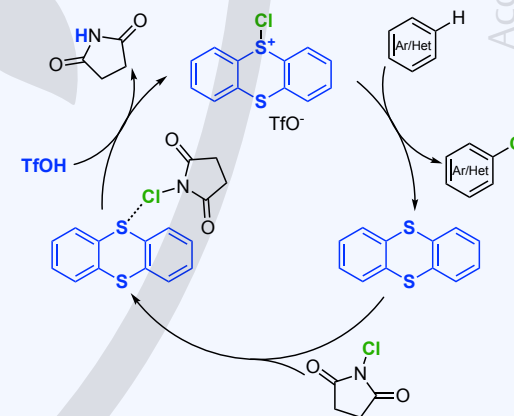
Selected Examples:**Proposed Mechanism**

Figure 10 Thianthrenium-aided chlorination of arenes^{10a,b}

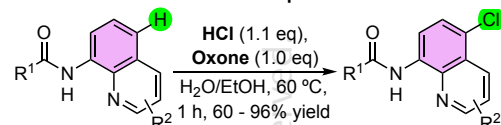
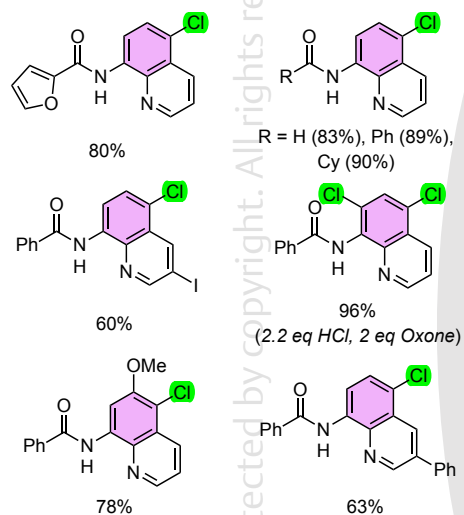
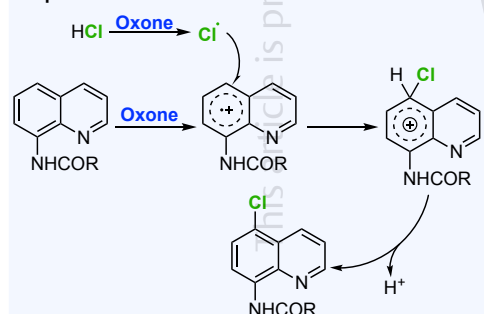
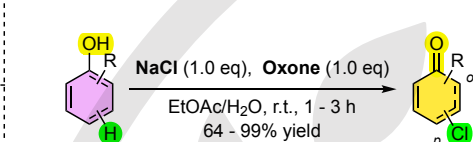
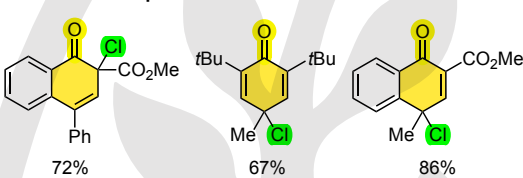
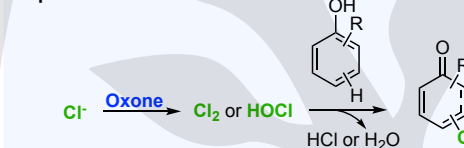
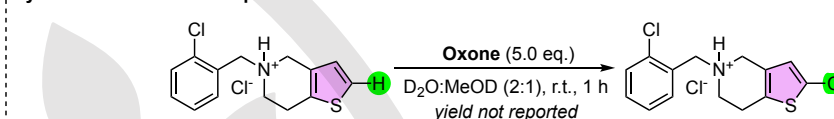
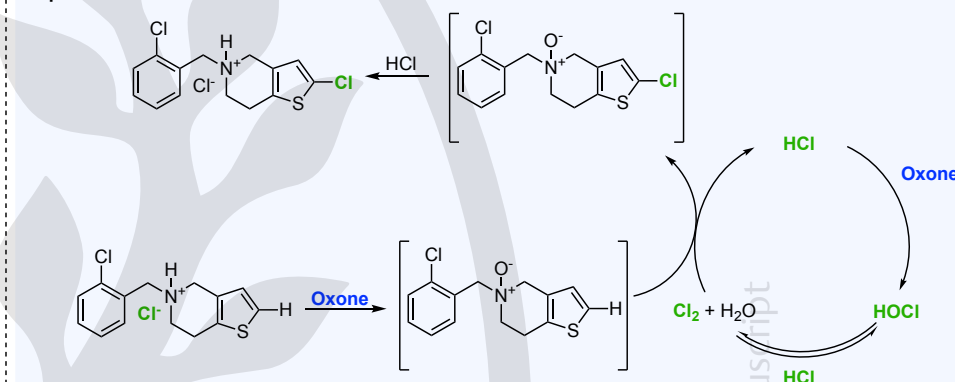
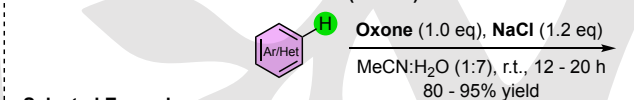
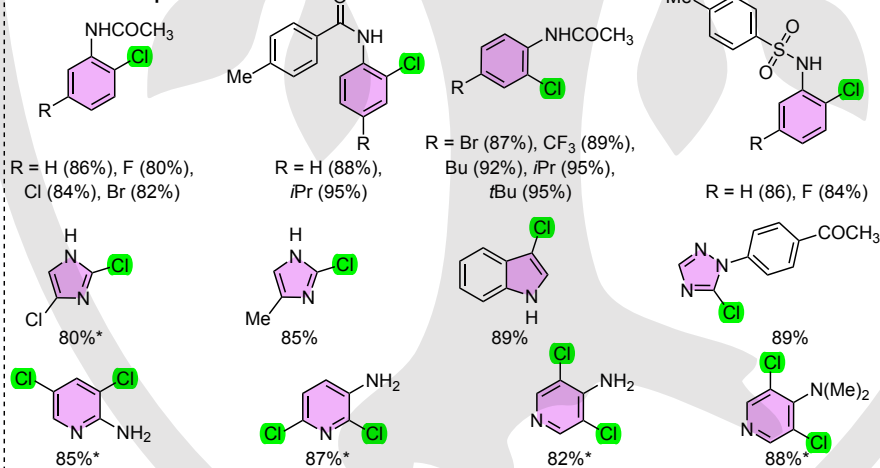
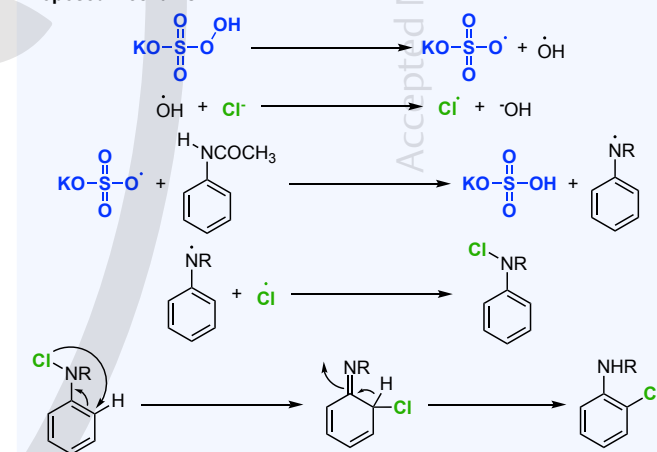
Notable features of Chlorosulfonium-Mediated Chlorination:

- High functional group tolerance
- Allow for only gaseous byproducts

Monochlorination of (Hetero)arenes with Electrophilic Chlorosulfonium**Proposed Mechanism**(11a) Gamba-Sánchez, *Adv. Synth. Catal.* **2023**, 365, 4576.**NCS Activation using a Thianthrene/TfOH System****Proposed Mechanism**(11b) Du, *Chem. Sci.* **2024**, 15, 13058.**Figure 11** Monochlorination of (hetero)arenes with electrophilic chlorosulfonium species^{11a,b}

Notable features of Oxone-Mediated Chlorination:

- Low cost
- Offers high practicality and versatility
- Enables chlorination of electron-rich and -deficient arenes

Radical Chlorination of Aminoquinolines with HCl**Selected Examples:****Proposed Mechanism**(12a) Zhang, *Tetrahedron Lett.* **2018**, 59, 2243.**NaCl/Oxone-Mediated Dearomative Chlorination of Arenols****Selected Examples:****Proposed Mechanism**(12b) Ishihara, *Eur. J. Org. Chem.* **2019**, 2019, 27.**Synthesis of 2-Chlorotoclopidine with Oxone****Proposed Mechanism**(12c) Baumann, *ChemistrySelect* **2019**, 4, 13479.**NaCl/Oxone-Mediated Chlorination of (Hetero)arenes****Selected Examples:****Proposed Mechanism**

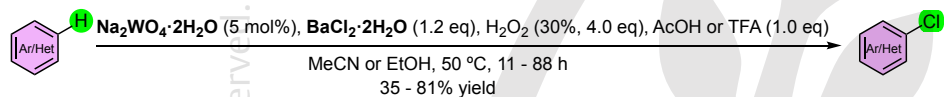
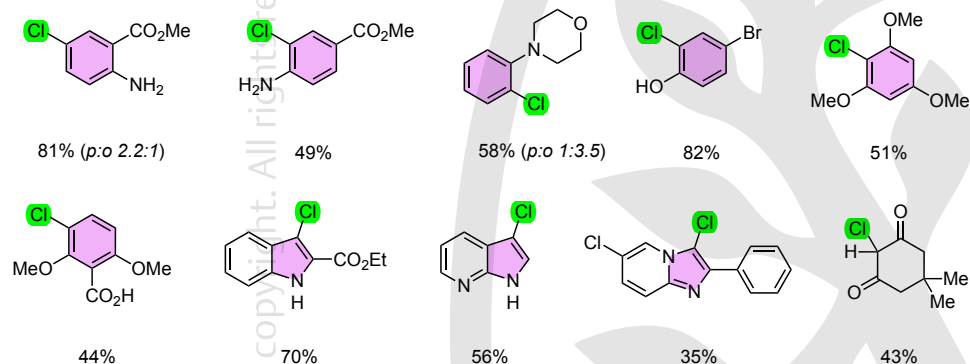
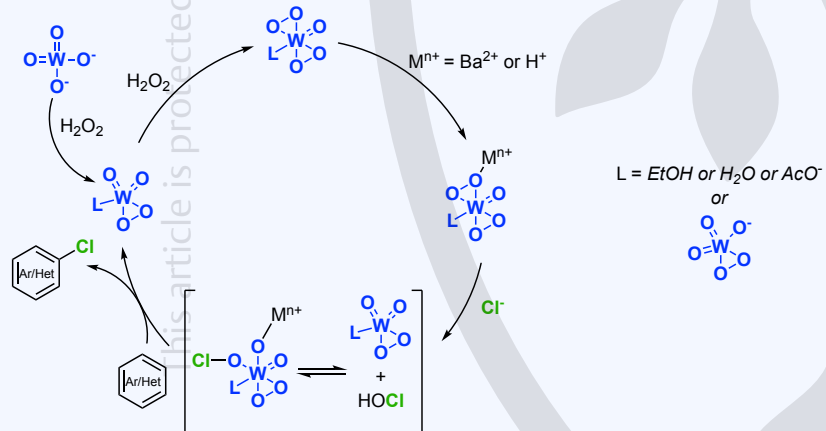
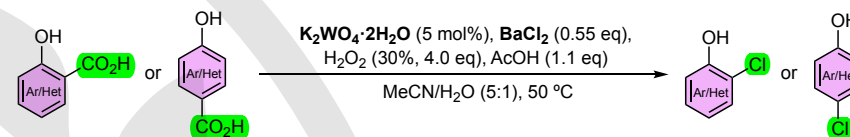
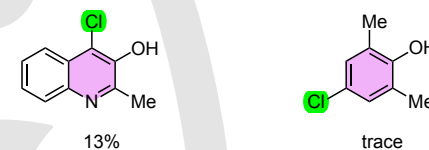
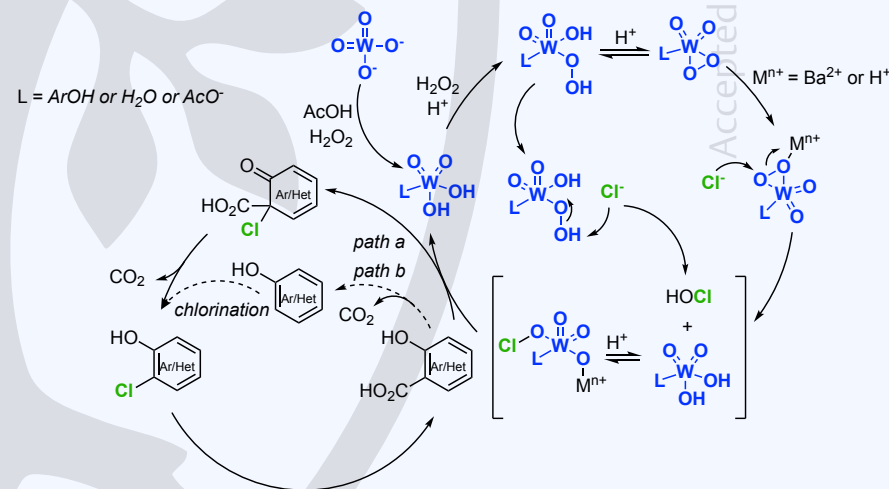
*2 eq NaCl, 1 eq Oxone
 (12d) Raju, *Asian J. Org. Chem.* **2019**, 8, 1380.

Further Reading:
 (12e) Lu, *Org. Lett.* **2017**, 19, 4560.

Figure 12 Oxone-mediated chlorination of (hetero)arenes^{12a-e}

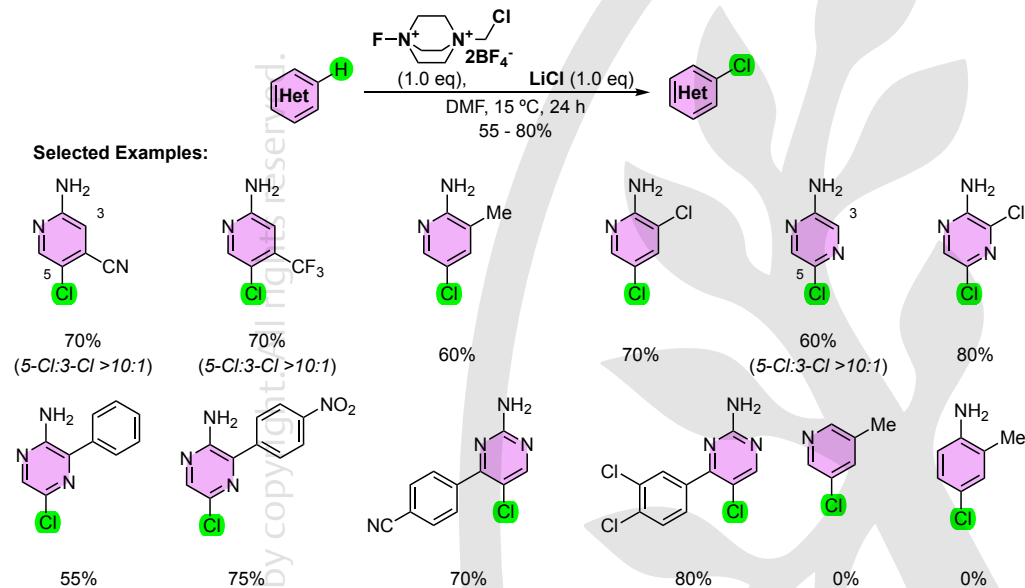
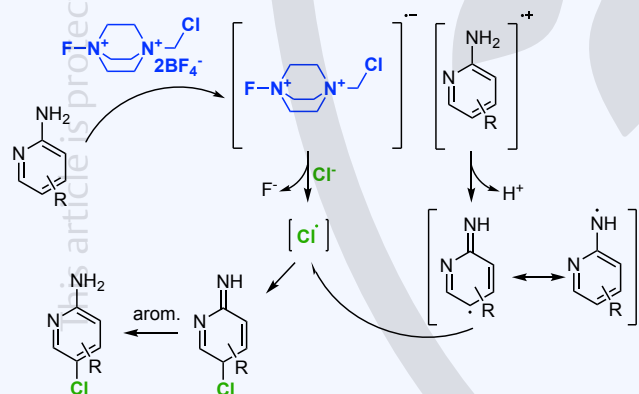
Notable features of *Bioinspired Tungstate-Catalyzed Chlorination*:

- Requires mild pH
- Notable chemo- and regioselectivity can be achieved
- Diverse functional group tolerance
- Cost-, environment- and operation-efficient
- Current limitations:**
- Long reaction times.
- Too electronically rich arenes lead to undesired oxidative transformations

Tungstate-Catalyzed Chlorination of (Hetero)arenes**Selected Examples:****Proposed Mechanism**(13a) Chen, *iScience* **2020**, *23*, 101072.**Tungstate-Catalyzed Decarboxylative Chlorination of (Hetero)phenolic Acids****Selected Examples:****Proposed Mechanism**(13b) Chen, *ACS Sustainable Chem. Eng.* **2022**, *10*, 7453.**Figure 13** Tungstate-catalyzed chlorination of (hetero)arenes^{13a,b}

Notable features of *Selectfluor*-Mediated Chlorination:

- Good regioselectivity can be achieved
- Uses easily obtainable chlorine sources
- Requires mild conditions
- Good functional group tolerance

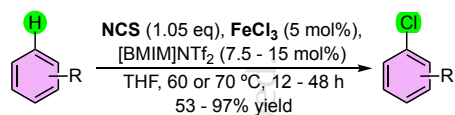
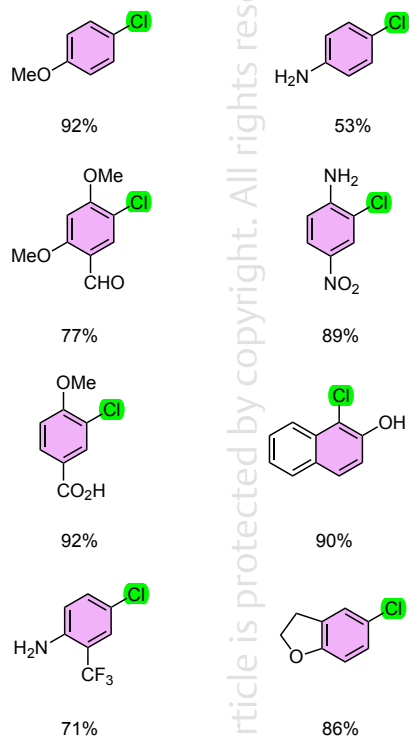
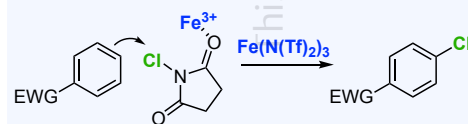
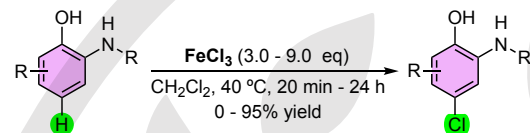
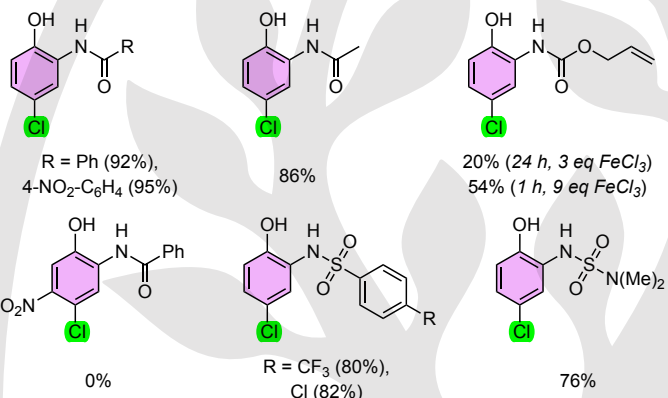
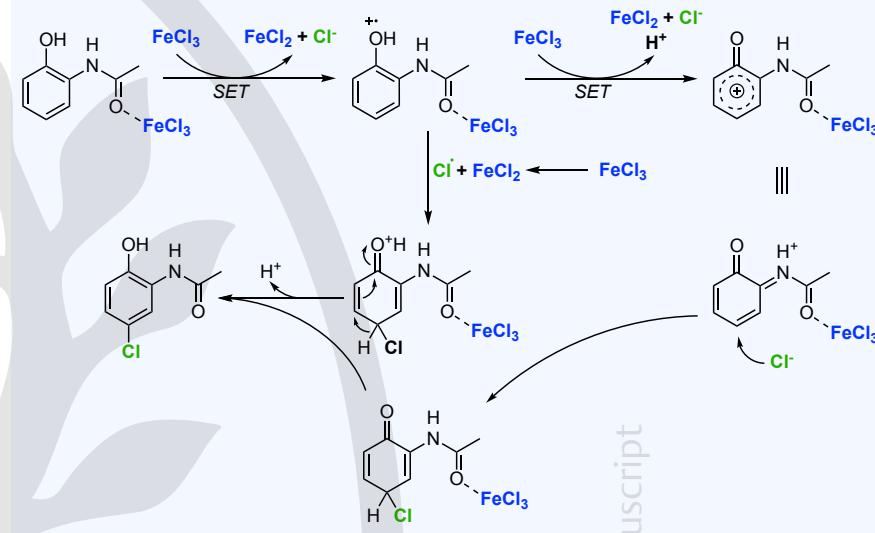
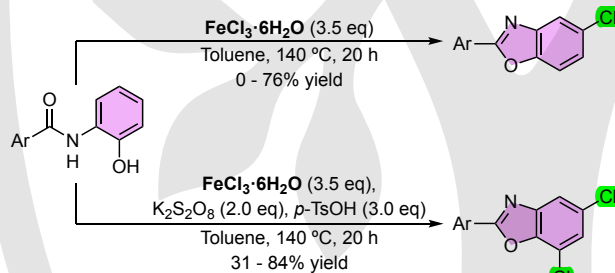
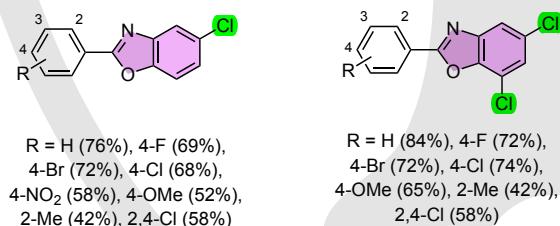
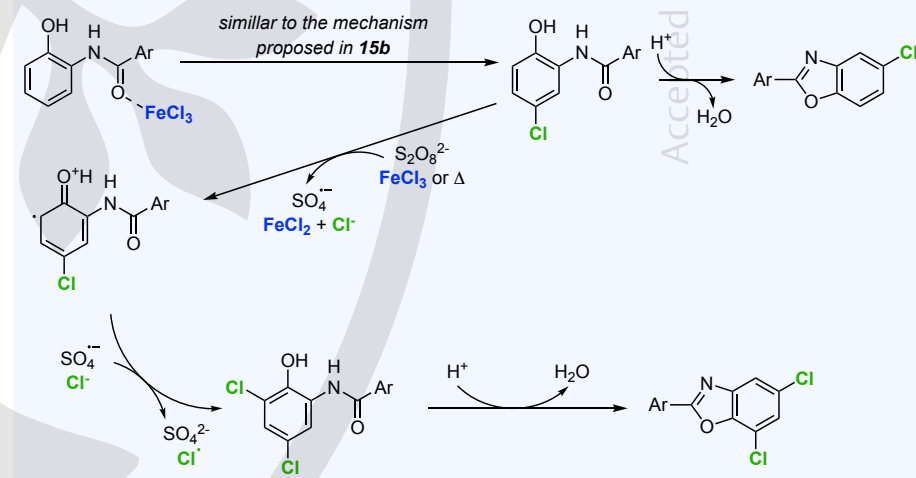
Regioselective Chlorination of 2-Aminopyridines and 2-Aminodiazines with LiCl**Proposed Mechanism**(14a) Zhao, *Org. Biomol. Chem.* **2019**, *17*, 6342.**Further Reading:**

- (14b) Rieth, *J. Org. Chem.* **2002**, *67*, 4487.
 (14c) Heinrich, *ChemMedChem.* **2023**, *18*, e202300144.
 (14d) Nişancı, *Org. Lett.* **2022**, *24*, 8261.

Figure 14 Selectfluor-mediated chlorination of 2-aminopyridines and 2-aminodiazines with LiCl ^{14a-d}

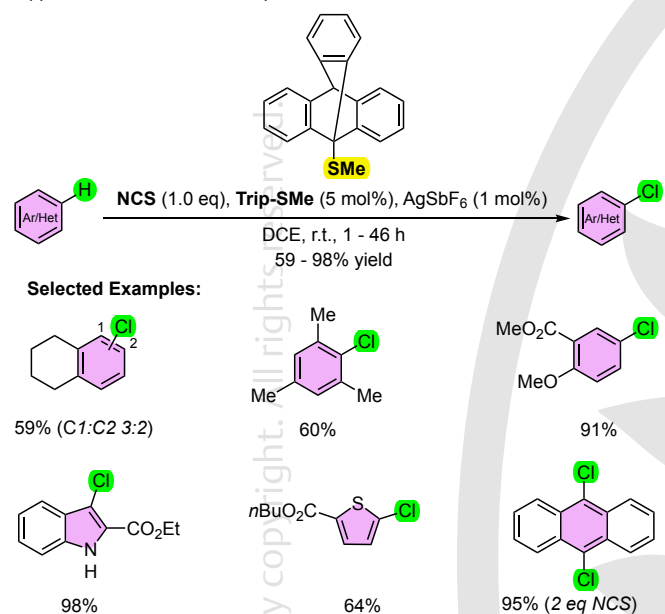
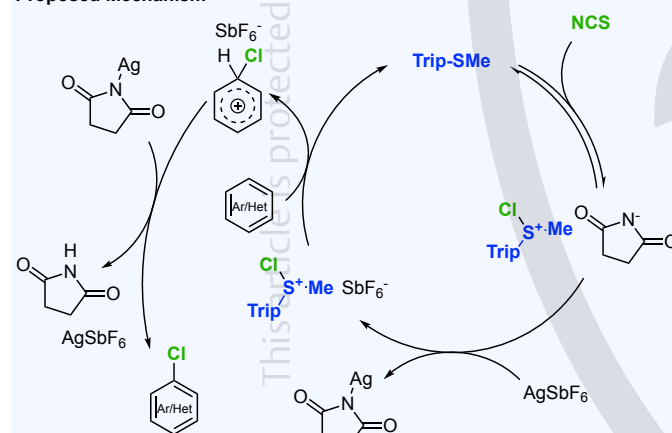
Notable features of Fe(III)-Mediated Chlorination:

- Desirable regioselectivity can be achieved
- Requires mild conditions

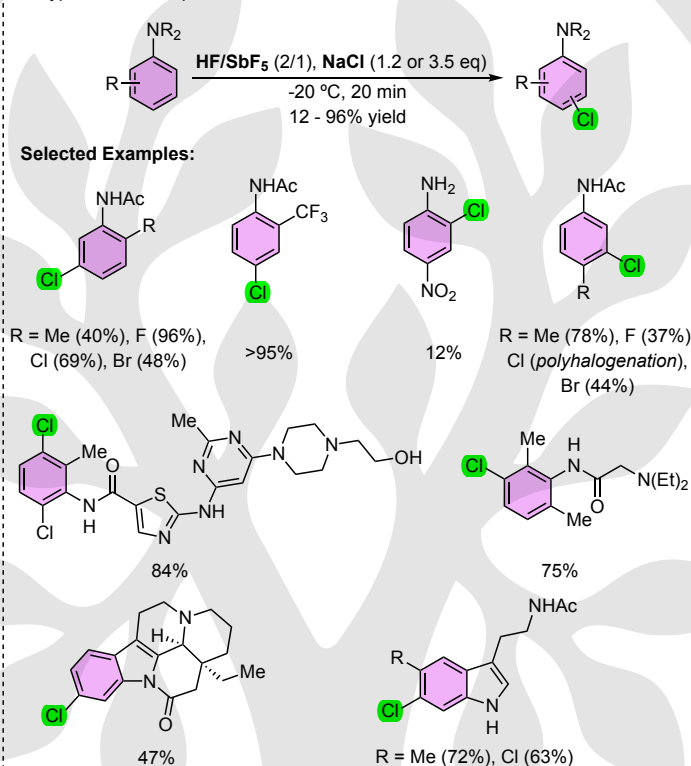
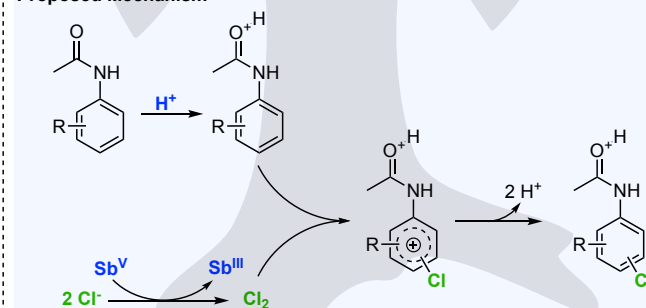
Fe(III)-Catalyzed Chlorination of Activated Arenes**Selected Examples:****Proposed Mechanism**(15a) Sutherland, *J. Org. Chem.* **2017**, *82*, 7529.**Fe(III)-Mediated Chlorination of 2-Amidophenols****Selected Examples:****Proposed Mechanism****Fe(III)-Mediated Synthesis of Chlorinated 2-Arylbenzoxazoles****Selected Examples:****Proposed Mechanism****Further Reading:**(15d) Chow, *Chem. Commun.* **2022**, *58*, 10627.**Figure 15** Fe(III)-mediated chlorination of arenes^{15a-d}

Notable features of Triptyceny Sulfide-Catalyzed Electrophilic Chlorination:

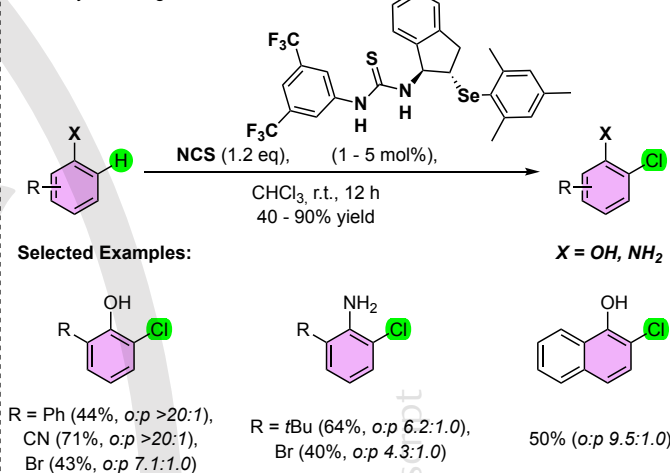
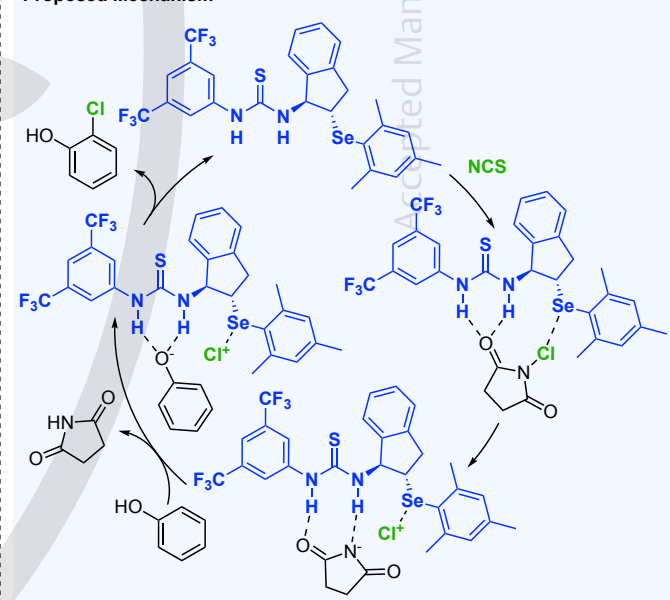
- Requires mild conditions
- Applicable to unactivated compounds

**Proposed Mechanism**(16a) Miura, *J. Am. Chem. Soc.* **2020**, *142*, 1621.**Notable features of Superacid-Mediated Chlorination of N-Containing Arenes:**

- Regioselective chlorination
- Chlorination at "non-classical" positions
- Polyprotonation as protection
- Uses NaCl as chlorine source

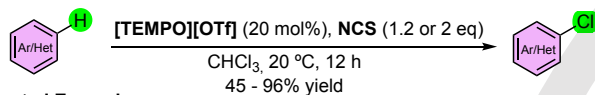
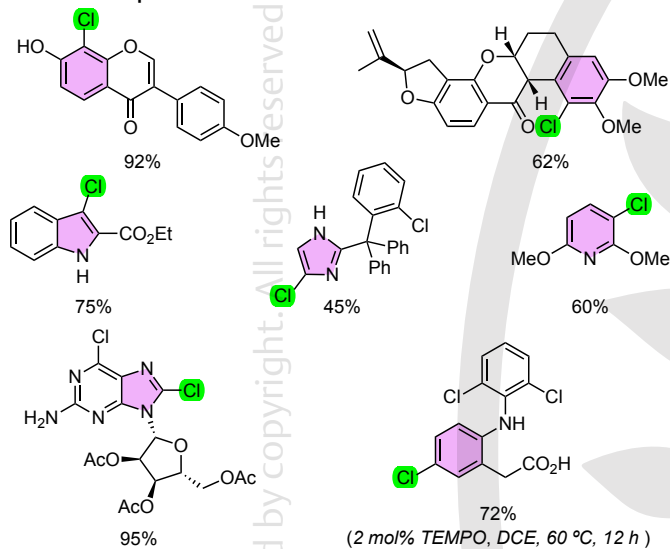
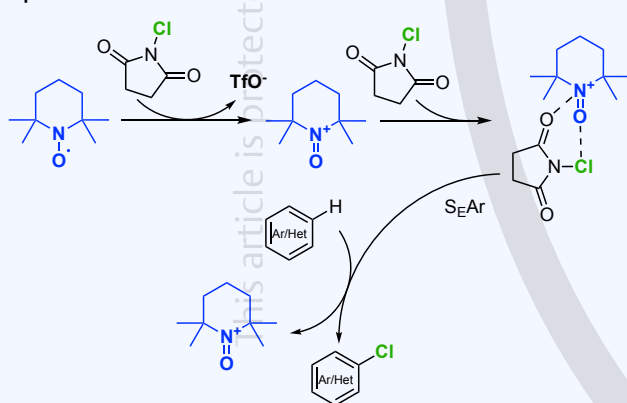
**Proposed Mechanism**(16b) Thibaudeau, *Chem. Eur. J.* **2020**, *26*, 10411.**Notable features of Chlorination with Lewis Basic Selenoether Catalyst:**

- *Ortho*-selective
- Appropriate to unprotected anilines
- Catalyst loading as low as 1 mol%

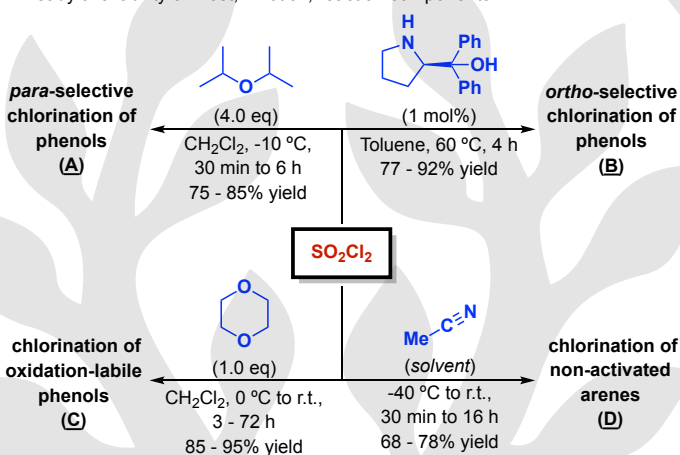
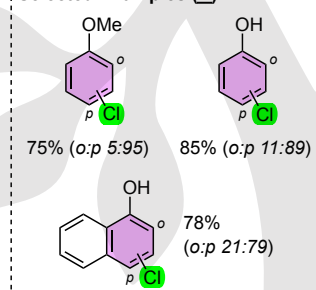
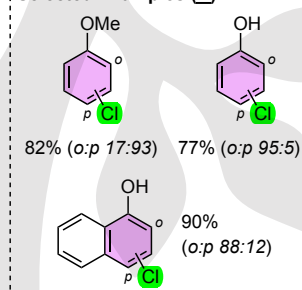
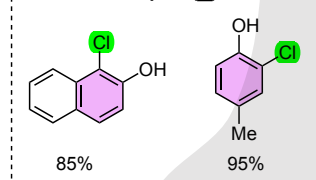
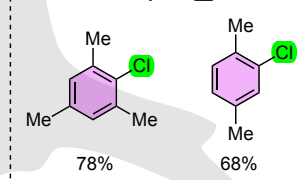
**Proposed Mechanism**(16c) Gustafson, *J. Org. Chem.* **2020**, *85*, 13895.**Figure 16 (Part 1)** Chlorination of (hetero)arenes using various catalysts^{16a-c}

Notable features of TEMPO-Catalyzed (Hetero)arene Chlorination:

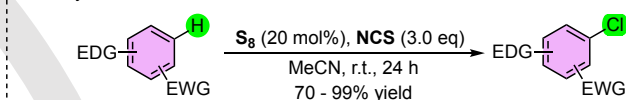
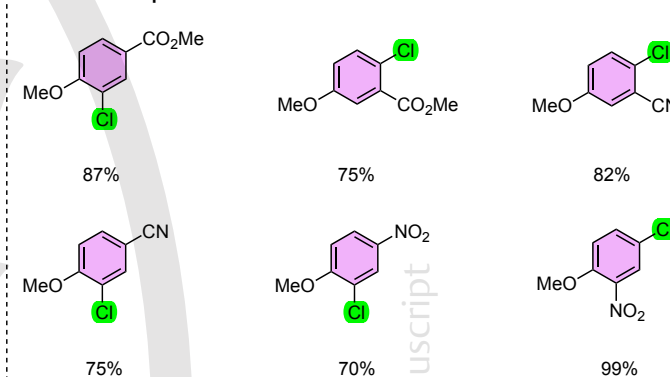
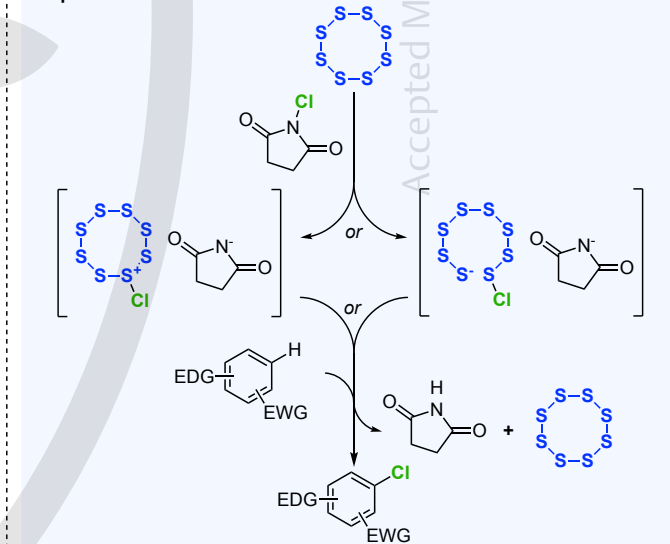
- Requires mild reaction conditions
- Not exclusive to aromatic halogenation
- Good functional group tolerance

**Selected Examples:****Proposed Mechanism**(16d) Song, *Nat. Commun.* **2021**, *12*, 3873.**Notable features of Catalyst-Tuned Chlorination of Arenes with SO₂Cl₂:**

- Same chlorine source for several types of chlorinations
- MeCN as a strong SO₂Cl₂ activator
- Ready availability of most, if not all, reaction components

**Selected Examples (A):****Selected Examples (B):****Selected Examples (C):****Selected Examples (D):**(16e) Ertürk, *J. Org. Chem.* **2022**, *87*, 19, 12558.**Notable features of Elemental Sulfur-Catalyzed Arene Chlorination:**

- Low price of catalyst
- Effective for less activated arenes
- Ready available chlorine source

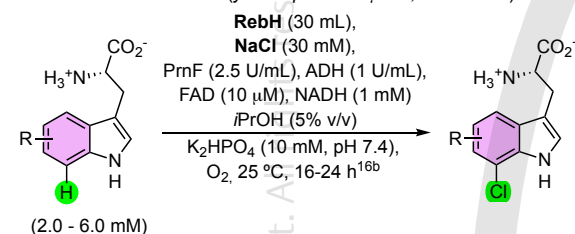
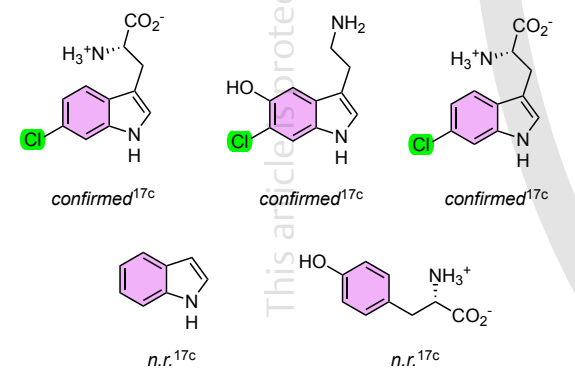
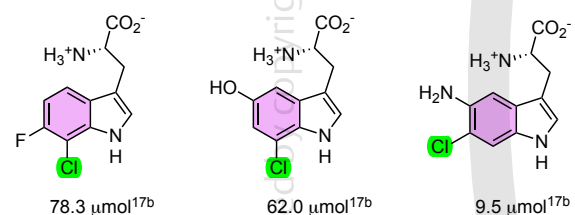
**Selected Examples:****Proposed Mechanism**(16f) Maegawa, *J. Org. Chem.* **2024**, *89*, 770.**Figure 16 (Part 2)** Chlorination of (hetero)arenes using various catalysts^{16d-f}

Notable features of Biocatalysed-Chlorination of (Hetero)arenes:

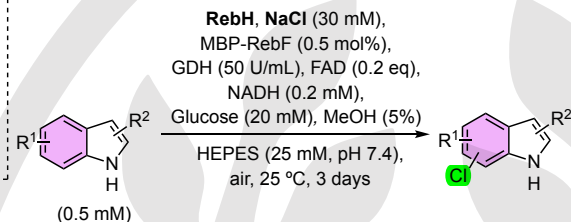
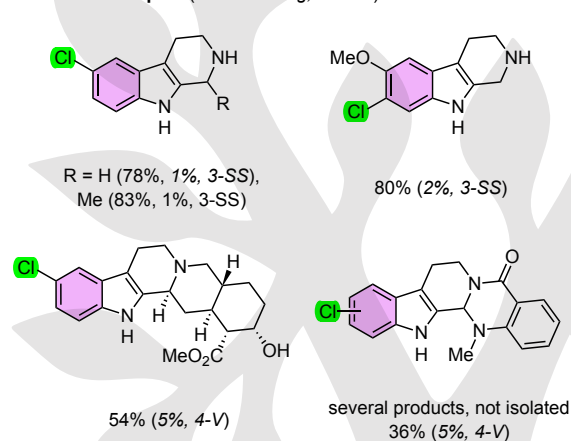
- Great stereo-, regio- and chemoselectivity
- Enzyme engineering allows adaptation for a specific process

Current limitations:

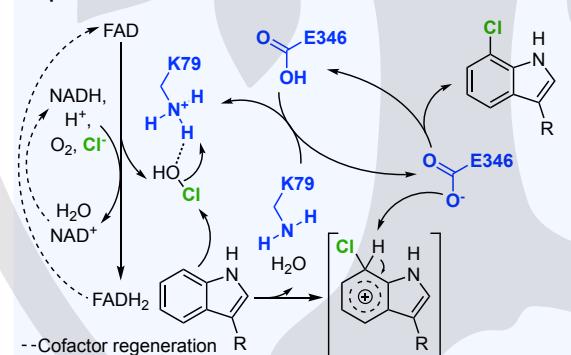
- High complexity of catalyst makes computational design highly challenging
- Catalyst stability issues may arise
- Cost required to the development of a suitable catalyst^{17a}

Chlorination of Tryptophan Derivatives using Recombinant Crude Extract of RebH (yield reported in μmol , if available)**Selected Examples:**

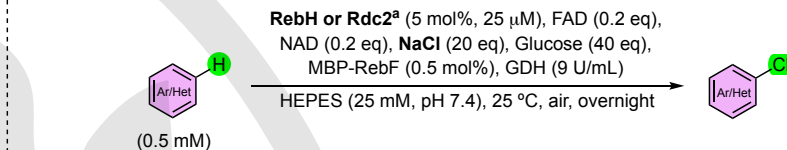
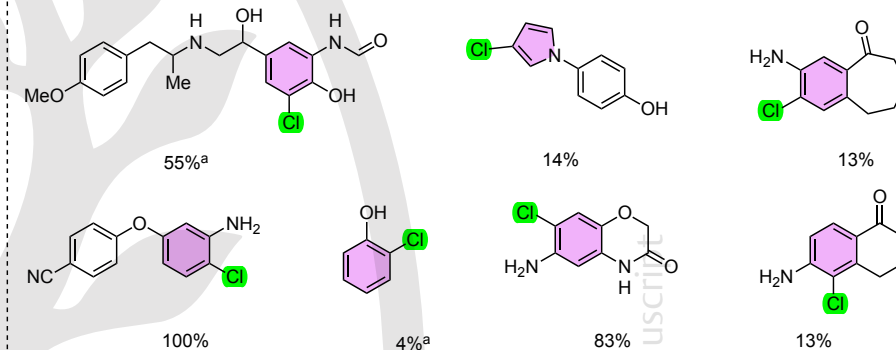
(17b) Sewald, *ChemCatChem*. **2014**, *6*, 1270.
 (17c) Goss, *ACS Chem. Biol.* **2017**, *12*, 1281.

Directed Evolution of RebH for Site-selective Chlorination of Other Indole-Based Molecules**Selected Examples (RebH loading, variant):**

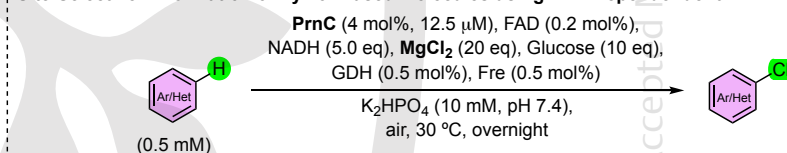
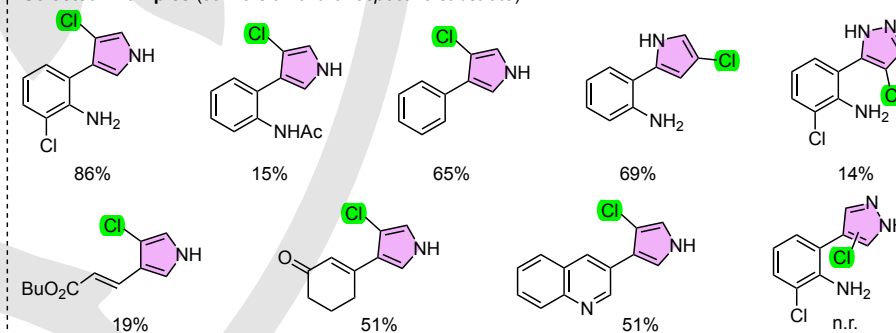
(16d) Lewis, *Angew. Chem. Int. Ed.* **2015**, *54*, 4226.

Proposed Mechanism

(17e) Naismith, *Science* **2005**, *309*, 2216.

Chlorination of Other (Hetero)arenes with RebH or Fungal Halogenase Rdc2**Selected Examples (conversion of the respective substrate):**

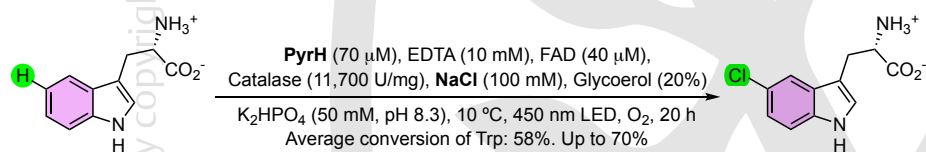
(16f) Lewis, *ACS Catal.* **2017**, *7*, 1897.

Site-Selective Chlorination of Pyrrole-Based Molecules using FAD-Dependent PrnC Enzyme**Selected Examples (conversion of the respective substrate):**

The mechanism is similar to other FAD-dependent halogenases
 (17g) Lim, *Commun. Chem.* **2024**, *7*.

Figure 17 (Part 1) Biocatalysed chlorination of (hetero)arenes^{17a-g}

Photochemically Driven Biocatalyzed Chlorination of Tryptophan with PyrH Enzyme



In this case, EDTA is used as a sacrificial reductant together with light irradiation for the regeneration of FADH_2

(17h) Kottke, *ChemCatChem*. **2018**, *10*, 3336.

Further Reading:

- (17i) Lewis, *Chem. Sci.* **2016**, *7*, 3720.
- (17j) Liu, *Nat. Chem. Biol.* **2014**, *10*, 921.
- (17k) Moore, *J. Am. Chem. Soc.* **2018**, *140*, 17840.
- (17l) Moore, *Synlett*. **2018**, *29*, 41.
- (17m) Hoebenreich, *ACS Catal.* **2020**, *10*, 1272.

Figure 17 (Part 2) Biocatalyzed chlorination of (hetero)arenes^{17h-m}

Conclusion

In conclusion, recent advances in (hetero)arene chlorination have introduced a wide variety of novel reagents and methodologies that have significantly expanded the capabilities of this field. Most contemporary methods rely on electrophilic aromatic substitution (S_EAr), with direct chlorinating agents such as Palau'chlor, CFBSA, CMOBSA, and NCBSI as key examples. Other approaches, including sulfoxide-mediated, amine-catalyzed, and various catalyzed processes, also utilize this mechanism. In biocatalysis, FAD-dependent halogenases are exclusively used for electrophilic chlorination.

In contrast, some innovative methods involve chlorination through nucleophilic aromatic substitution (S_NAr). These include electrochemical and photocatalytic processes, Selectfluor-mediated halogenation of 2-aminopyridines and 2-aminodiazines, Oxone- and Fe(III)-mediated chlorination. Additionally, Ni-catalyzed chlorination operates through ligand exchange and reductive elimination.

A notable trend is the integration of green chemistry principles, with many methods utilizing readily available and environmentally benign chlorine sources such as NaCl, LiCl, KCl, $MgCl_2$, and HCl. This shift towards sustainable practices reflects the broader movement in chemical synthesis towards minimizing environmental impact and increasing practicality.

Despite these advances, nucleophilic chlorination remains relatively rare, often implying the presence of electron-donating groups (EDGs) on the arene moiety, which can limit the range of substrates. Electrochemical methods are particularly noteworthy for their versatility and capability of minimal environmental footprint, using simple and accessible chlorine sources with minimal waste. However, their practical application constrains the need for specialized electrochemical equipment.

Overall, the progress in chlorination techniques highlights a significant evolution towards greater efficiency and sustainability, with emerging methods improving both atom economy and environmental impact.

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Conflict of Interest

The authors declare no conflict of interest.

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