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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.

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Nuno R Candeias, Tampere University, Faculty of Engineering and Natural Sciences, Tampere, Finland

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

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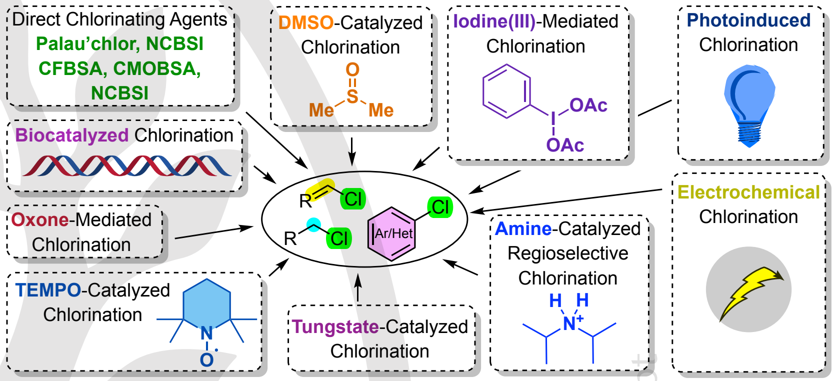

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Abstract Chlorinated compounds are vital in organic synthesis, impacting nucleophilic substitutions, β-elimination, and C-H acidity. This review highlights recent advances in (hetero)arene chlorination, focusing on novel reagents and methods developed 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*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.

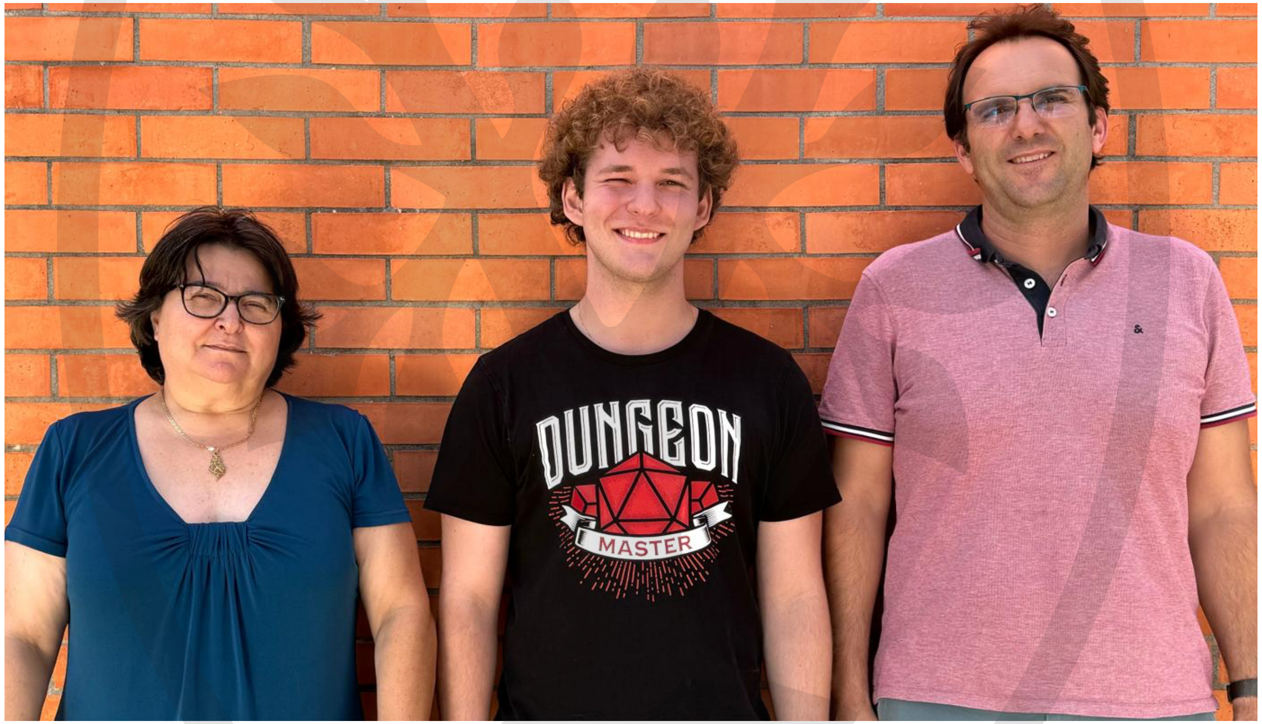
This graphical review highlights key advancements in the chlorination of organic molecules, particularly (hetero)arenes, over the past decade, with a focus on the development of novel chlorinating reagents. The progress in direct chlorinating agents—where the chlorine source is embedded within the reagent's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

Biosketches

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.



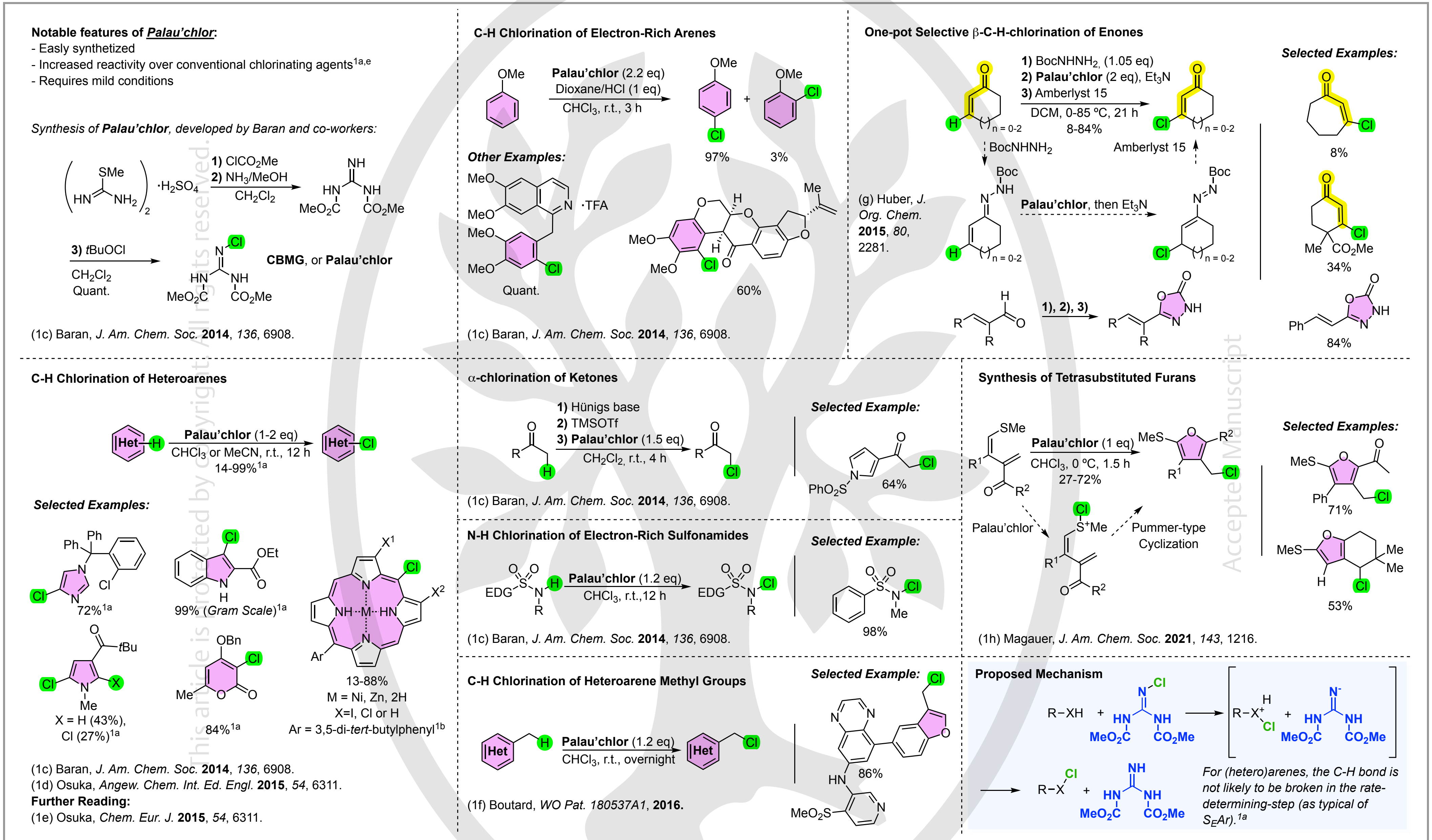


Figure 1 Diverse applications of Palau'chlor (chlorobis(methoxycarbonyl)guanidine)[1c-h]

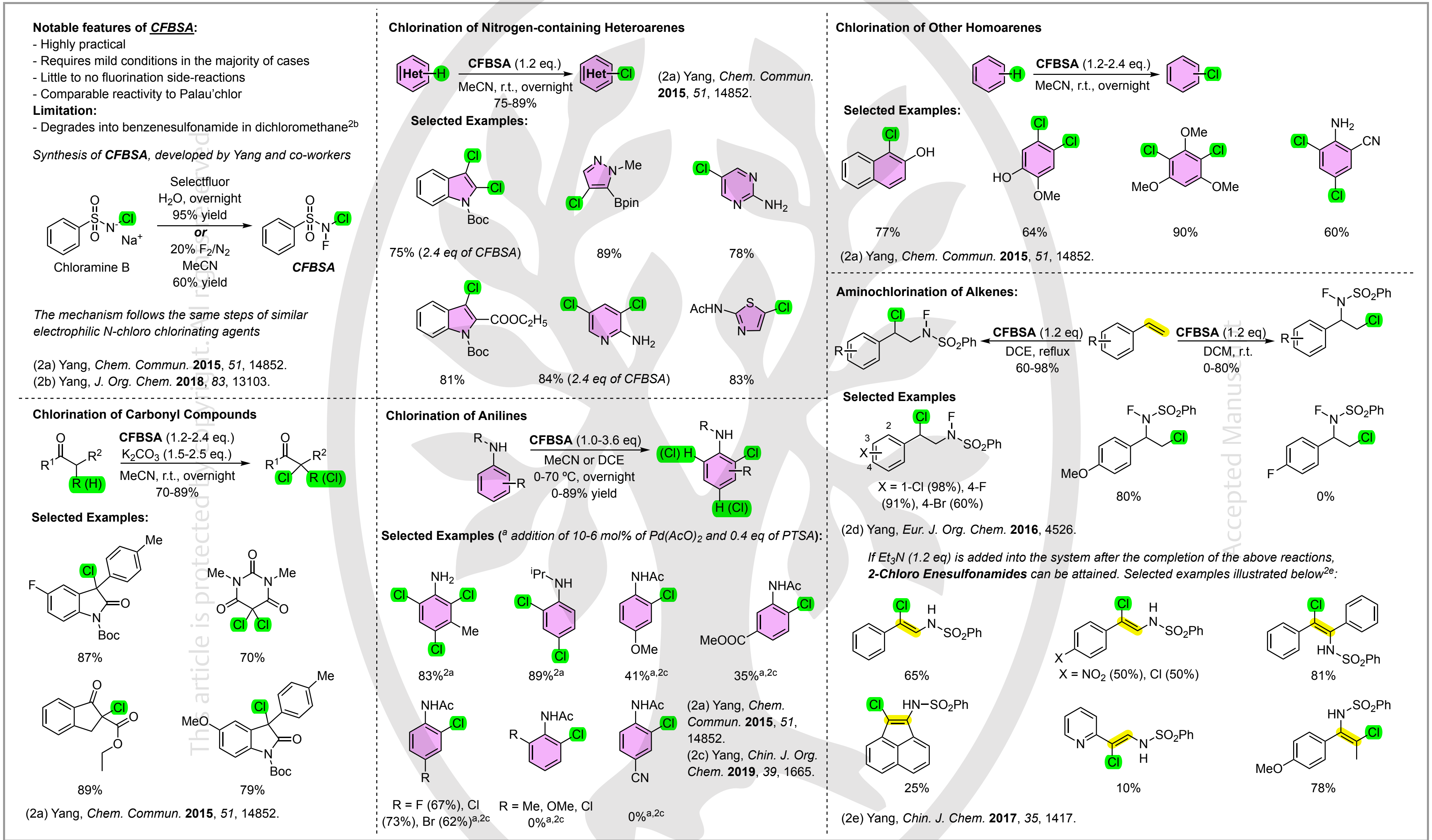
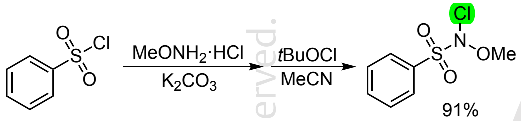


Figure 2 Diverse applications of CFBSA (*N*-chloro-*N*-fluorobenzenesulfonylamine)[2a-e]

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

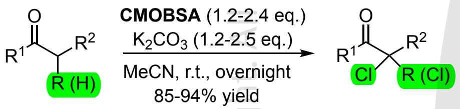
*Synthesis of **CMOBSA**, developed by Yang and co-workers*



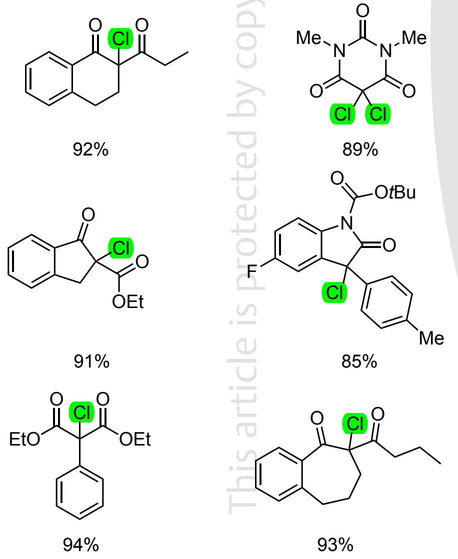
The mechanism follows the same steps of similar electrophilic N-chloro chlorinating agents

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

Chlorination of Carbonyl Compounds

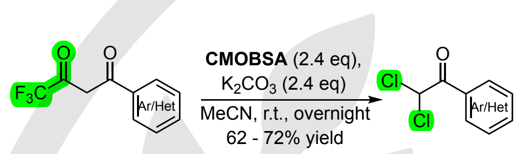


Selected Examples



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

Chlorination of Benzoyl Trifluoroacetones



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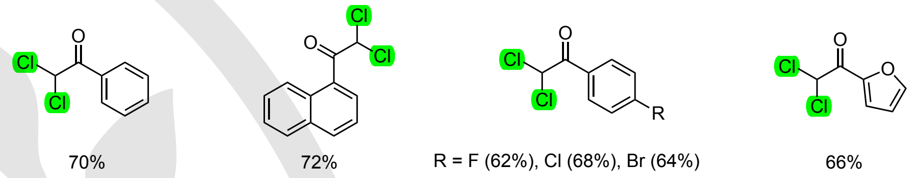
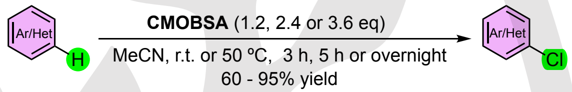
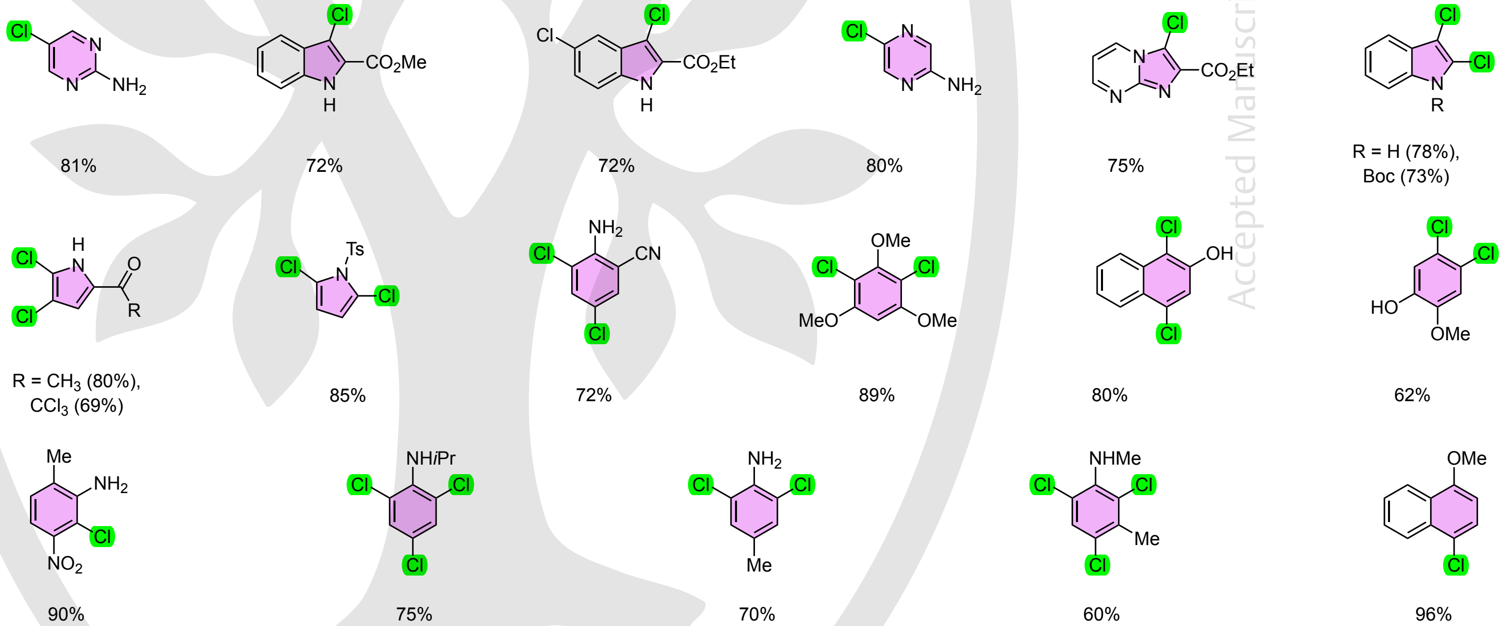


(3) Yang, *Eur. J. Org. Chem.* **2016**, *2016*, 5937.

Chlorination of (Hetero)arenes



Selected Examples:



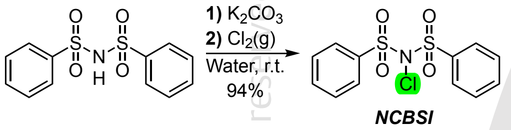
(3) Yang, *Eur. J. Org. Chem.* **2016**, *2016*, 5937.

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 Cl_2(g)

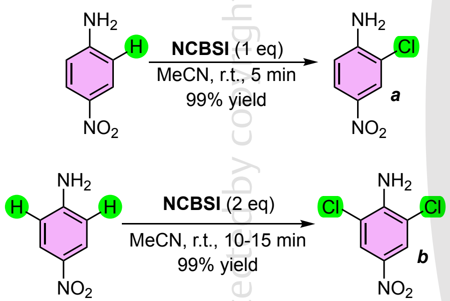
Synthesis of NCBSI, developed by Chaturbhuj and co-workers:



The mechanism follows the same steps of simillar 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(%)	Conversion b(%)	a(%)
THF		45	100	-	98
Dioxane	10-15	20	100	-	98
$CHCl_3$	30-35	3	98	2	96

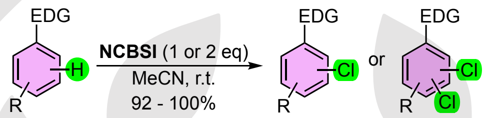
EtOH/water (1:1) gives ***b*** as the major product, being ***a*** generated in only 12%

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

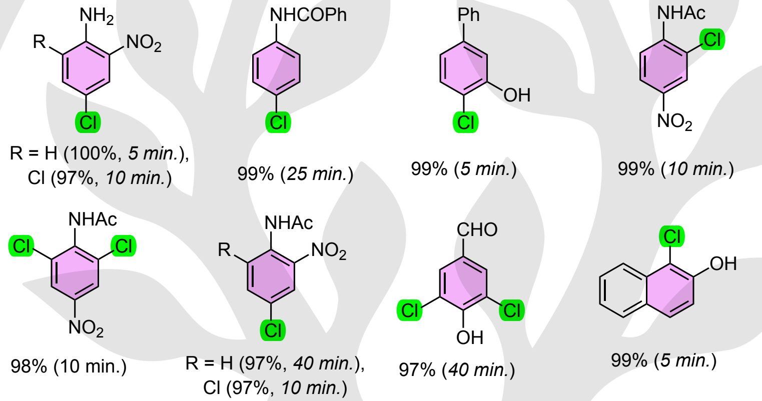
Further Reading:

(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

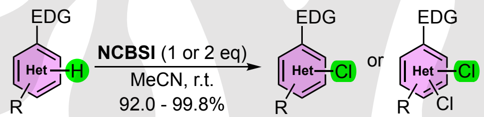


Selected Examples:

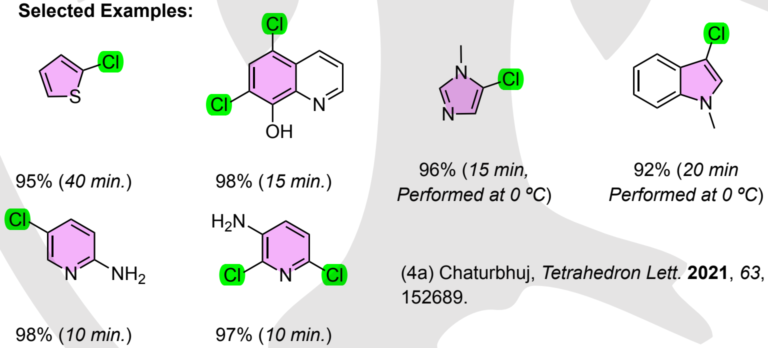


(4a) Chaturbhuj, *Tetrahedron Lett.* **2021**, *63*, 152689.

Chlorination of Heterorenes

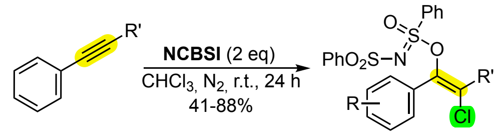


Selected Examples:



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

***Anti*-oxychlorination of Alkynes**



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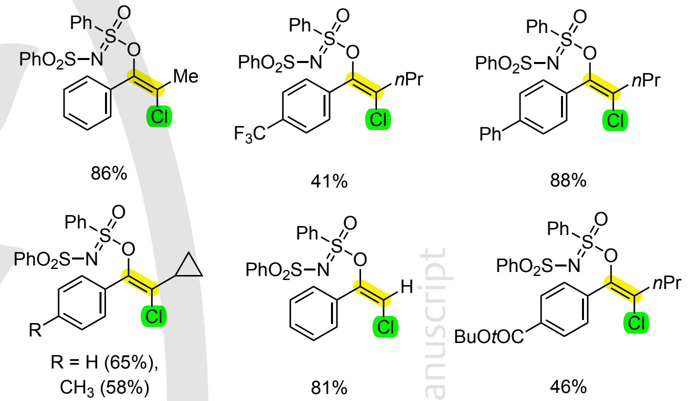
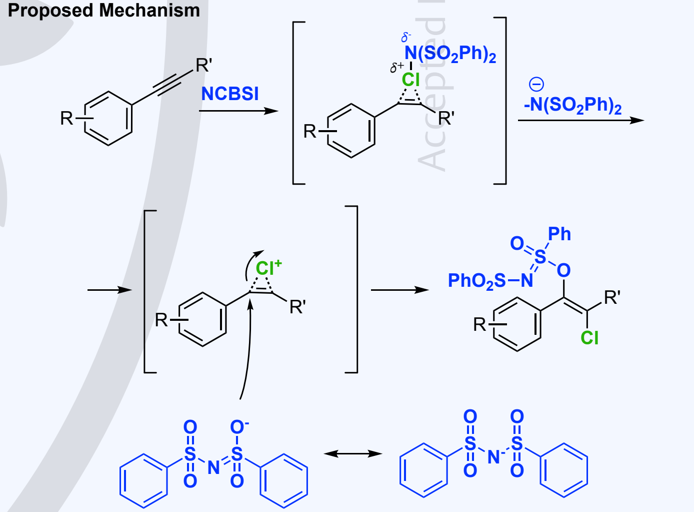


Proposed Mechanism



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

Figure 4 Chlorination reactions using NCBSI (*N*-chloro-*N*-(phenylsulfonyl)benzene sulfonamide) as the chlorinating agent[4a-e]

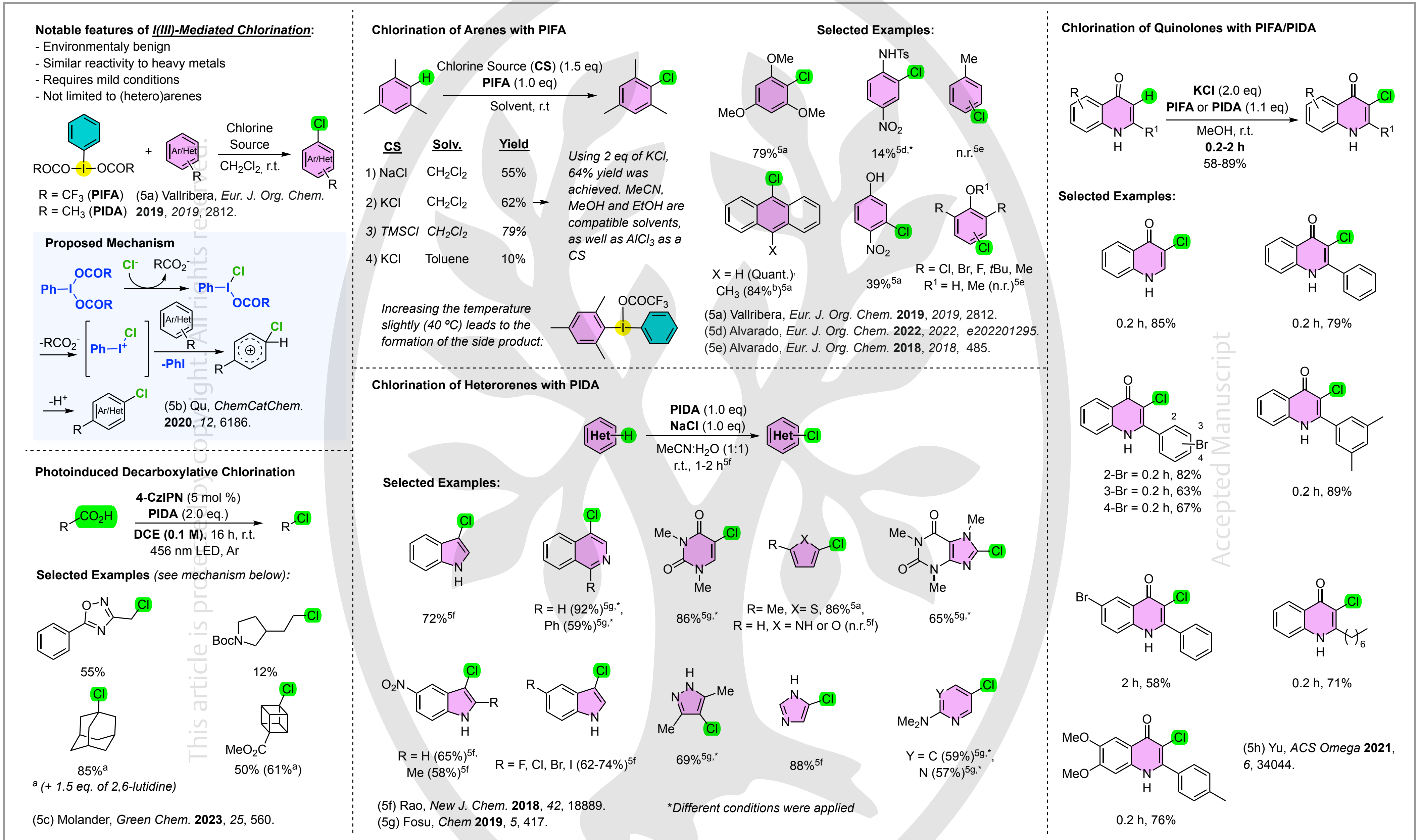
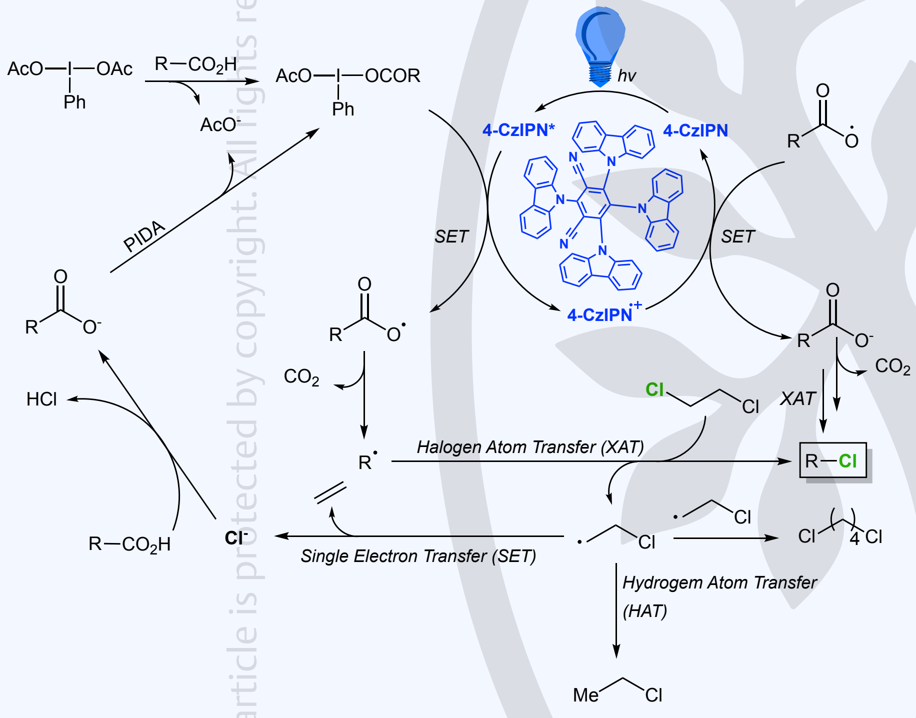


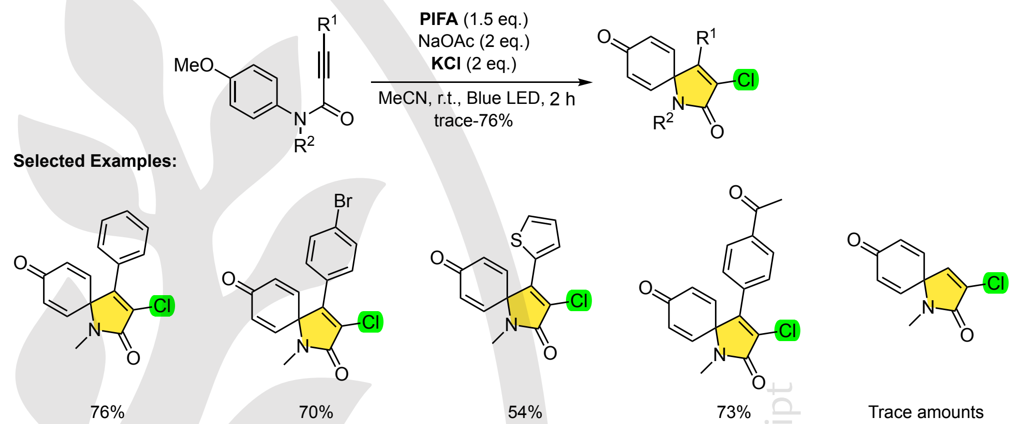
Figure 5 (Part 1) Recent chlorination methods based on the use of hypervalent iodine reagents PIFA (bis(trifluoroacetoxy)iodo)benzene) and PIDA (phenyliodine(III) diacetate) (Part 1)[5a-h]

Proposed Mechanism for the Photoinduced Decarboxylative Chlorination Using PIDA

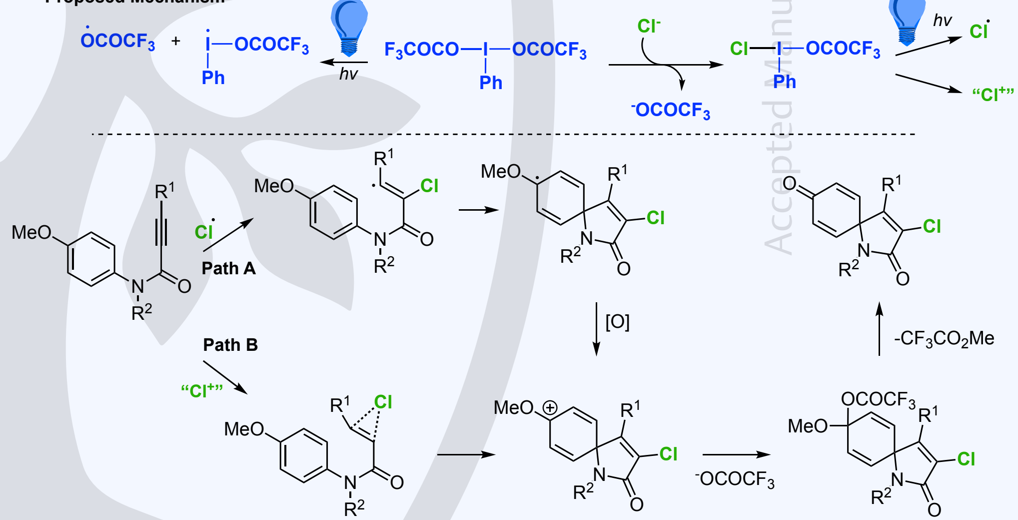


(5c) Molander, *Green Chem.* **2023**, *25*, 560.

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) Vallribera, *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]

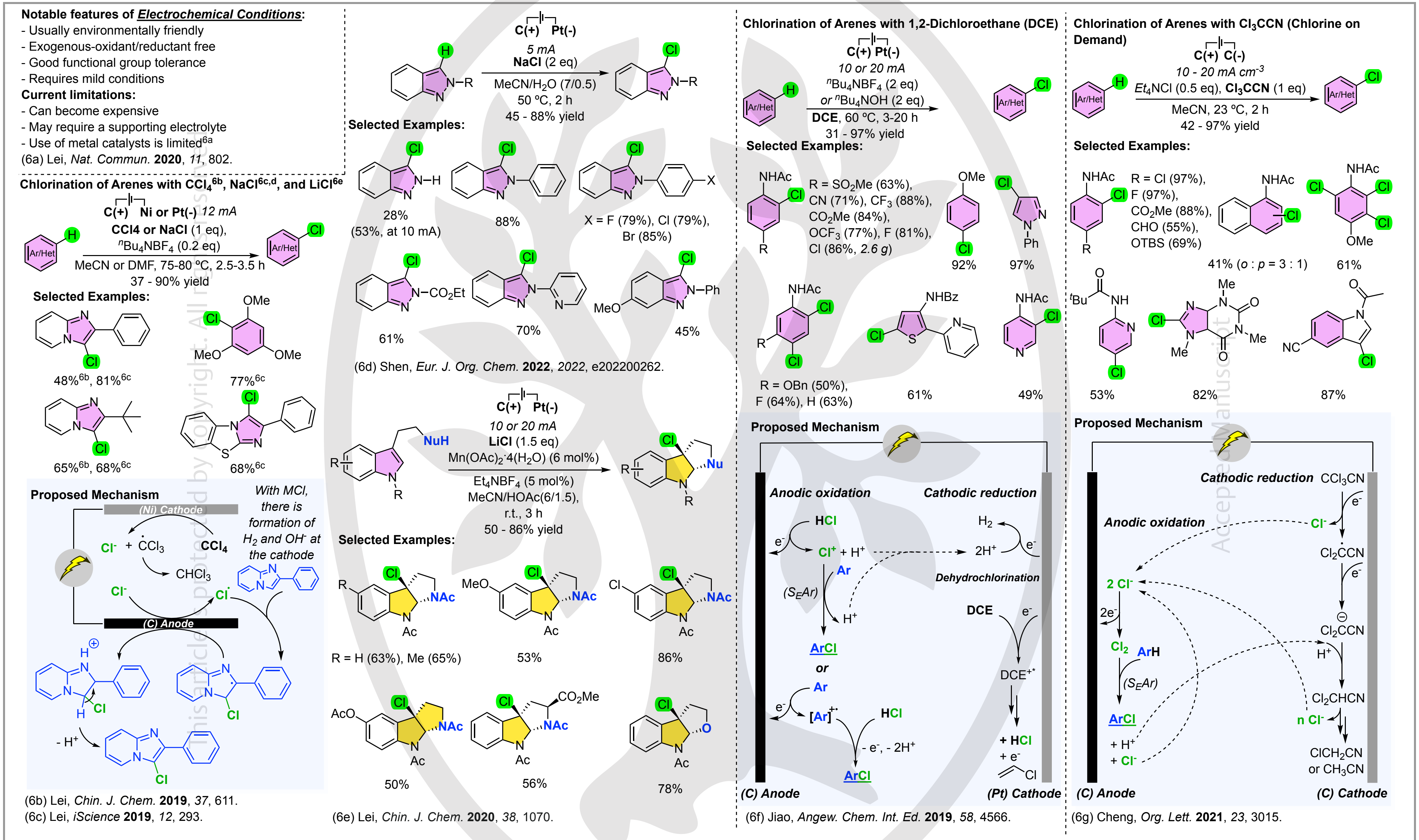
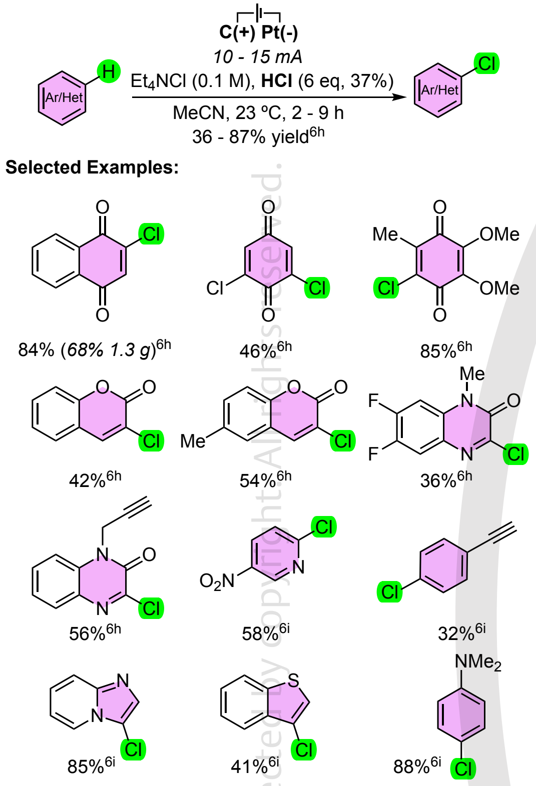
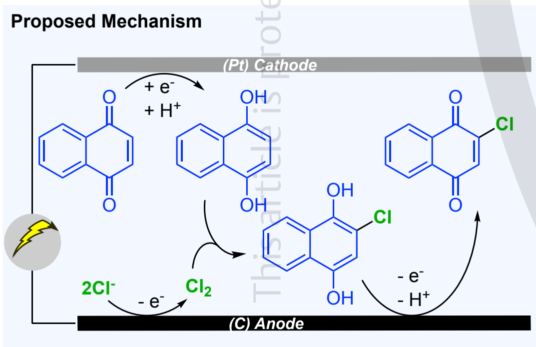


Figure 6 (Part 1) Electrochlorination of (hetero)arenes[6a-g]

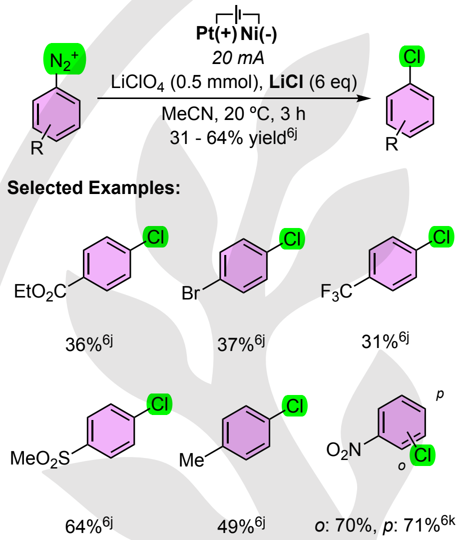
Clorination of (Hetero)arenes with HCl

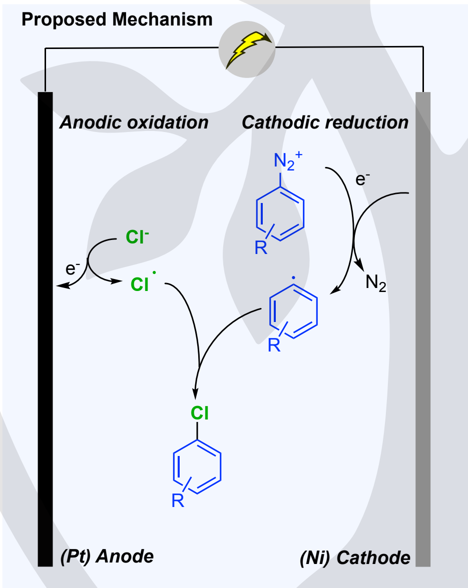




(6h) Liu, *Tetrahedron Lett.* **2021**, *86*, 153514.
(6i) Zhou, *ACS Sustainable Chem. Eng.* **2024**, *12*, 3289.

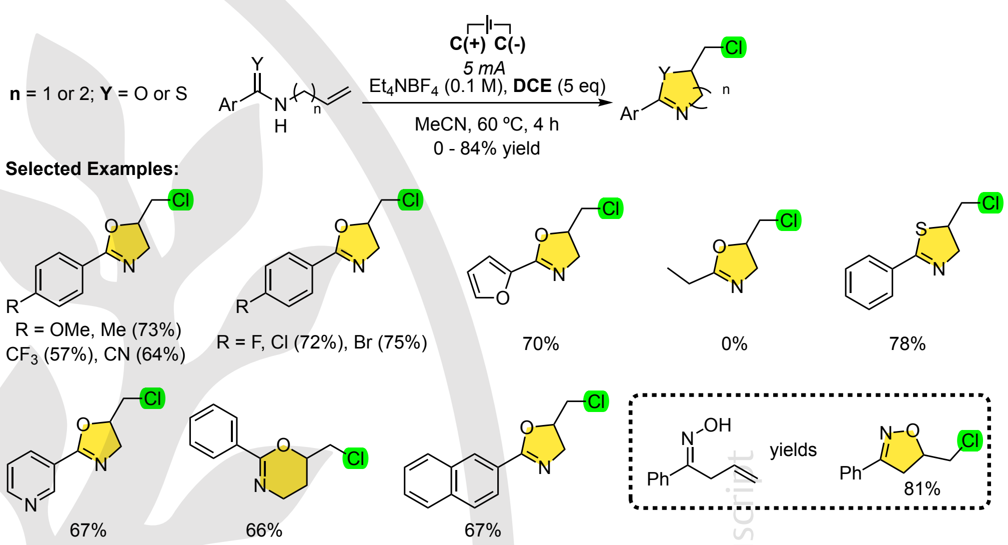
Electrochemical Approach to the Sandmeyer Reaction

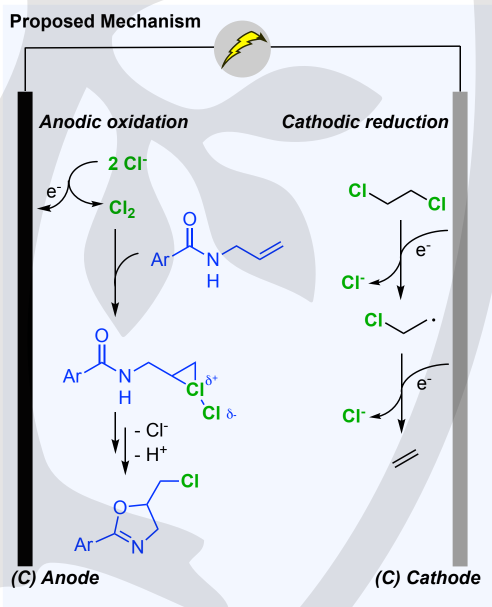




(6j) Mo, *Chem. Sci.* **2018**, *9*, 8731.
(6k) Nematollahi, *Org. Lett.* **2020**, *22*, 5920.

Intramolecular haloheterocyclization of 1,2-dihaloethanes





(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]

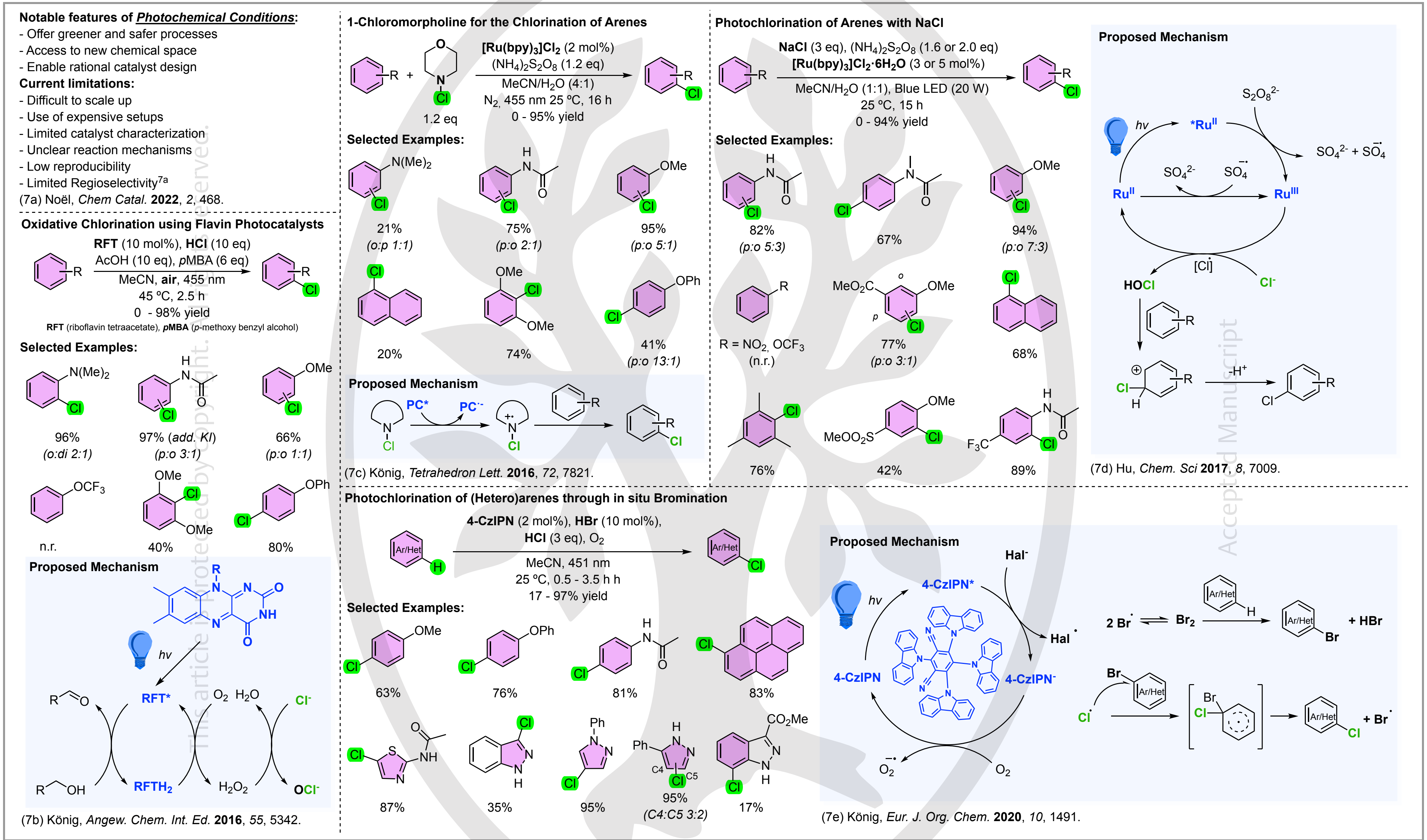
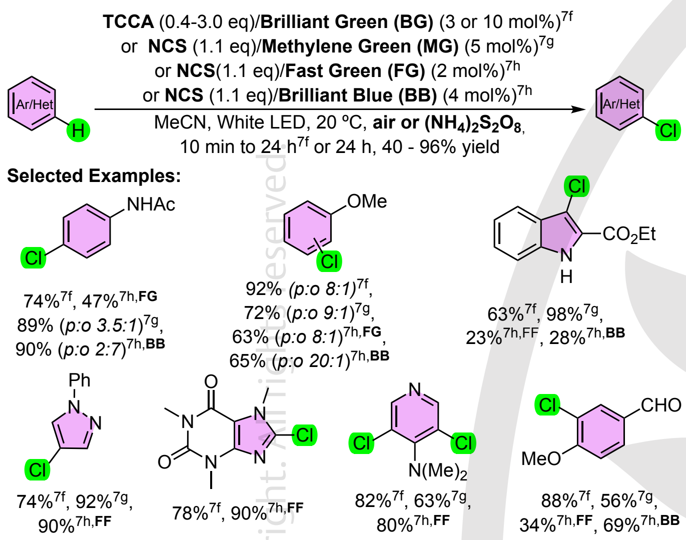
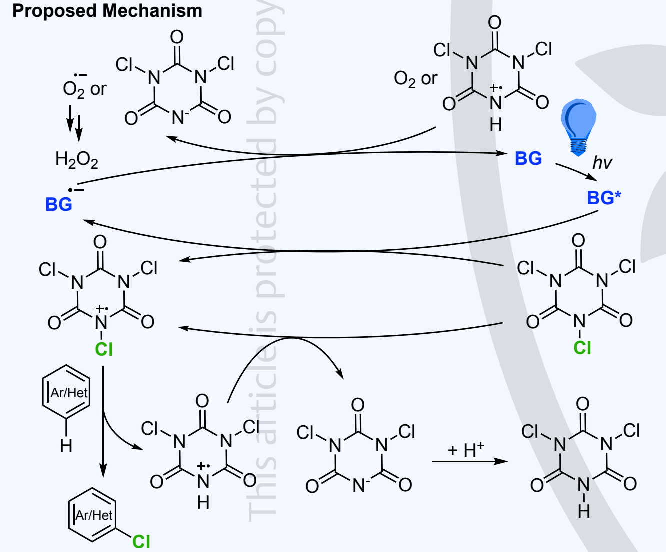


Figure 7 (Part 1) Photochlorination of (hetero)arenes[7a-e]

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

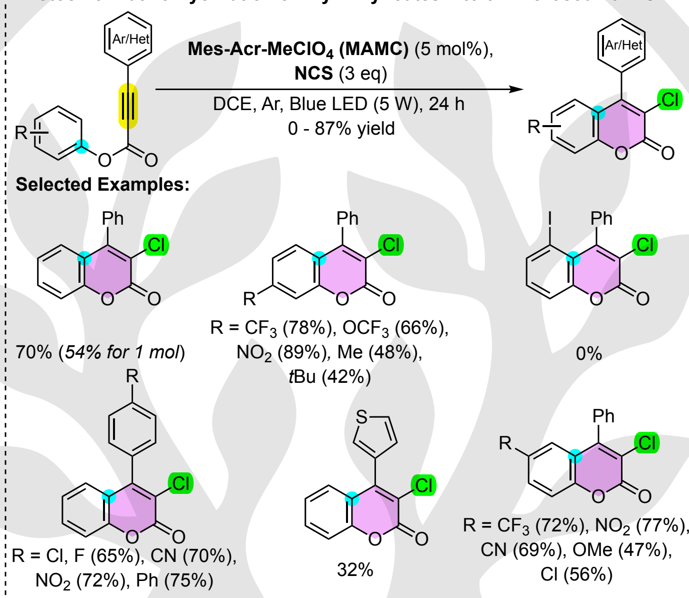


Proposed Mechanism

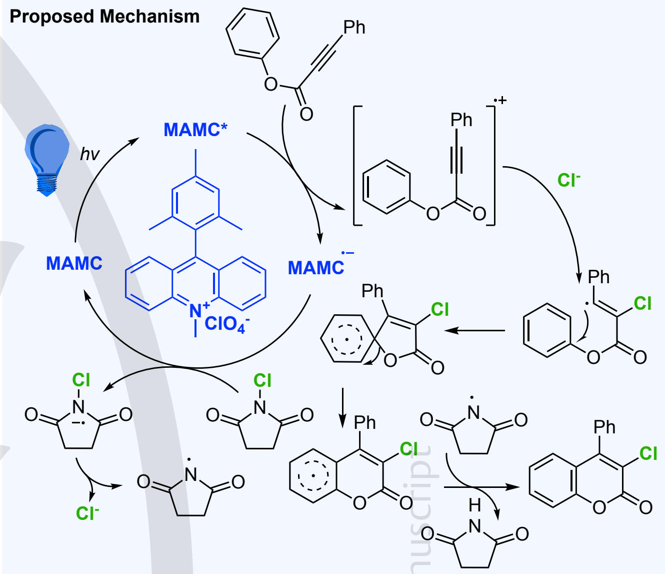


(7f) Lamar, *Org. Lett.* **2019**, *21*, 4229.
(7g) Lamar, *Tetrahedron Lett.* **2019**, *75*, 130498.
(7h) Lamar, *ACS Omega* **2020**, *5*, 7693.

Photochlorinative Cyclization of Aryl Alkynoates into 3-Chlorocoumarins

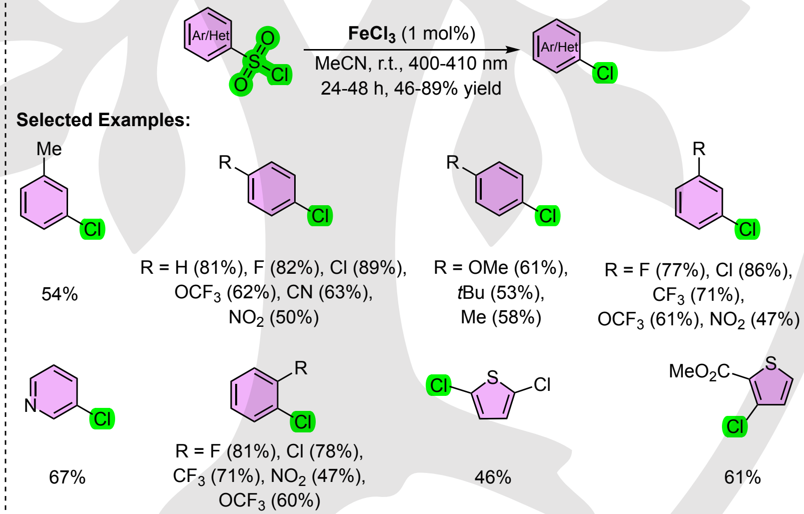


Proposed Mechanism

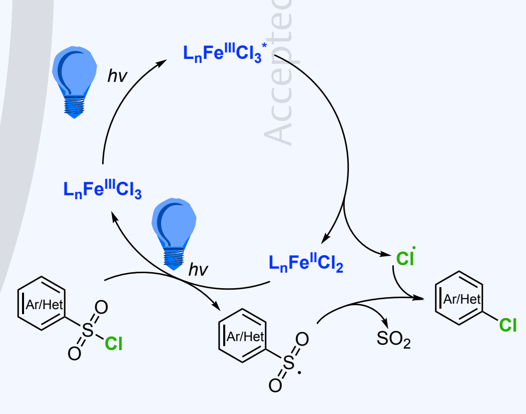


(7i) Mal, *Org. Lett.* **2021**, *23*, 8088.

Photochlorination of Aromatic Sulfonyl Chlorides using FeCl$_3$



Proposed Mechanism



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

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]

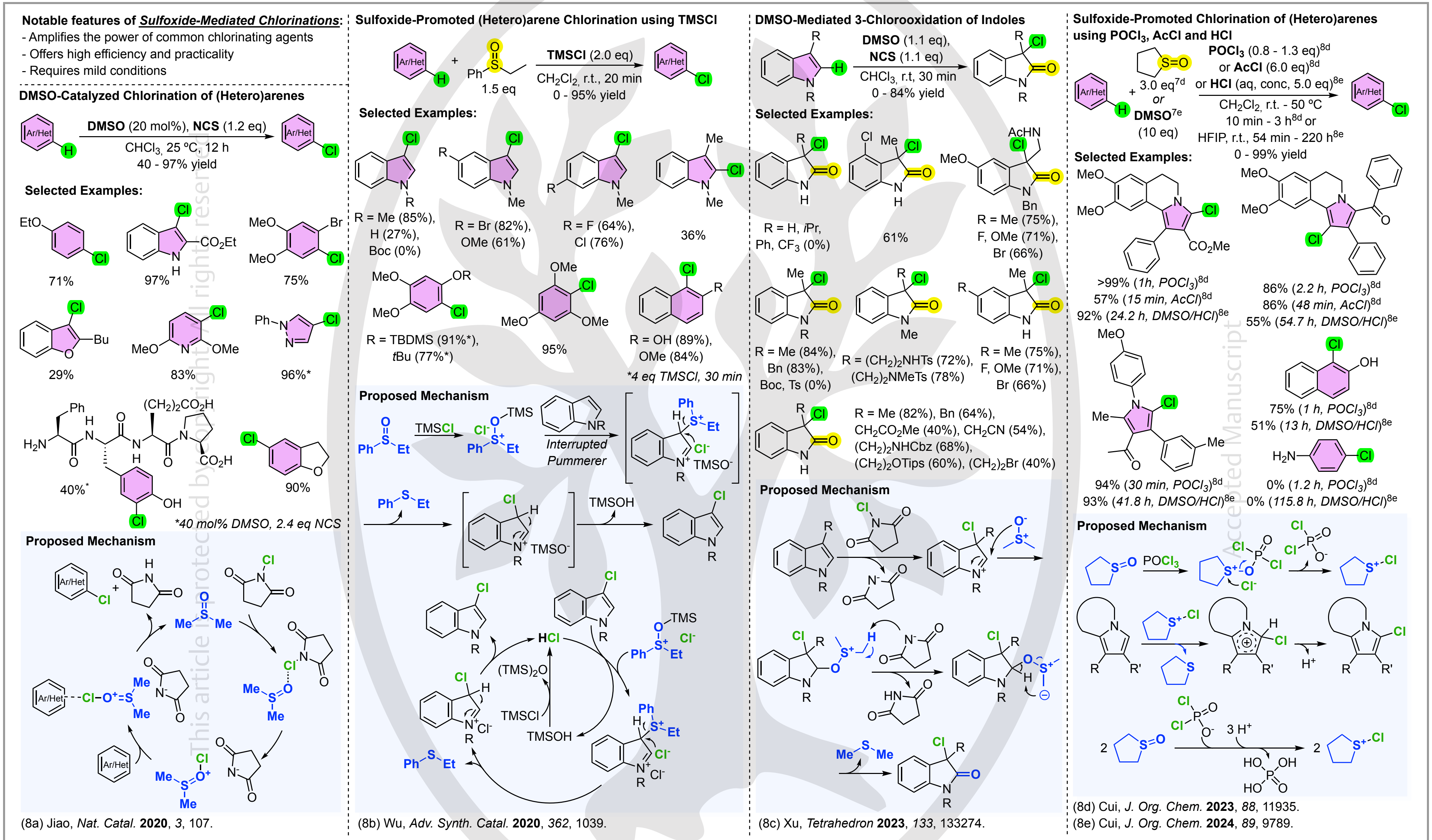
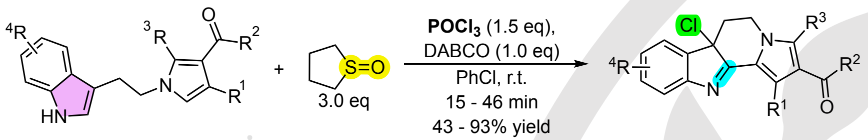
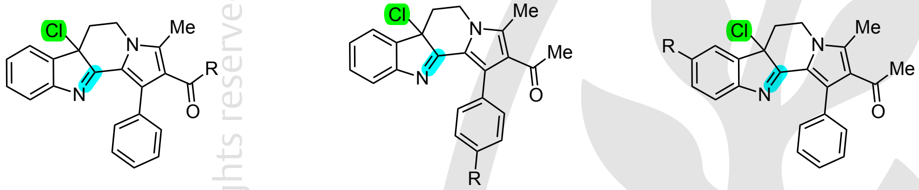


Figure 8 (Part 1) Sulfoxide-mediated chlorination of (hetero)arenes[8a-e]

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



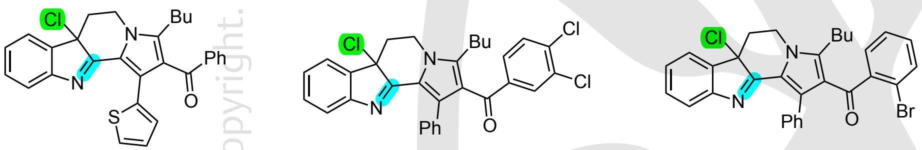
Selected Examples:



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*)

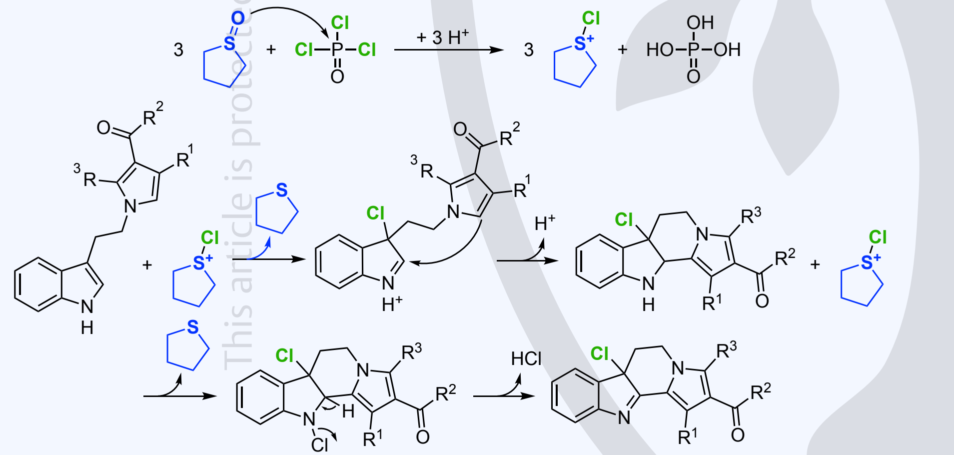


49% (*21 min*)

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]

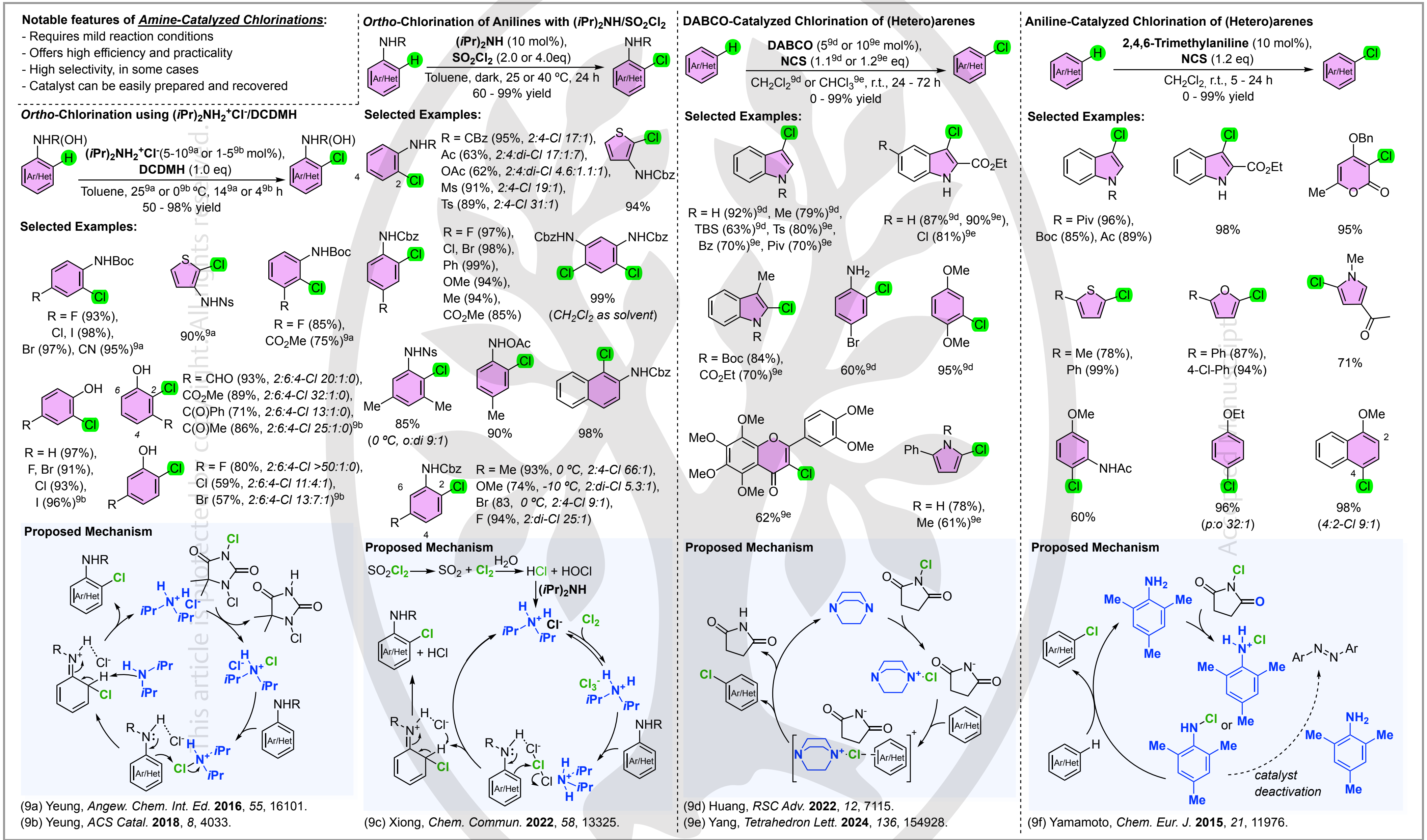
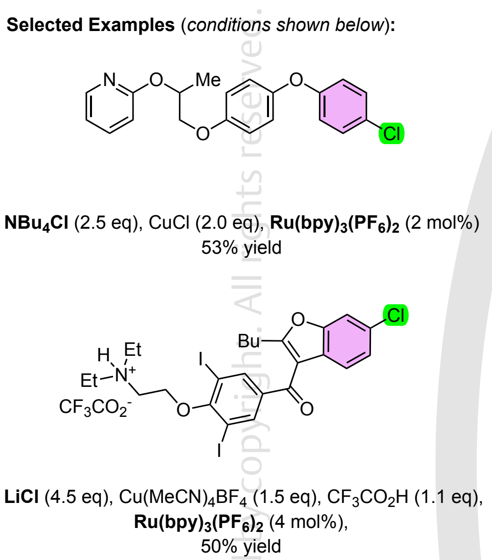
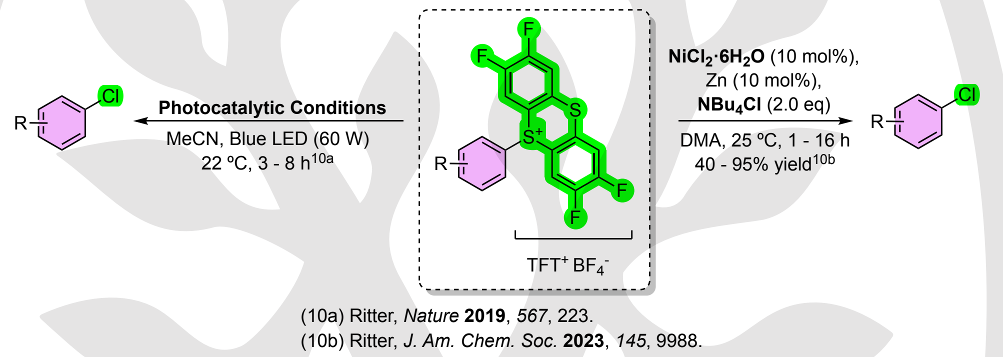


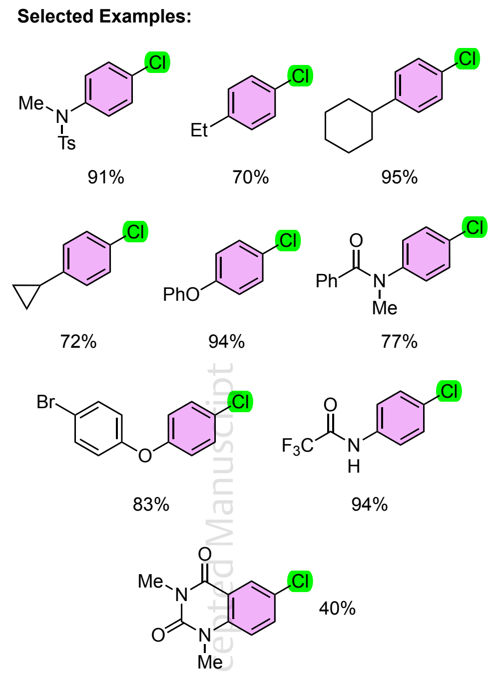
Figure 9 Amine-catalyzed chlorination of (hetero)arenes[9a-f]

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)







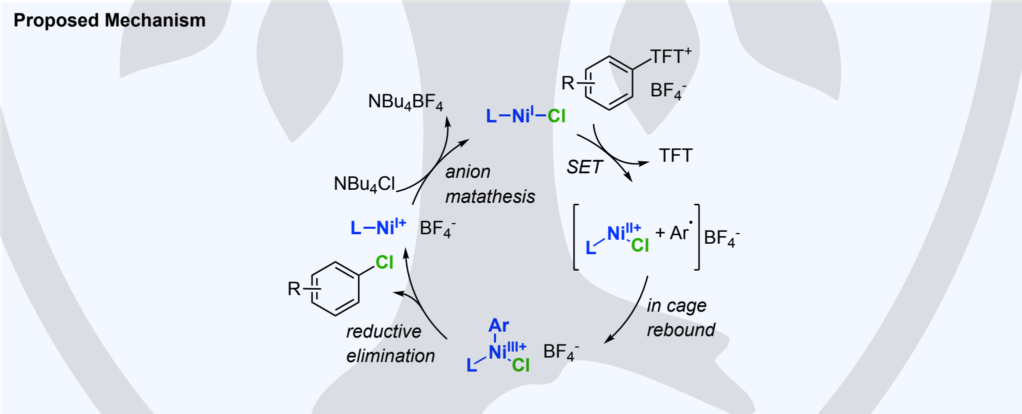


Figure 10 Thianhtrenium-aided chlorination of arenes[10a,b]

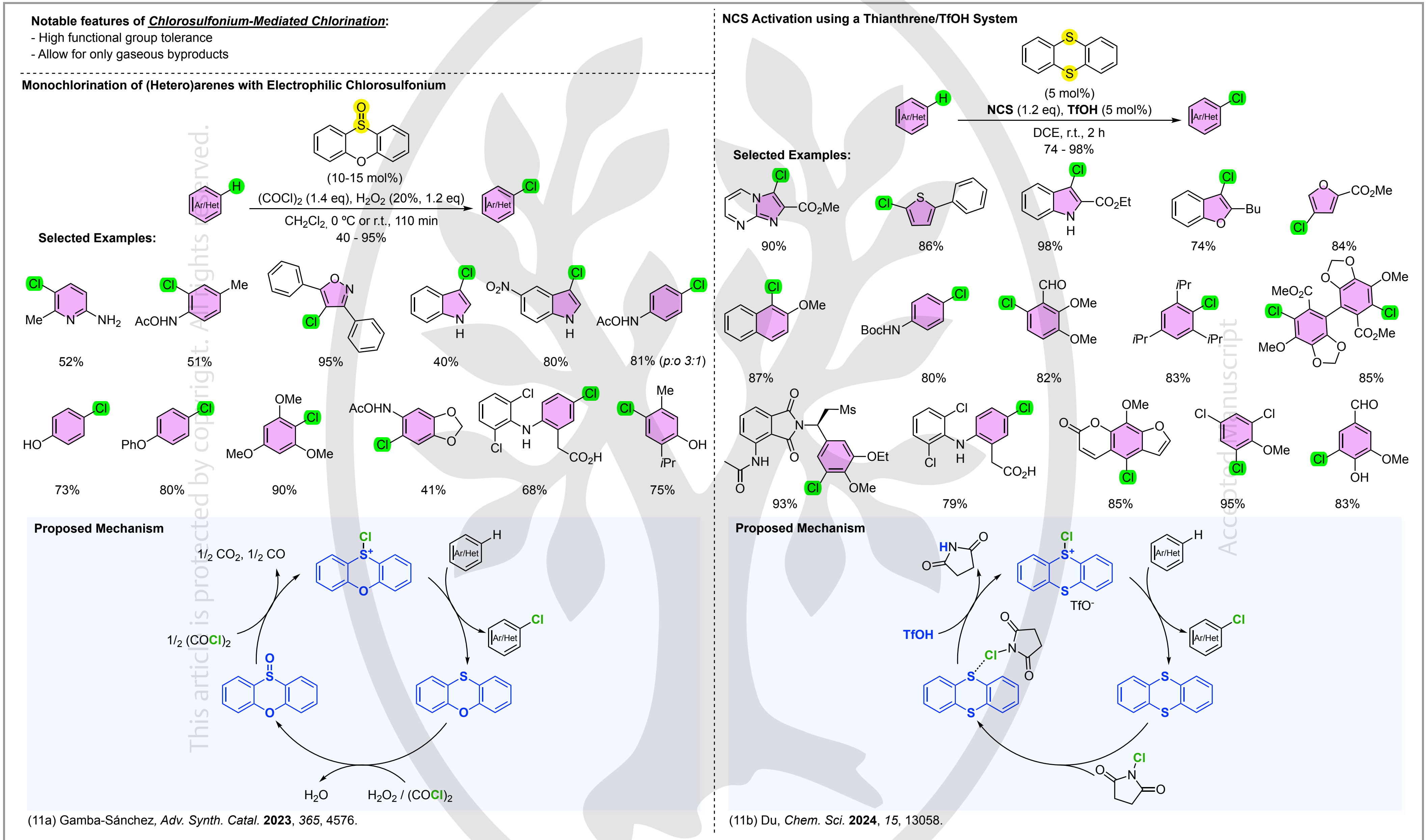


Figure 11 Monochlorination of (hetero)arenes with electrophilic chlorosulfonium species[11a,b]

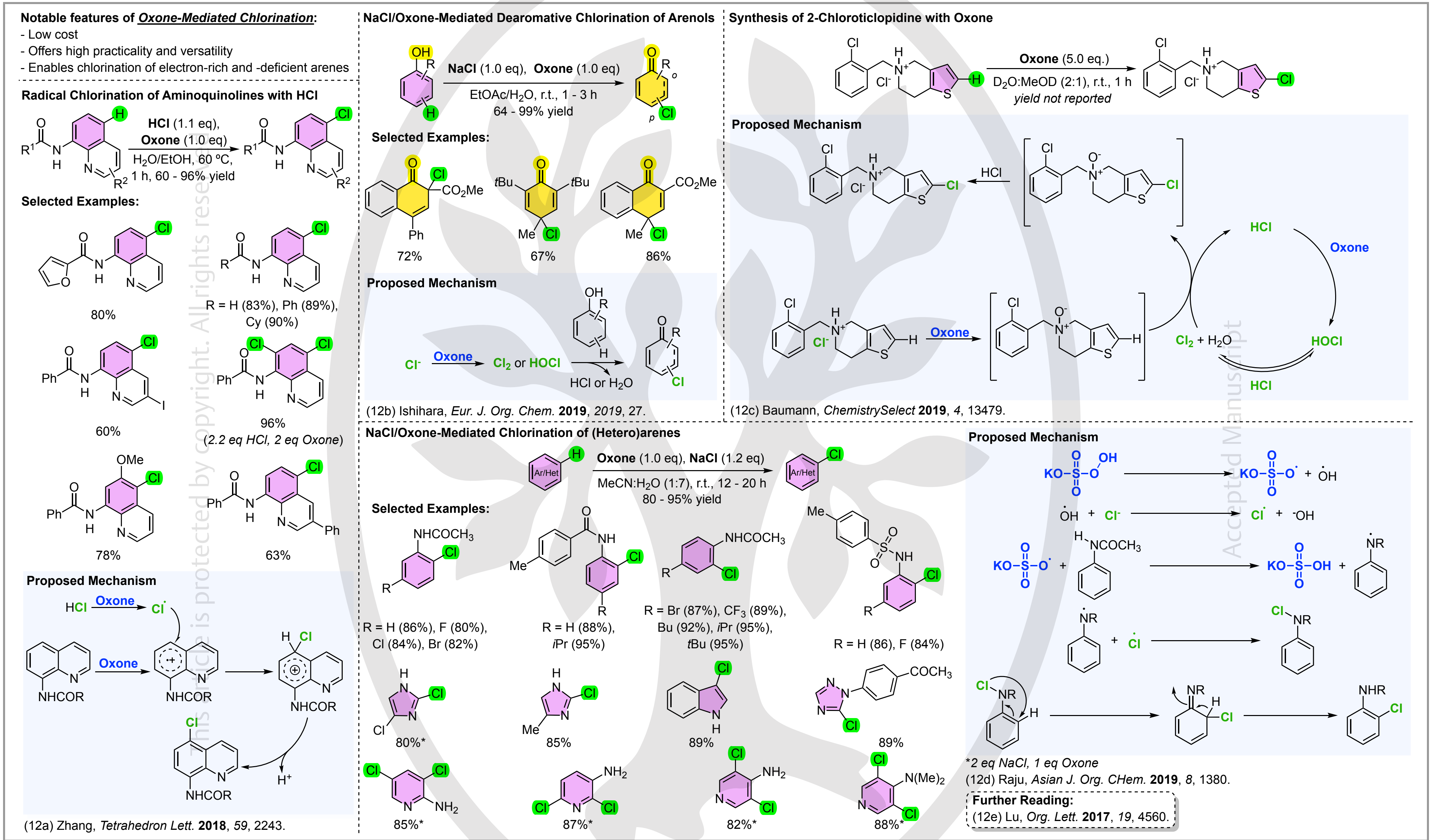


Figure 12 Oxone-mediated chlorination of (hetero)arenes[12a-e]

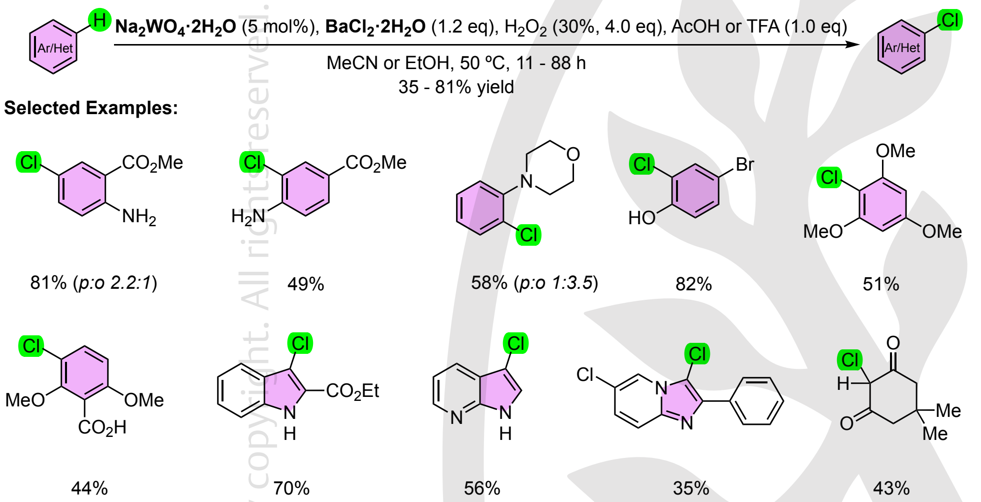
Notable features of *Bioinspired Tungstate-Catalyzed Chlorination:*

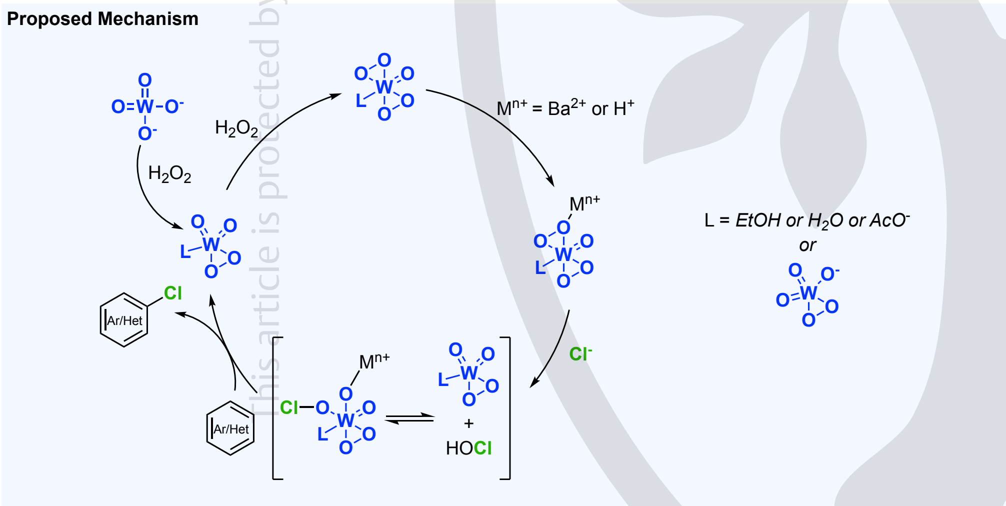
- Requires mild pH
- Diverse functional group tolerance
- Notable chemo- and regioselectivity can be achieved
- Cost-, environment- and operation-efficient

Current limitations:

- Long reaction times.
- Too electronically rich arenes lead to undesired oxidative transformations

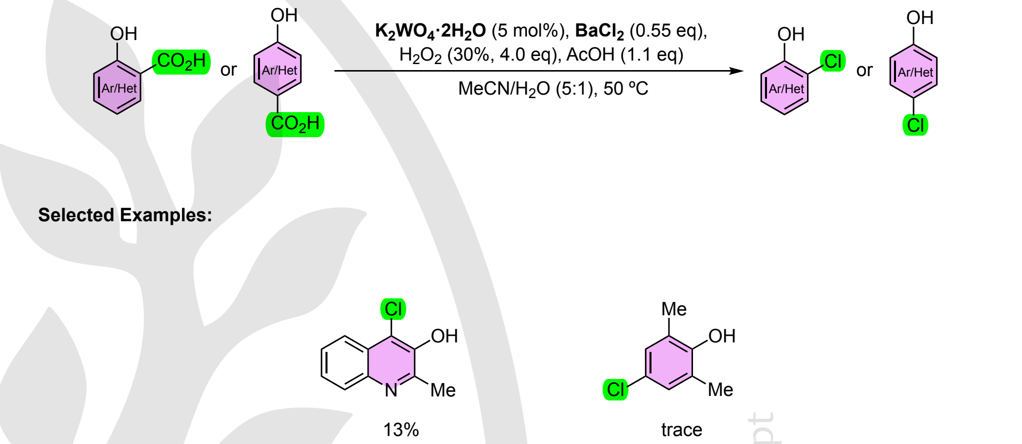
Tungstate-Catalyzed Chlorination of (Hetero)arenes

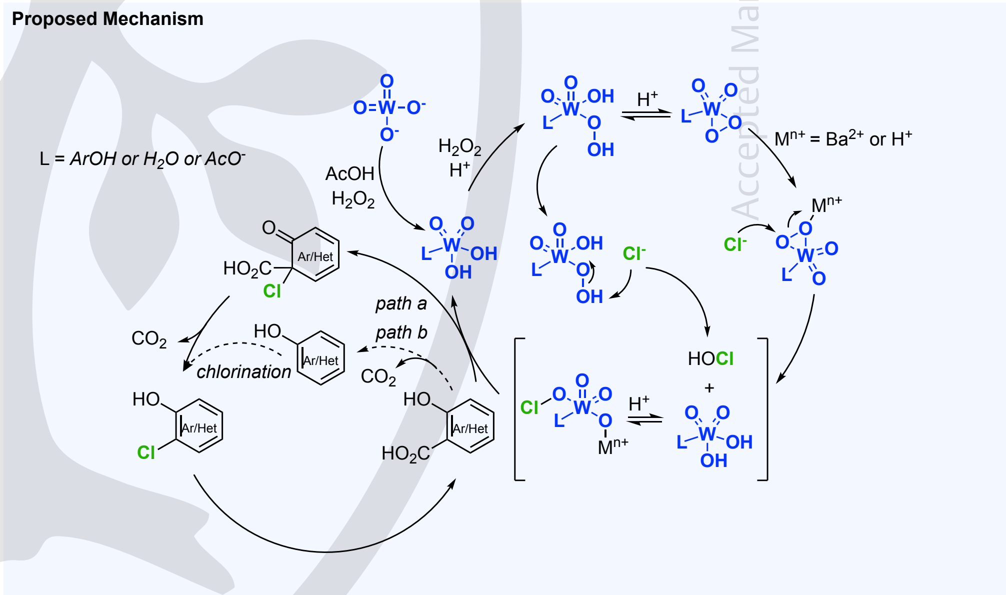




(13a) Chen, *iScience* **2020**, *23*, 101072.

Tungstate-Catalyzed Decarboxylative Chlorination of (Hetero)phenolic Acids





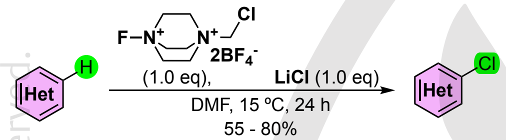
(13b) Chen, *ACS Sustainable Chem. Eng.* **2022**, *10*, 7453.

Figure 13 Tungstate-catalyzed chlorination of (hetero)arenes[13a,b]

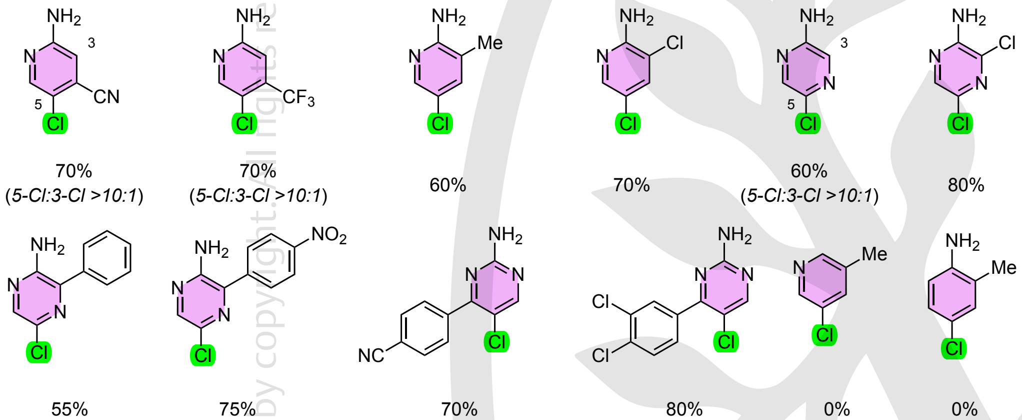
Notable features of *Selectfluor-Mediated Chlorination*:

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

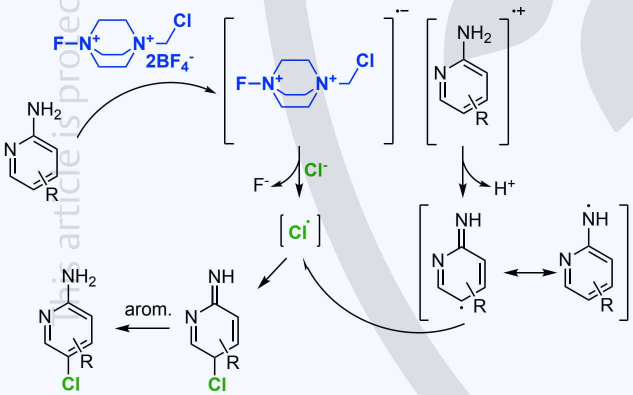
Regioselective Chlorination of 2-Aminopyridines and 2-Aminodiazines with LiCl



Selected Examples:



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]

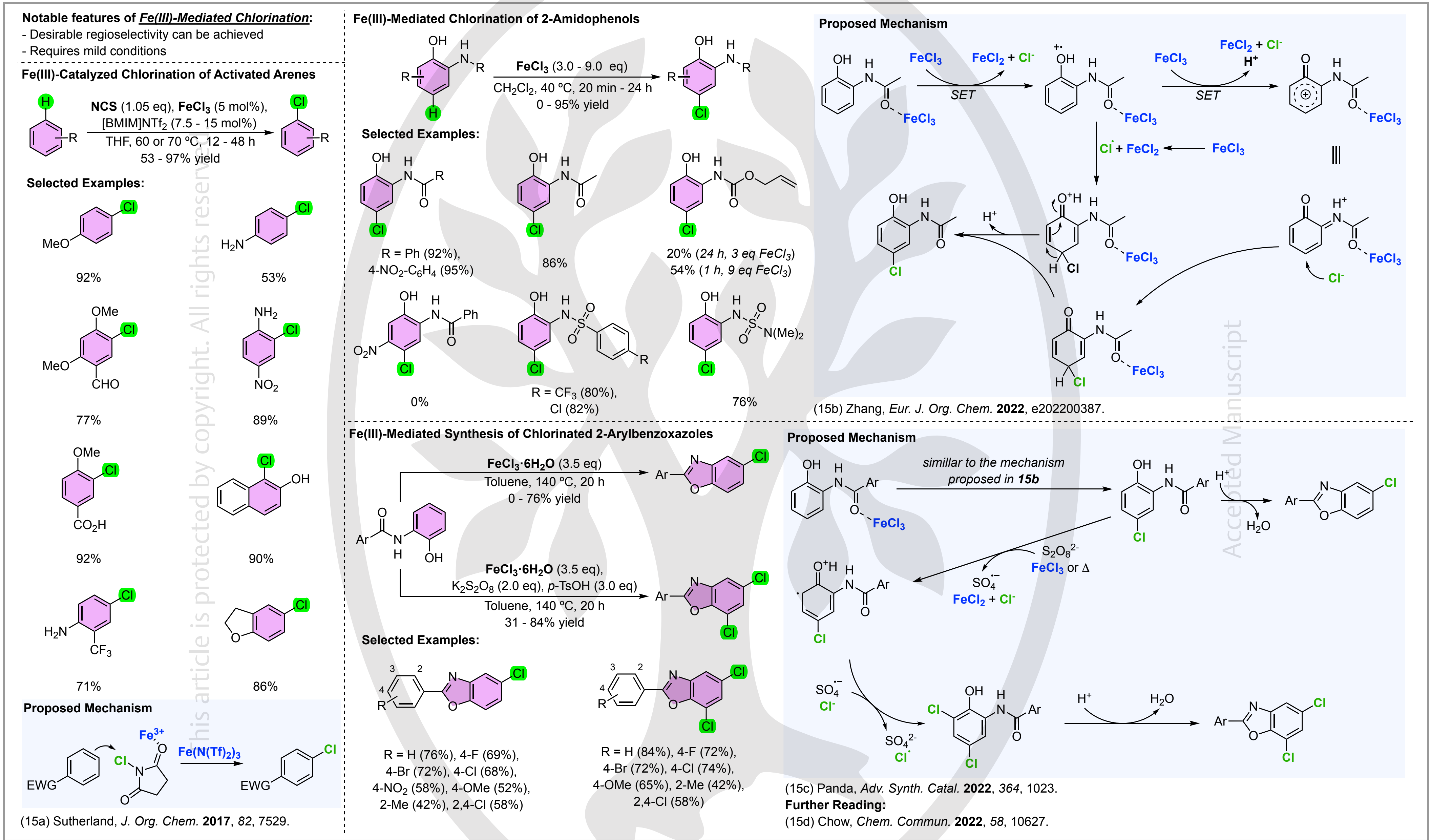


Figure 15 Fe(III)-mediated chlorination of arenes[15a-d]

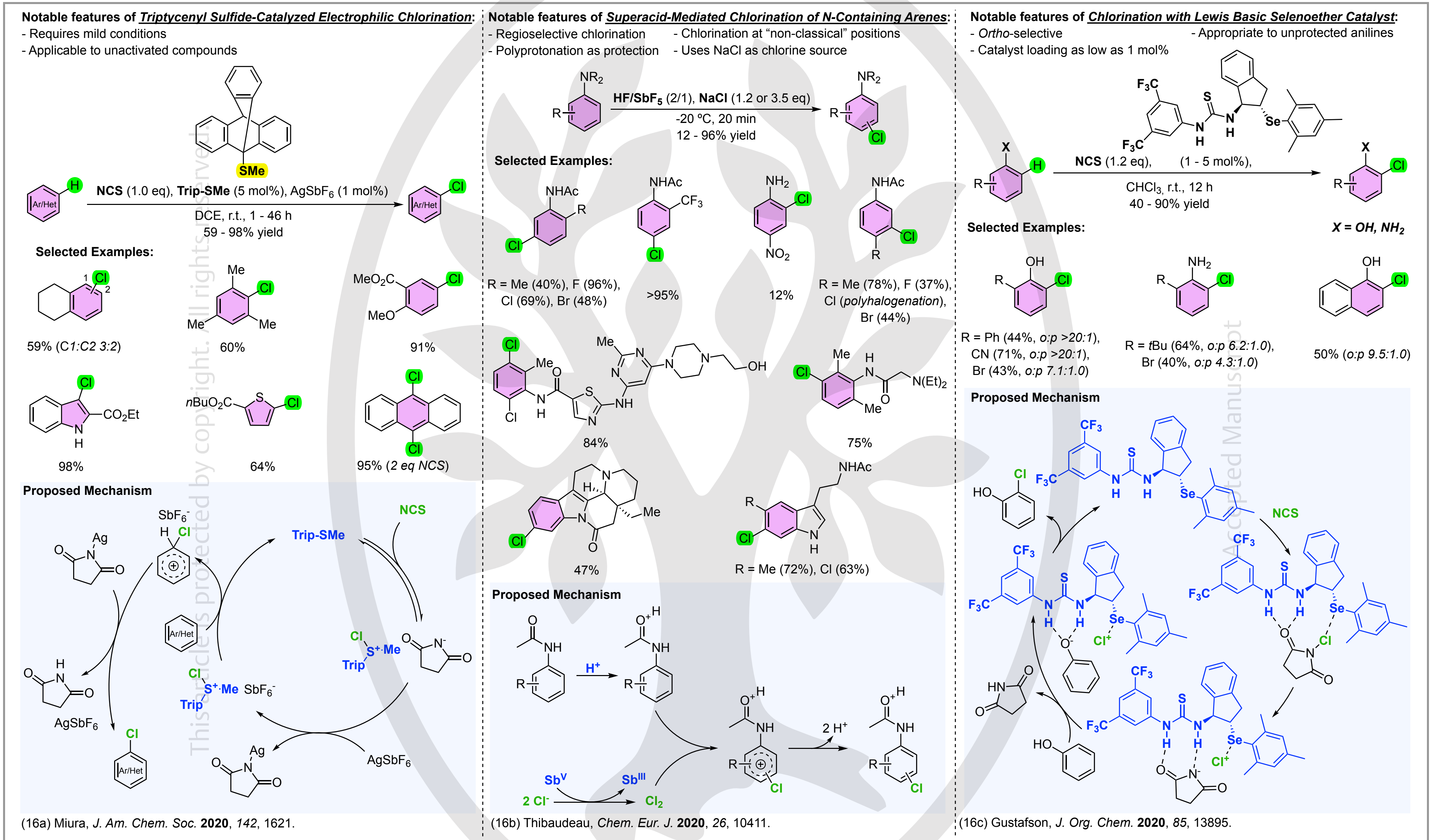
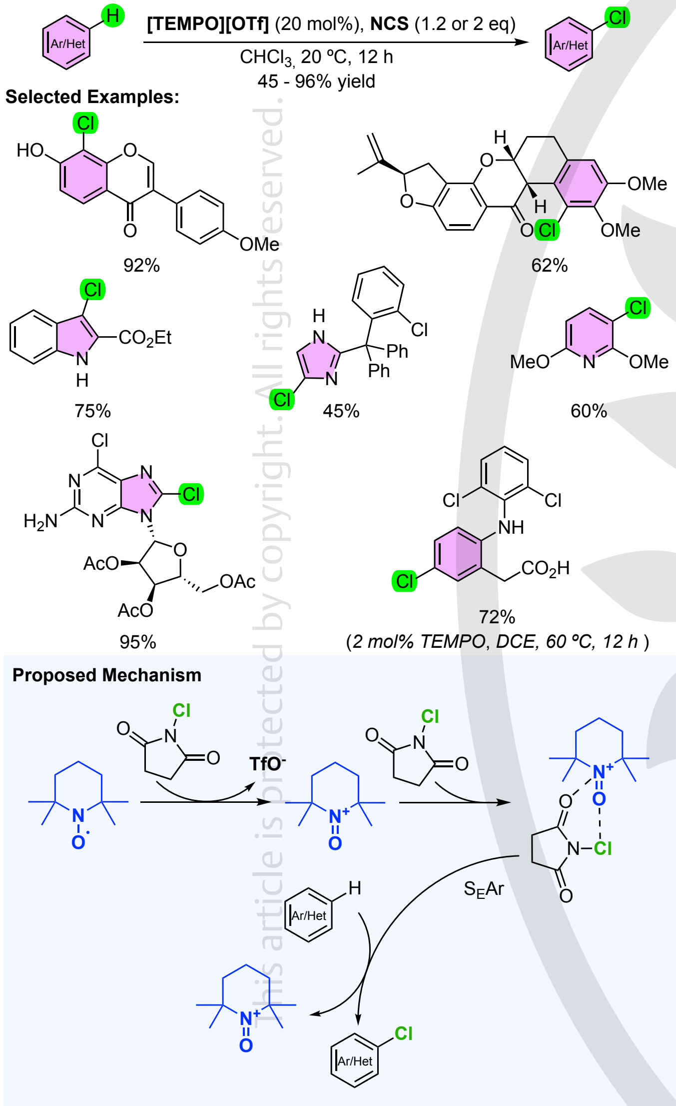


Figure 16 (Part 1) Chlorination of (hetero)arenes using various catalysts[16a-c]

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

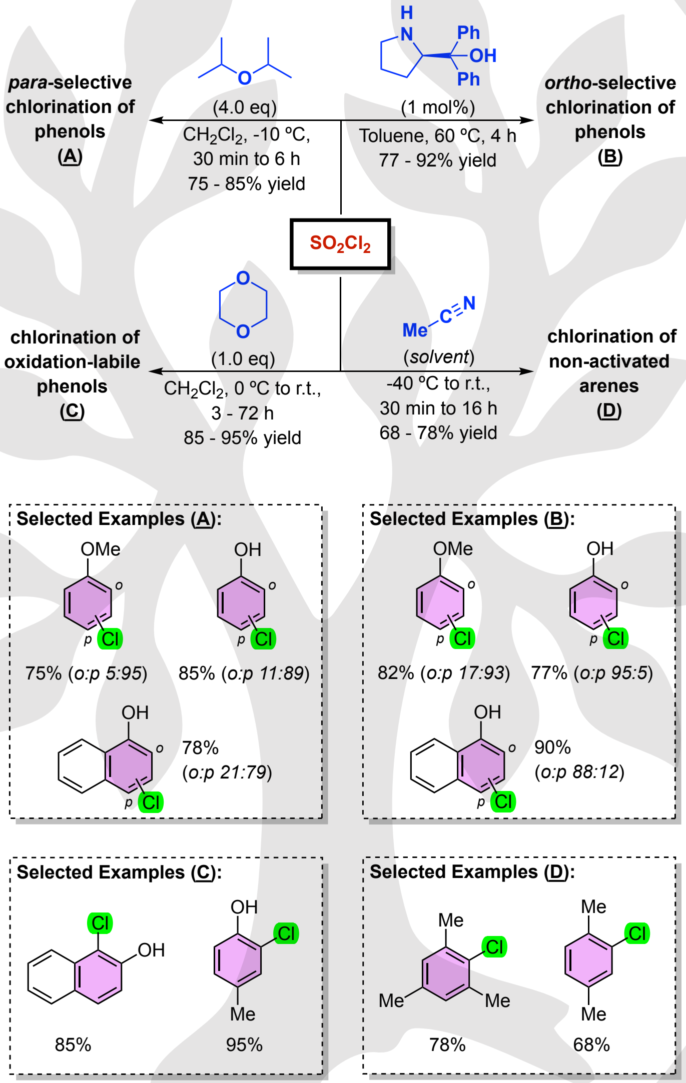
- Requires mild reaction conditons
- Not exclusive to aromatic halogenation
- Good functional group tolerance



(16d) Song, *Nat. Commun.* **2021**, *12*, 3873.

Notable features of *Catalyst-Tuned Chlorination of Arenes with SO_2Cl_2*:

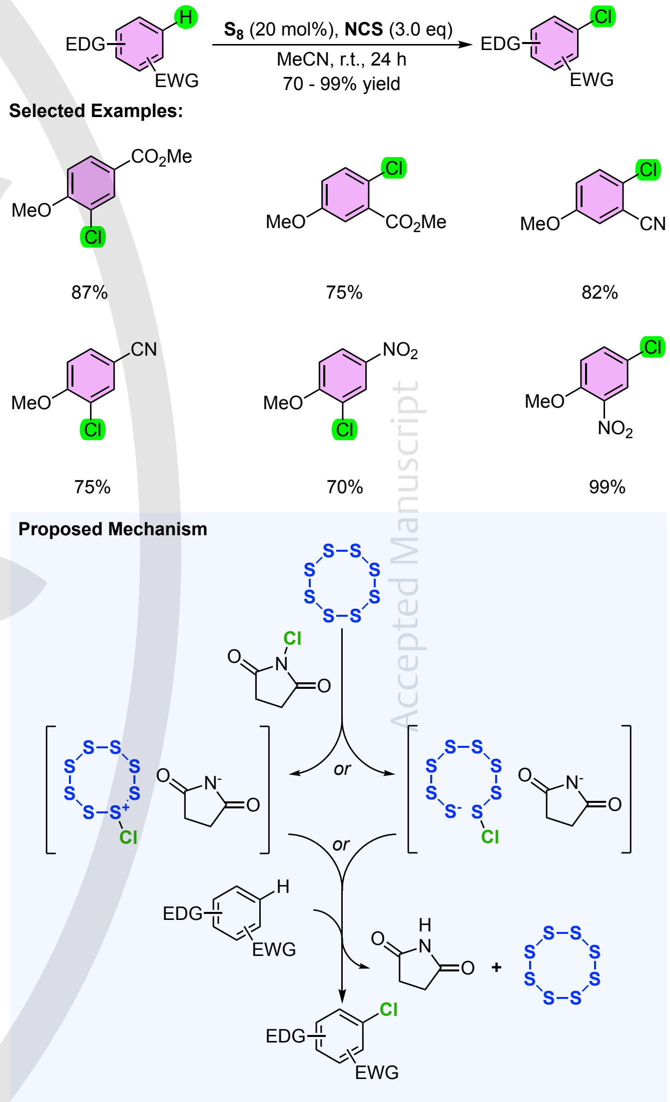
- Same chlorine source for several types of chlorinations
- MeCN as a strong SO_2Cl_2 activator
- Ready availability of most, if not all, reaction components



(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



(16f) Maegawa, *J. Org. Chem.* **2024**, *89*, 770.

Figure 16 (Part 2) Chlorination of (hetero)arenes using various catalysts[16d-f]

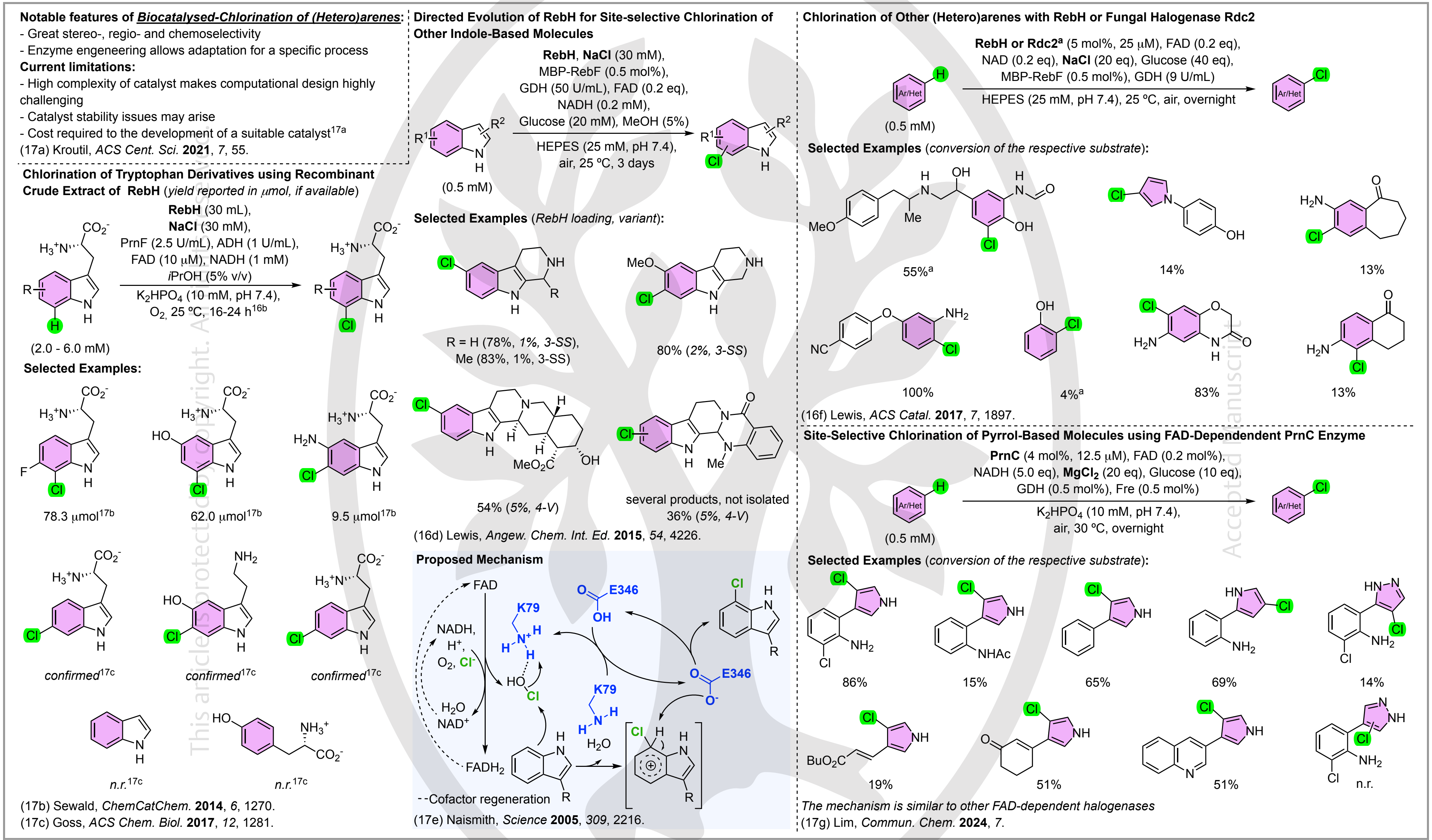
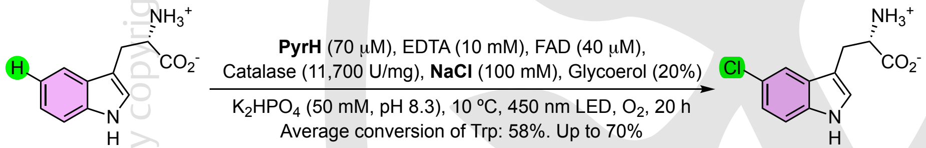


Figure 17 (Part 1) Biocatalyzed chlorination of (hetero)arenes[17a-g]

Photochemically Driven Bioctalyzed Chlorination of Tryptophan with PyrH Enzyme



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

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

Further Reading:

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(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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