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

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DOI: 10.1055/a-2446-9165

Please cite this article as: Vogel I C, Pinto D C, Candeias N R. Recent Advances in Chlorination: Novel Reagents and Methods from the Last Decade. SynOpen 2024. doi: 10.1055/a-2446-9165

Conflict of Interest:

This study was supported by Fundação para a Ciência e a Tecnologia (http://dx.doi.org/10.13039/501100001871), PTDC/QUI-QOR/1131/2020,UIDB/50006/2020 | UIDP/50006/2020

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 Cl₂ and PCl₅ 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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Received: Accepted: Published online: DOI:	copy			

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 Cl₂ and PCl₅ 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 Cl₂, SO₂Cl₂, SbCl₅, PCl₅, and *t*BuOCl, though effective, present challenges due to their high toxicity and reactivity. Similarly, widely used reagents such as NCS, DCDMH, TCCA, and PhICl₂ 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, SO₂Cl₂, POCl₃, 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.



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Graphical Review



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



Template for SynOpen

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Graphical Review
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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}





Figure 6 (Part 1) Electrochlorination of (hetero)arenes^{6a-g}











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













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









Figure 17 (Part 1) Biocatalyzed chlorination of (hetero)arenes17a-g



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, Nicatalyzed 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, MgCl₂, 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.

Funding Information

This work received financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) through the projects PTDC/QUI-QOR/1131/2020, and LAQV-REQUIMTE UIDB/50006/2020 | UIDP/50006/2020).

Acknowledgment

Financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) are acknowledged. I. V. acknowledges Fundação Calouste Gulbenkian for the "Novos Talentos" funding programme.

Conflict of Interest

The authors declare no conflict of interest.

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