Vinylogous Nitro-Haloform Reaction Enables Aromatic Amination

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ABSTRACT: The first example of an aromatic haloform reaction is reported, defining a conceptually new haloform-type approach to the metal-free functionalization of arenes. We demonstrated that heteroarenes bearing a vinylogous nitromethane system, via the stage of a trichloromethane derivative, could undergo aromatic amination to produce N-functionalized arenes in quantitative yields and without the need for transition-metal catalysis. The haloform-type amination was implemented in the development of effective orthogonal N-protection strategies, establishing a new promising N-protecting reagent.

Aromatic amines are ubiquitous structural motifs found in both natural and synthetic compounds and are important building blocks of bioactive species and active pharmaceutical ingredient (APIs).1 The chemistry of aromatic amines plays a central role in modern organic synthesis due to their prevalent occurrence across a broad range of applications. Their primary industrial relevance which, through the decades, has driven an intense research effort, delivered many opportune strategies for their construction.2 Hence, the preparation of aromatic amines has undergone substantial advancement, from classic non-catalytic S,N-Ar processes3 to the emergence of transition-metal catalyzed methodologies.4 The establishment, in the late 1990s, of palladium-catalyzed cross-coupling amination5 marked a major breakthrough in the field and quickly became the benchmark for the preparation of aromatic amines, providing unmatched levels of efficiency and versatility in important industrial and commercial applications.6 In recent years, despite the leading role of transition-metal catalysis, the field has experienced a renewed interest in the delivery of new reagents and transformations,7 driven by the increasing demand for long-term sustainability and the concerns about the future supply of rare metal species. Although the replacement of transition-metal catalysis seems unrealistic in the near future, alternative approaches could play an important role by providing solutions for specific issues affecting metal-catalyzed processes. For instance, transition-metal species, due to their Lewis acid nature, are known to suffer from compatibility issues in the presence of strongly coordinating substrates. Specifically, small N2, O-heteroarenes, featuring reduced aromaticity and a substantial Lewis base character, still account for challenging substrates,8 due to their ability to engage the metal catalyst in stable coordination complexes, disrupting the catalytic cycle.9 The origin of such incompatibility is to be sought in the inherent chemical nature of N2, O-heteroarenes and transition metals (Lewis base/Lewis acid, respectively), which has hampered the development of a general solution so far. This suggests that switching to metal-free conditions is required in the case of heteroaromatic substrates, thus conferring primary relevance to the development of new metal-free amination methodologies. In this context, our ongoing interest in the chemistry of small N2, O-heteroarenes prompted us to investigate the development of new metal-free strategies enabling them to react with N-nucleophiles under mild conditions and most crucially without the need for transition-metal catalysis. 3,5-Dimethyl-4-nitroisoxazole 610 (Scheme 1 and Figure 1) was chosen as a model substrate in light of the poor aromaticity and the unique ambiphilic reactivity11 displayed by the vinylogous nitromethane system embedded in the 4-nitroisoxazole ring.12

The peculiar chemical features of 6 have established it as a versatile tool in organic synthesis, finding application in a broad range of transformations13 and in the preparation of valuable APIs.14 Most significantly, our previous studies demonstrated the existence of profound analogies between the reactivity of heteroaromatic vinylogous nitromethanes, such as 6, and carbonyl species such as methylketones 1 (Figure 1).15 Following from these considerations, the mechanistic rationale underpinning the design of the new amination took inspiration from the classic haloform reaction.16 Taking into account the established behavior of methylketones 1 under haloform conditions (Scheme 1a and b),17 we envisaged that 6, through the stage of 4-nitro-5-trihalomethyl derivative 7, could undergo regioselective amination to 5-aminoisoxazole 8, via an unprecedented haloform-type process, i.e., vinylogous nitro-
haloform reaction (Scheme 1c). We hypothesized that, in the presence of a source of halonium ions X⁺, exhaustive α-halogenation of 6 would deliver the trihalogenated derivative 7 which, in the presence of N-nucleophiles, would then undergo haloform-type aromatic amination to 8, with concomitant formation of CHX₃ (Scheme 1c). Herein we describe the development of a novel haloform-type strategy for the metal-free aromatic amination of some heteroarenes. The work outlines an innovative application of the haloform reactivity, reaching beyond the limits of the classic carbonyl-based transformation, and provides a conceptually new approach to the functionalization of aromatic compounds.

At the onset of the project, we focused on the study of the haloformation of 3,5-dimethyl-4-nitroisoxazole 6 and reactivity analogies with methylketones 1.

Scheme 1. Haloform Reactivity and Applications

a) Classic haloform reaction:

\[ \text{R} + \text{NOS} \rightarrow \text{R}^+ + \text{X}^- + \text{CHX}_3 \]

b) Haloform-type amidation:

\[ \text{R} + \text{NOR} \rightarrow \text{R}^+ + \text{NHR} \]

c) This work: haloform-type aromatic amination

\[ \text{R} + \text{NOR} \rightarrow \text{R}^+ + \text{CHX}_3 \]

Figure 1. Ambiphilic reactivity of vinylogous nitromethane 3,5-dimethyl-4-nitroisoxazole 6 and reactivity analogies with methylketones 1.
stoichiometric amounts of both aniline and K$_2$CO$_3$. Under optimized conditions, 8a was obtained in 94% yield and in pure form after a simple extractive workup (Table 2, entry 11). With optimized conditions in hand, we investigated the scope of the transformation by reacting different aromatic and aliphatic amines with 7a to produce 5-aminoisoxazoles 8a−s (Scheme 2). Excellent results were obtained in the presence of primary and secondary amines, together with a remarkable functional group compatibility. Moreover, the products were obtained in pure form after extractive workup, avoiding the need for purification. An NMR study carried out on the crude mixture (see the Supporting Information (SI) for details) identified chloroform as the sole halogenated byproduct, which suggested the participation of a polar mechanism rather than a radical pathway.²¹

The excellent yields and operational simplicity of the methodology prompted us to explore its use as novel a N-protection strategy for amines (Scheme 3). We reasoned that the unique reactivity of 7a, together with the mild conditions and selectivity of the transformation, constituted an ideal set of features for its use as a N-protecting reagent. Primary and secondary amines could be efficiently protected, in the form of N-isoxazolyl amines 8, via haloform-type amination with 7a. The subsequent deprotection step could exploit the known ability of 4-nitroisoxazoles to undergo ring-opening to carboxylates, known as the Sarti Fantoni reaction.²² Deprotection of 8 to free amine 4 would entail a novel cascade pathway involving tandem ring-opening/decarboxylation, via the stage of carbamate intermediate 11 (Scheme 3, a).

Table 2. Screening of Conditions for the Haloform-type Aromatic Amination of 7a with aniline 4a

| entry | 4a | solvent | base | $T$ (°C) | 8a yield (%) |
|-------|----|---------|------|---------|-------------|
| 1     | 10.0− | −− | 20 | 12 |
| 2     | 10.0− | −− | 50 | 79 (16) |
| 3     | 2.5 DCM− | − | 20 | 8 |
| 4     | 2.5 toluene− | − | 20 | 5 |
| 5     | 2.5 THF− | − | 20 | 11 |
| 6     | 2.5 toluene− | − | 50 | 15 |
| 7     | 2.5 THF− | − | 50 | 54 (19) |
| 8     | 2.5 THF DABCO− | − | 50 | 45 |
| 9     | 2.5 THF KOH− | − | 50 | n.d. |
| 10    | 2.5 THF K$_2$CO$_3$− | − | 50 | 89 (<5) |
| 11    | 1.1 THF K$_2$CO$_3$− | − | 50 | 94 |

"Reaction conditions: 2 (0.25 mmol), solvent (0.25 mL), sealed tube. 
Yields determined by $^1$H NMR analysis of the crude reaction mixture, unless otherwise stated. 
Isolated yields. The values in brackets refer to the yield of 9a. 
Base (0.50 mmol, 2.0 equiv). 
Fast degradation of 7a. 
K$_2$CO$_3$ (0.25 mmol, 1.0 equiv)"

Scheme 2. Scope of the Metal-Free Haloform-type Aromatic Amination of 7a with Amines 4a−s

To demonstrate the feasibility of the proposed strategy, we first focused on the search of suitable deprotection conditions, using N-Boc,N'-isoxazolyl diamine 8q as the model substrate (Scheme 3b). Selective deprotection of 8q to 4q took place smoothly by treatment with aqueous NaOH in THF, thus indicating the base-labile nature of the N-isoxazolyl protecting group. The nature of the basic system was critical to the reaction, as replacing NaOH/THF with K$_2$CO$_3$/MeCN proved ineffective. In addition, the N-isoxazolyl functionality showed remarkable stability toward acids as well as compatibility with both oxidative and reductive conditions; see the SI for details on the reaction conditions screened. On the basis of these findings, we finally applied 7a to the development of new effective orthogonal N-protection strategies for diamines in combination with acid-labile N-Boc functionalities (Scheme 3c).²³

4731
In conclusion, we have developed a conceptually new haloform-type approach to the metal-free aromatic amination of some type of heteroarenes. The aromatic haloform-type reaction reported herein enables the straightforward preparation of functionalized amino arenes under mild conditions and avoiding the use of transition-metal catalysis. We demonstrated of functionalized amino arenes under mild conditions and reaction reported herein enables the straightforward preparation of some type of heteroarenes. The aromatic haloform-type process, for the first time extending the classic haloform mechanism, involving the 1,4-conjugate addition of N-nucleophiles to a vinylogous nitro-trichloro-methane system, followed by chloroform elimination, and was therefore accordingly named vinylogous nitro-haloform reaction. The study represents the first example of aromatic haloform-type process, for the first time extending the classic haloform reactivity to an unprecedented class of aromatic substrates. The haloform-type amination provided a new approach to the N-protection of primary and secondary amines and to the orthogonal protection of diamines, demonstrating the synthetic utility of the method. Building on the preliminary findings reported herein, further studies are underway to widen the scope to structurally diverse substrates as well as different classes of aromatic transformations.

### ASSOCIATED CONTENT
**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01494.

### REFERENCES

(1) (a) Vogt, P. F.; Gerullis, J. J. In Ullmann’s Encyclopedia of Industrial Chemistry; Wiley-VCH Verlag GmbH & Co. KGaA, 2000. (b) Lawrence, S. A. Amines: synthesis, properties and applications; Cambridge University Press, 2004.

(2) Taillefer, M.; Ma, D. Amination and Formation of sp2 C-N Bonds; Springer: Berlin, Heidelberg, 2013.

(3) Terrier, F. Modern Nucleophilic Aromatic Substitution; Wiley-VCH Verlag GmbH & Co. KGaA, 2013.

(4) Sambiagi, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. Copper catalysed Ullmann type chemistry: from mechanistic aspects to modern development. Chem. Soc. Rev. 2014, 43, 3525–3550.

(5) (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. A simple catalytic method for the conversion of aryl bromides to arylamines. Angew. Chem., Int. Ed. 1995, 34, 1348–1350.

(6) Ruiz-Castillo, P.; Buchwald, S. L. Applications of palladium-catalyzed C–N cross-coupling reactions. Chem. Rev. 2016, 116, 12564–12649.

(7) (a) Li, G.; Qin, Z.; Radoевич, A. T. P (III)/P (V)-catalyzed methylation of aryloboric acids and esters: reductive C–N coupling with nitromethane as a methylamine surrogate. J. Am. Chem. Soc. 2020, 142, 16205–16210. (b) Wang, T.; Hoffmann, M.; Dreeu, A.; Hasagić, E.; Hu, C.; Stein, P. M.; Witzel, S.; Shi, H.; Yang, Y.; Rudolph, M.; Stuck, F.; Rominger, F.; Kerscher, M.; Comba, P.; Hashmi, A. S. K. A metal-free direct aren C−H amination. Adv. Synth. Catal. 2021, 363, 2783–2795.

(8) Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. Aromativity as a cornerstone of heterocyclic chemistry. Chem. Rev. 2004, 104, 2777–2812.

(9) Hartwig, J. F. Organotransition Metal Chemistry, from Bonding to Catalysis; University Science Books: New York, 2010.

(10) Cordero, F. M.; Giomi, D.; Machetti, F. Isoxazoles, in Comprehensive Heterocyclic Chemistry IV; StC Black, D., Cossy, J.; Stevens, C. V. Eds.; Elsevier, 2022; p 308–434.

(11) Curti, C.; Battistini, L.; Sartori, A.; Zanardi, F. New developments of the principle of vinylogy as applied to π-extended enolate-type donor systems. Chem. Rev. 2020, 120, 2448–2612.

(12) (a) Adamo, M. F. A.; Chimirchi, S.; De Sio, F.; Donati, D.; Sarti-Fantonii, P. The reactivity of 3-methyl-4-nitro-5-styrylisoxazole with some bis-enolisable ketones. Tetrahedron Lett. 2002, 43, 4157–4160. (b) Adamo, M. F. A.; Donati, D.; Duffy, E. F.; Sarti-Fantonii, P. Multicomponent Synthesis ofSpiroisoxazolines. J. Org. Chem. 2005, 70, 8395–8399. (c) Adamo, M. F. A.; Duffy, E. F. Multicomponent Synthesis of 3-heteroarylpropionic acids. Org. Lett. 2006, 8, 5157–5159. (d) Adamo, M. F. A.; Konda, V. R. Multicomponent Synthesis of 3-Indolopropionic Acids. Org. Lett. 2007, 9, 303–307. (e) Baschieri, A.; Bernardi, L.; Ricci, A.; Suresh, S.; Adamo, M. F. A. Catalytic asymmetric...
conjugate addition of nitroalkanes to 4-nitro-5-styrylisoxazoles. Angew. Chem., Int. Ed. 2009, 48, 9342–9345. (f) Fini, F.; Nagabelli, M.; Adamo, M. F. A. Development of a mild procedure for the addition of bisulphite to electrophilic olefins. Adv. Synth. Catal. 2010, 352, 3163–3168.

(13) (a) Illera, D. S.; Suresh, S.; Moccia, M.; Bellini, G.; Saviano, M.; Adamo, M. F. A. N-heterocyclic carbene catalysed homoenoconate addition to 3-methyl-4-nitro-5-styrylisoxazoles. Tetrahedron Lett. 2012, 53, 1808–1811. (b) Chauhan, P.; Mahajan, S.; Raabe, G.; Enders, D. Organocatalytic one-pot 1, 4-/1, 6-/1, 2-addition sequence for the stereocontrolled formation of six consecutive stereocenters. Chem. Commun. 2015, 51, 2270–2272.

(14) Moccia, M.; Cortigiani, M.; Monasterolo, C.; Torri, F.; Del Fiandra, C.; Fuller, G.; Kelly, B.; Adamo, M. F. A. Development and Scale-up of an Organocatalytic Enantioselective Process to Manufacture (S)-Pregabalin. Org. Process Res. Dev. 2015, 19, 1274–1281.

(15) (a) Disetti, P.; Moccia, M.; Salazar Illera, D.; Suresh, S.; Adamo, M. F. A. Catalytic enantioselective addition of isocyanooacetate to 3-methyl-4-nitro-5-styrylisoxazoles under phase transfer catalysis conditions. Org. Biomol. Chem. 2015, 13, 10609–10612. (b) Nagaraju, S.; Sathish, K.; Kashinath, D. Applications of 3,5-dialkyl-4-nitroisoxazoles and their derivatives in organic synthesis. ChemistrySelect 2021, 6, 7736–7793.

(16) Fuson, R. C.; Bull, B. A. The haloform reaction. Chem. Rev. 1934, 15, 275–309.

(17) (a) Cao, L.; Ding, J.; Gao, M.; Wang, Z.; Li, J.; Wu, A. Novel and direct transformation of methyl ketones or carbinals to primary amides by employing aqueous ammonia. Org. Lett. 2009, 11, 3810–3813. (b) Doši, S.; Moriyama, K.; Togo, H. Transition-metal-free transformation of aryl bromides into aromatic esters and amides via aryl trichloromethyl ketones. Eur. J. Org. Chem. 2013, 2013, 7815–7822.

(18) The halogenation of 4-nitroisoxazoles has received limited attention until recently, when we first reported the preparation of the monochlorinated derivative of 6; see: (a) Dere, R.; Monasterolo, C.; Moccia, M.; Adamo, M. F. A. Preparation and reactivity of [2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-amines. Tetrahedron Lett. 2015, 56, 7168–7171. (b) Dočekal, V.; Petrželová, S.; Cisaňová, I.; Veselý, J. Enantioselective cyclopropanation of 4-nitroisoxazole derivatives Adv. Synth. Catal. 2020, 362, 2597–2603.

(19) Unlike trichloromethylketones 3, 7a demonstrated a remarkable stability and could be isolated in pure form, without degradation upon prolonged storage.

(20) The chemoselectivity of the chlorination of 6 could be rationalized according to the progressive enhancement of the α-protons acidity by the adjacent chlorine atoms; see the SI.

(21) A plausible mechanism could be proposed proceeding through the established SₗAr two-stage addition/elimination sequence, via the intermediate Meisenheimer complex; see: (a) Blažiak, K.; Danikiewicz, W.; Mąkoza, M. How does nucleophilic aromatic substitution really proceed in nitroarenes? Computational prediction and experimental verification. J. Am. Chem. Soc. 2016, 138, 7276–7281. However, the involvement of an alternative concerted mechanism (cSₗAr) cannot be ruled out; see: (b) Rohrbach, S.; Smith, A. J.; Hao Pang, J.; Poole, D. L.; Tuttle, T.; Chiba, S.; Murphy, J. A. Concerted nucleophilic aromatic substitution reactions. Angew. Chem. Int. Ed. 2019, 58, 16368–16388. See the SI for a detailed discussion.

(22) The ring-opening of 8 has not been reported to date, while it is known to proceed on 4-nitroisoxazole analogues under both basic and oxidative conditions; see: Del Fiandra, C.; Piras, L.; Fini, F.; Disetti, P.; Moccia, M.; Adamo, M. F. A. Phase transfer catalyzed enantioselective cyclopropanation of 4-nitro-5-styrylisoxazoles. Chem. Commun. 2012, 48, 3863–3865.

(23) The present work aimed at demonstrating the viability of the proposed N-protection strategy. A comprehensive study of the use of 7a as a N-protecting reagent is currently underway and will be reported in due course.