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Oxidative photochlorination of electron rich arenes via *in situ* bromination

Simon Josef Siegfried Düsel^[a] and Burkhard König*^[a]

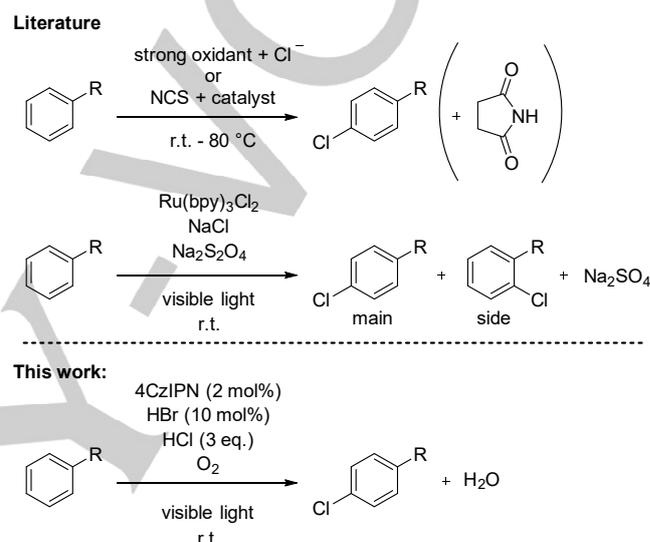
Abstract: Electron rich arenes are oxidatively photochlorinated in the presence of catalytic amounts of bromide ions, visible-light and 4CzIPN as organic photoredox catalyst. The substrates are *in situ* brominated in a first photoredox-catalyzed oxidation step, followed by a photocatalyzed ipso-chlorination yielding the target compounds in high ortho/para regioselectivity. Dioxygen serves as a green and convenient terminal oxidant. Aqueous hydrochloric acid serves as the chloride source, reducing the amount of saline by-products

Introduction

Chlorinated organic compounds are ubiquitously present in chemical synthesis, such as natural product synthesis, catalysis and material science.^[1] The robustness and electronic properties of the C-Cl bond enables the use of the halogenated compounds as pharmacophores and crop protection agents.^[2] Simple chlorinated arenes are produced in ton scales via chlorination by gaseous chlorine under harsh conditions, requiring elaborated safety conditions.^[3] In contrast, stoichiometric amounts of strong oxidants in combination with diverse chloride sources or preformed "Cl⁺"-species (e.g. N-chlorosuccinimide (NCS)) are utilized when compounds shall be obtained on smaller scale.^[4]

Visible-light photocatalysis has become an important tool for the promotion of new reaction pathways and overcoming energetic barriers at ambient temperature.^[5] Our group recently reported the visible-light driven bromination of aromatic systems.^[6] However, direct chlorination of arenes by photoredox-catalysis, starting from chloride ions, is challenging. The group of Hu described a synthetic visible-light driven protocol in 2017.^[7] The authors use Ru(bpy)₃Cl₂ in combination with Na₂S₂O₄ as oxidant, which is postulated to subsequently oxidize photocatalytically generated chlorine radicals to the reacting "Cl⁺"-species. Hu and coworkers present a wide substrate scope with high yields. However, strong oxidants are typically required for the formation of electrophilic Cl-species, and the generation of organic or saline byproducts (see Scheme 1) reduce the efficiency in terms of atom economy. Therefore, we investigated a metal-free oxidative chlorination under dioxygen atmosphere based on radical chemistry, avoiding stoichiometric amounts of oxidants other than dioxygen in a visible-light mediated reaction. A key

feature of the developed system is the presence of a catalytic amount of HBr for *in situ* bromination activation.



Scheme 1. Chlorine-free methods for the chlorination of arenes.^[4, 7a]

Results and Discussion

We observed the formation of 4-chloroanisole (**2**) with excellent regioselectivity upon blue-light irradiation of a mixture containing anisole, aqueous hydrochloric acid and 4CzIPN,^{[8][9]} when a catalytic amounts of bromide ions was present (see Table 1). Light, oxygen and the organic photocatalyst (4CzIPN) are essential for the reaction to proceed, whereas the type bromide salt seemed to be less important. In order to achieve efficient reactivity with a decreased amount of saline byproducts, we decided to apply aqueous HBr as a simple bromide source for our standard conditions (Table 1, entry 4).^[10] The reaction proceeds well with aerial oxygen under open-air conditions (Table 1, entry 12). To create optimal oxidative conditions, the headspace of the closed reaction vials was saturated with oxygen. Other organic photocatalysts, chloride sources, solvents or an increased amount of catalyst did not provide higher yields (additionally see SI, Tables S1-S2).

We then investigated the scope of this reaction (Table 2) and observed that a variety of activated arenes and heteroarenes is chlorinated under the optimized reaction conditions. The monochloroarenes are generally obtained in moderate to good yields as single isomers. Only compound **4** was isolated as double-chlorinated benzene derivative, together with 5% of the

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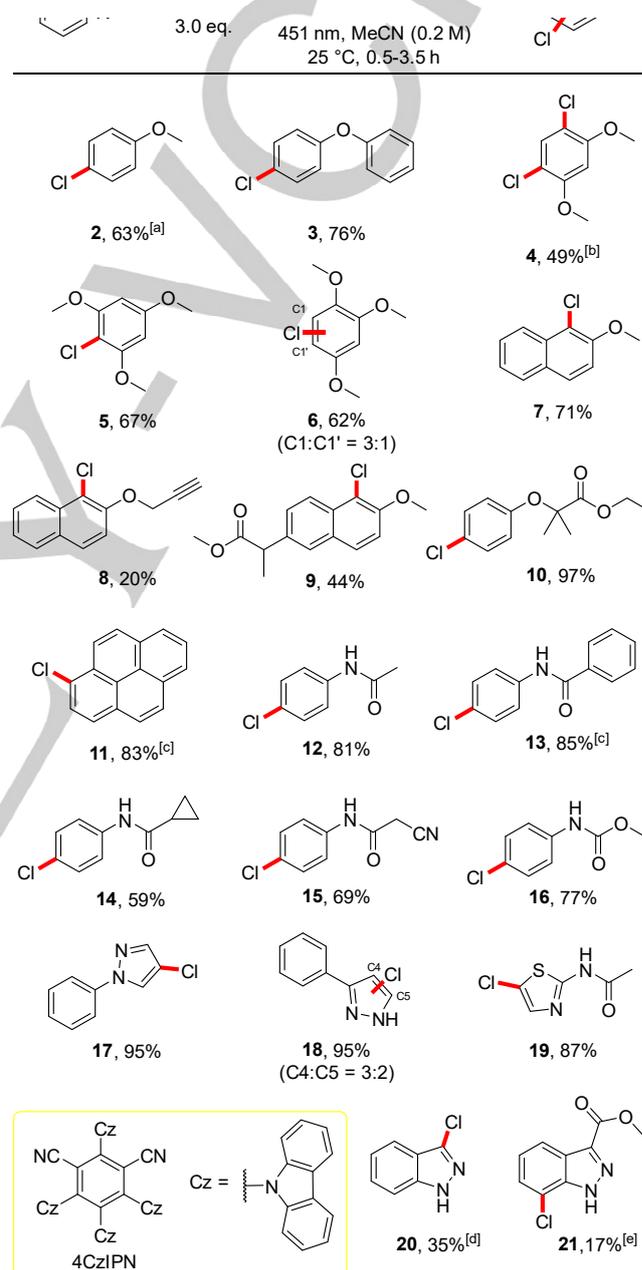
Table 1. Optimization table for the photocatalytic chlorination of anisole.

Entry	HCl [eq.]	Bromide source [eq.]	4CzIPN [mol%]	M [mol·L ⁻¹]	Yield ^[a] [%]
1 ^[b]	1.0	HBr (0.1)	2	0.1	37
2 ^[b]	2.0	HBr (0.1)	2	0.1	57
3 ^[b]	3.0	HBr (0.1)	2	0.1	57
4	3.0	HBr (0.1)	2	0.2	63
5 ^[b, c]	3.0	HBr (0.1)	2	0.2	56
6	3.0	HBr (0.1)	1	0.2	59
7	3.0	HBr (0.1)	3	0.2	58
8	3.0	NEt ₄ Br (0.1)	2	0.2	64
9	3.0	KBr (0.1)	2	0.2	30
10	3.0	HBr (0.05)	2	0.2	33
11	3.0	HBr (0.15)	2	0.2	61
12 ^[d]	3.0	HBr (0.1)	2	0.2	59
13	3.0	-	2	0.2	13
14	3.0	HBr (0.1)	0	0.2	0
15 ^[e]	3.0	HBr (0.1)	2	0.2	0
16 ^[f]	3.0	HBr (0.1)	2	0.2	0

Conditions: Anisole (0.1 mmol), HCl, 4CzIPN and bromide source in MeCN (0.5 mL), irradiated under oxygen atmosphere by 451 nm LEDs at 25 °C for 1.5 h. [a] GC-yields with *tert*-butylbenzene as standard. [b] 1.0 mL of MeCN. [c] 0.2 mmol of anisole. [d] Open to air. [e] Absence of light. [f] Under nitrogen atmosphere.

mono-chlorinated starting material. Naphthalene derivatives **7-9** or unsubstituted pyrene (**11**) are functionalized, although oxidation of the triple bond of **8** is observed under the applied conditions. Anilides were para-chlorinated with yields up to 85% and benzanilide (**13**) was selectively chlorinated on the activated phenyl ring, whereas the second electron-deficient ring was unaffected. To our delight, the nitrile group of compound **15** remained stable under the acidic conditions and the protocol could also be applied to a more labile carbamate, to obtain **16** in reasonable yields. However, we noticed that for this compound and other molecules, such as the naproxen^[11] derivative **9**, the products degrade, if too long reaction times were applied. For that reason, the reaction time was adjusted for each compound (please see the supporting information). The physiological active clofibrate^[12] **10** and heterocycles **17-18** remained stable and were therefore obtained in nearly quantitative yields. In contrast, the observed conversion of benzimidazole was very slow, which is why a high amount of starting material remained and **20** was only isolated in 35% yield. Its less activated derivative **21** showed even

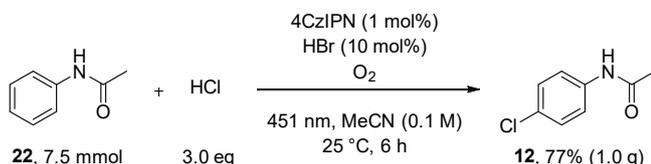
lower conversion.^[13] For unsubstituted benzene (**30**) and more electron deficient arenes no, or only traces of product were detected.

Table 2. Scope of the photocatalytic chlorination reaction.

Conditions: Substrate (0.1 mmol), HCl (3 eq.), HBr (10 mol%), 4CzIPN (2 mol%) in MeCN (0.5 mL), irradiated under oxygen atmosphere at 25 °C. Isolated yields. [a] GC-yield with *tert*-butylbenzene as standard. [b] The major product is shown. A mixture of **8** with 5% of the mono-chlorinated starting material was obtained. [c] Due to solubility, 1.0 mL of MeCN was used. [d] 43% of starting material reisolated. [e] 43% of starting material reisolated.

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To demonstrate the application of the method to a larger scale, we performed a reaction with 7.5 mmol of acetanilide (**22**), with a reduced amount of catalyst. Due to the lower light output of the gram-scale photo-reactor, the reaction time was prolonged to 6 h, whereupon product **12** was isolated in 77% yield together with 8% of starting material and 4% of the respective para-brominated product.



Scheme 2. Gram-scale reaction of acetanilide.

The kinetic reaction profile (see Figure 1) of the model reaction (see Table 1) provides a better understanding of processes occurring in the reaction mixture. Already after 5 minutes of irradiation, the bromide salts are consumed and have nearly quantitatively substituted the para-position of the methoxy group of anisole (**1**), whereas the formation of 4-chloroanisole (**2**) is delayed. During the next 20 minutes the amount of 4-bromoanisole (**27**) remains relatively constant and the concentration of 4-chloroanisole (**2**) is steadily increasing. After ca. 60 minutes, the consumption of starting material and the product formation slow down. The highest amount of **2** is obtained after ca. 90 minutes. For longer reaction times, increasing amounts of undesired degradation products are detected by GC-analysis for this compound.

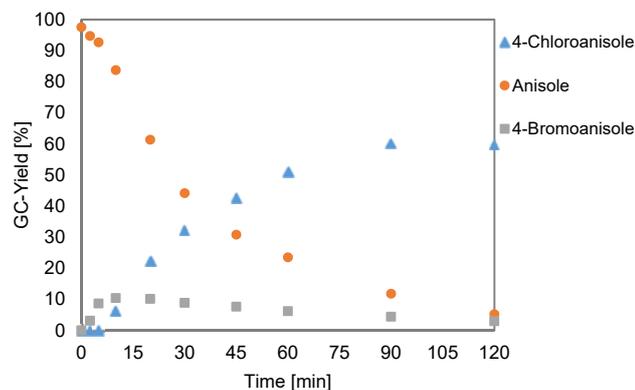
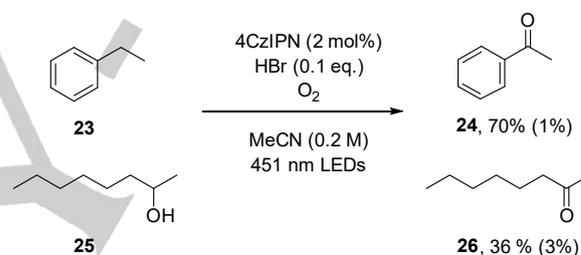


Figure 1. Kinetic reaction profile of the model reaction (see Table 1) under standard conditions: Anisole (0.1 mmol), HCl (3.0 eq.), HBr (10 mol%), and 4CzIPN (2 mol%) in MeCN (0.5 mL), irradiated under oxygen atmosphere by 451 nm LEDs at 25 °C. For each data point, 10 μ L of the reaction mixture were taken from the reaction vessel and analyzed with a GC-FID system after addition of *tert*-butylbenzene as standard.

Upon investigating the scope of the reaction, we noticed that benzylic alkyl groups, as well as, benzylic and aliphatic alcohols

were oxidized. As the reported oxidation potential of the excited catalyst ($E_{ox} = 1.35$ V vs vs SCE^[12]) would not be sufficient for this process, we further investigated this phenomena, to get more insight into the whole reaction mechanism. We performed the reaction with ethylbenzene (**23**) and 2-octanol (**25**) in the presence of photocatalyst, oxygen, with and without 10 mol% of HBr (see Scheme 3). Whereas, the starting material was barely consumed in the absence of HBr, high conversion to the oxidized products was detected in the presence of bromide ions.^[14] It was previously reported that bromine radicals are reasonable good hydrogen atom transfer (HAT) reagents and can be used in catalytic systems, developed for the generation of carbon radicals and the subsequent formation of new bonds.^[15] However, the reaction of carbon radicals with triplet oxygen (our conditions) will further oxidize the respective organic compounds. Whereas highly oxidizing photoredox catalysts can achieve the oxidation of aromatic systems, followed by the subsequent oxidation of benzylic positions, direct oxidation of unactivated aliphatic alcohols is less common.^[16]



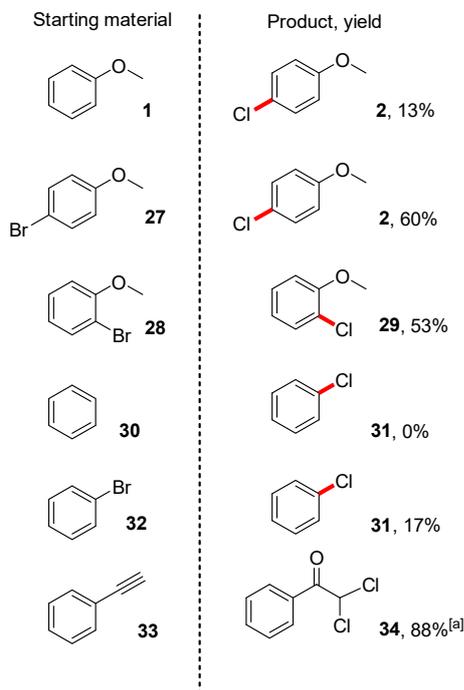
Scheme 3. Photocatalytic oxidation of organic compounds by generated bromine radicals via HAT. Yields without bromide source in parenthesis.

In 2014, the group of Chen postulated a $FeCl_3$ mediated halide exchange under UV-light conditions.^[17] They showed that liberated chlorine radicals readily react with aryl bromides, resulting in the formation of ipso-substituted chloroarenes. We assume that under our reaction conditions, chlorine radicals, generated by visible-light photoredox catalysis, may react in a comparable fashion. As the kinetic data (Figure 1) clearly demonstrated the initial formation of 4-bromoanisole (**27**) and its later consumption, we confirmed the consecutive chlorination step in the comparison experiments shown in Scheme 4.

When HCl, but no bromide source is present in the reaction mixture, anisole (**1**) is converted with a 13% yield of the desired product. However, 4-bromoanisole (**27**) as starting material will result in a 60% yield. Furthermore, 2-bromoanisole (**28**) as starting material yields 53% of ipso-substituted compound **29**, while only trace amounts of this ortho-product can be detected under standard reaction conditions. Moreover, less activated bromobenzene (**32**) can be converted, even if benzene itself is not halogenated under the photocatalytic conditions. All experiments support the proposed regioselective radical ipso-substitution of the bromine atom. To obtain further proof for the formation of an oxidized chlorine species, we exposed phenylacetylene (**33**) to our reaction conditions. As a result, we

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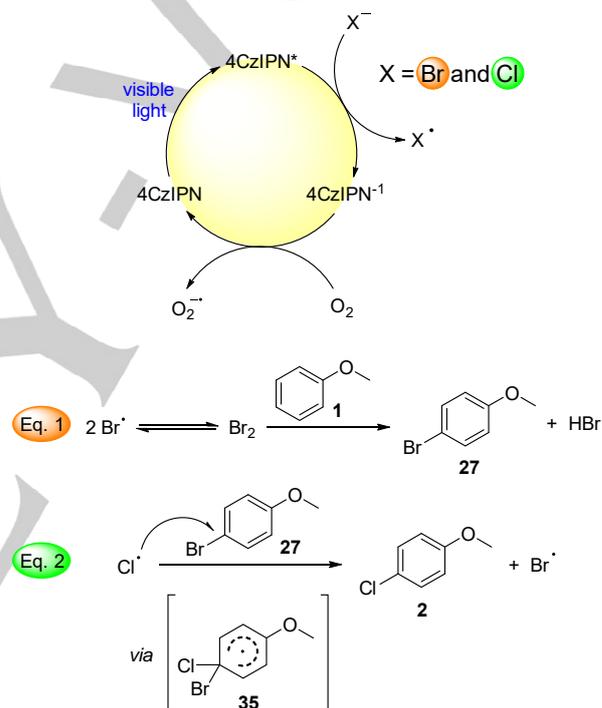
isolated **34** in high yield. Both, cationic and radical pathways are possible for the formation **34**.^[18]



Scheme 4. Halide exchange in the absence of a bromide source. Conditions: Starting material (0.1 mmol), HCl (3 eq.), and 4CzIPN (2 mol%) in MeCN (0.5 mL), irradiated under oxygen atmosphere by 451 nm LEDs at 25 °C for 1.5 h. GC-yields with *tert*-butylbenzene as standard. [a] Isolated yield.

Based on our observations and literature reports, we propose a mechanism for the described reaction (Scheme 5). The photoredox catalyst has a dual role, as it is oxidizing both, bromide and chloride anions, to their respective radical species. The formation of bromine radicals that can recombine to bromine as the active brominating agent, should occur faster. The in-situ formed bromoarenes are subsequently attacked by chlorine radicals, yielding the desired chlorinated compounds.^[17, 19] In addition to the kinetic data, showing a fast consumption of bromide and quasi stoichiometric formation of bromoanisole (**27**), this assertion is supported by fluorescence quenching experiments (please see supporting information, Figure S1). The interaction of the respective halide anions with the excited state of 4CzIPN is clearly demonstrated, whereas the observed quenching effect is stronger for the bromide ions. This observation also resembles the different oxidation potentials of Br⁻ ($E_{ox} = 0.74$ V vs SCE) and Cl⁻ ($E_{ox} = 1.05$ V vs SCE). Bromide can easier be oxidized by the catalyst ($E_{ox} = 1.35$ V vs SCE^[2]), which might result in a delayed oxidation of Cl⁻. The oxidation potential of our model substrate **1** ($E_{ox} = 1.75$ V vs SCE) exceeds the catalyst's excited state potential, consequently, the excited state quenching experiments show neglectable interaction of starting material with 4CzIPN*. As a result, and in contrast to reported photocatalytic brominations, we do not postulate the formation of aryl radical

cations as reaction intermediates.^[20] In the herein described process, the halogenation occurs with high regioselectivity due to the intermediary para-selective bromination step. The fate of the superoxide radicals, which are proposed to be generated from the reaction of O₂ with 4CzIPN⁻, is not completely clear yet. Often H₂O₂ is a final byproduct in photocatalytic reactions under aerial conditions.^[21] Yet, we could only detect low amounts of H₂O₂, as it is well known that hydrogen peroxide can be decomposed in the presence of bromide anions, whereupon elementary Br₂ is formed.^[22] This species can then further promote the described reaction pathway of the herein described reaction, as Br₂ readily reacts with electron rich arenes in the absence of light and catalyst,^[23] whereas unactivated benzene is not converted (for comparison experiments see SI, scheme S1).



Scheme 5. Mechanistic proposal for the visible-light mediated chlorination.

Conclusions

In summary, a new visible-light mediated oxidative chlorination of electron rich arenes yielding chloroarenes is reported. The mechanistic investigations support a subsequent *in situ* bromination and halogen exchange pathway, yielding chloroarenes with high regioselectivity. The presence of 4CzIPN, an organic photoredox catalyst, light, and oxygen are crucial for the fast oxidation of bromide ions, as well as, for the chloride oxidation.

Experimental Section

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General procedure for the chlorination of electron rich arenes

A 5 mL glass crimp vial was charged with 0.1 mmol of the respective substrate, 4CzIPN (1.6 mg, 2 mol%), MeCN (0.5 mL) and 27.4 μ L of a freshly prepared mixture of aqueous HCl and HBr (0.3 mmol, 3.0 eq. and 0.01 mmol, 0.1 eq.). The vial was closed with a septum and flushed two times with oxygen from a balloon connected to a syringe needle. The reaction vial was placed into a custom-built cooling system (pictures provided in the SI) at 25 °C and irradiated under stirring by two 451 nm LEDs through the bottom side (ca. 5 mm distance to the LEDs). The reaction progress was monitored by TLC or GC-FID and the reaction was stopped after 0.5 - 3.5 h, when all starting material was consumed, or no further progress was detected. To obtain an average result, two reaction mixtures were united and the solvent was removed under reduced pressure after the addition of silica gel. The products were purified by automated silica gel flash column chromatography with a mixture of petrol ether and ethyl acetate as eluent.

Acknowledgments

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Keywords: Chlorination • photoredox catalysis • oxidation • ipso-substitution • chloroarene

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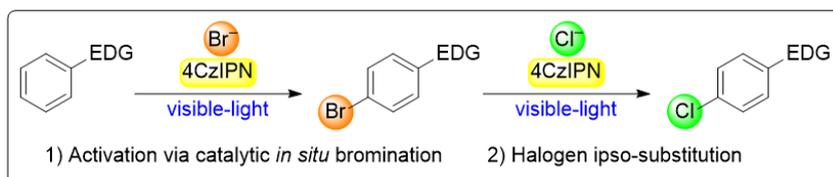
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Entry for the Table of Contents

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Chlorination of aromatic compounds is a basic, but important reaction in chemical synthesis. In this study, simple reagents, such as aqueous hydrochloric acid and dioxygen, are applied for the metal-free visible-light driven photochlorination of electron rich arenes. The reaction proceeds via oxidative photoredox-catalyzed halogenation steps.

Photochlorination

S.J.S. Düsel, B. König*

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