



Copper-catalyzed carbochlorination or carbobromination via radical cyclization of aryl amines



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ABSTRACT

A copper-catalyzed radical carbochlorination or carbobromination is reported. Intramolecular cyclization occurred through aryl radicals generated in situ from bench-stable aryl amines with aqueous hydrogen halides as the halogen sources. A variety of (3-halomethyl)-1,2-dihydrobenzofuran derivatives were prepared in up to 92% yield through this one-pot protocol utilizing widely available starting materials.

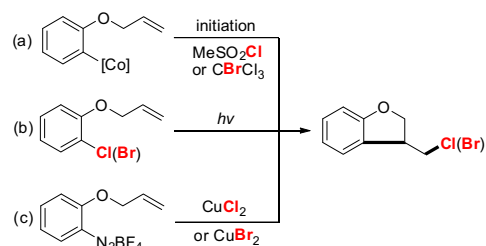
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Radical cyclizations followed by trapping with radical scavengers have been proven to be a powerful and versatile way for construction of mono- or polycyclic compounds bearing additional functional groups.¹ Featured with mild reaction conditions and high regioselectivities, intramolecular radical addition of aryl radicals² to the *O*-tethered C–C double bonds and subsequent trapping by halogen sources would probably be one of the most direct strategies to (3-halomethyl)-1,2-dihydrobenzofuran derivatives.

Early in 1987, Pattenden and coworkers documented a radical trapping methodology to the synthesis of (3-chloromethyl)-1,2-dihydrobenzofuran or (3-bromomethyl)-1,2-dihydrobenzofuran.³ This protocol was based on the irradiation of an organocobalt complex with excess amount of methanesulfonyl chloride (7 equiv) or bromotrichloromethane (10 equiv) as halogen sources (Fig. 1a). Separately in 2006 and 2014, Fagnoni group and Yoshimi group reported atom-economical approaches to the synthesis of (3-halomethyl)-1,2-dihydrobenzofuran derivatives via photolysis of aryl chlorides, aryl bromides or aryl iodides, albeit with limited substrate scopes and moderate regioselectivities (Fig. 1b).⁴ Mejis and Beckwith group developed alternative methods for the formation of these compounds through radical cyclization starting from aryl diazonium salts, with stoichiometric amount of corresponding cupric halides acting both as the radical initiators and halogen sources (Fig. 1c).^{5a–d} With cupric halides as the SET (single electron-transfer) reagents, aryl radicals were generated from the

aryl diazonium salts and underwent further intramolecular cyclization and halogenation. Given the fact that most diazonium salts are explosive and relatively difficult to store and handle, Wang group explored the use of aryl amines for the generation of the corresponding aryl diazonium salts in situ.^{6a,b,f} Recently, Studer and coworkers disclosed an efficient carboiodination reaction via intramolecular radical cyclization of aryl diazonium salts which were generated in situ from aryl amines.⁷ In an effort to develop a facile access to 3-(halomethyl)-2,3-dihydrobenzofuran analogues, we enclosed herein a search for a useful copper-catalyzed

Previous strategies:



This work:

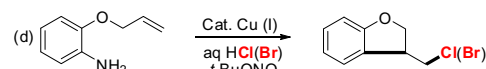
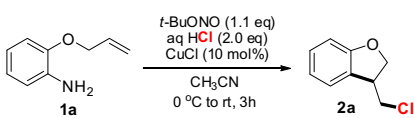


Figure 1. Radical carbochlorination/carbobromination.

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Table 1
Optimization of the reaction conditions^a



Entry	Variations from the standard conditions	Yield ^{b,c} (%)
1	Without CuCl	N.P.
2	CuCl ₂ instead of CuCl	N.P.
3	None	24
4	Fe(II) or Fe(III) salts instead of CuCl	N.P.
5	CuTc instead of CuCl	N.P.
6	CuI instead of CuCl	N.P.
7	CuBr instead of CuCl	N.P.
8	<i>n</i> -Bu ₄ NI instead of CuCl	N.P.
9	CH ₂ Cl ₂ instead of CH ₃ CN	Trace
10	CH ₃ OH instead of CH ₃ CN	N.P.
11	DMSO instead of CH ₃ CN	53
12	Acetone instead of CH ₃ CN	77
13	2.5 equiv HCl, with acetone as the solvent	86
14	3.0 equiv HCl, with acetone as the solvent	74
15	Cu(CH ₃ CN) ₄ BF ₄ instead of CuCl, with 2.5 equiv HCl and acetone as the solvent	92

^a Reaction conditions: *t*-BuONO (0.55 mmol) was added to a mixture of **1a** (0.50 mmol), the catalyst (0.05 mmol), and aq HCl in solvent (5.0 mL) at 0 °C, and then the reaction system was warmed to room temperature and stirred for 3 h.

^b Yield of isolated **2a**.

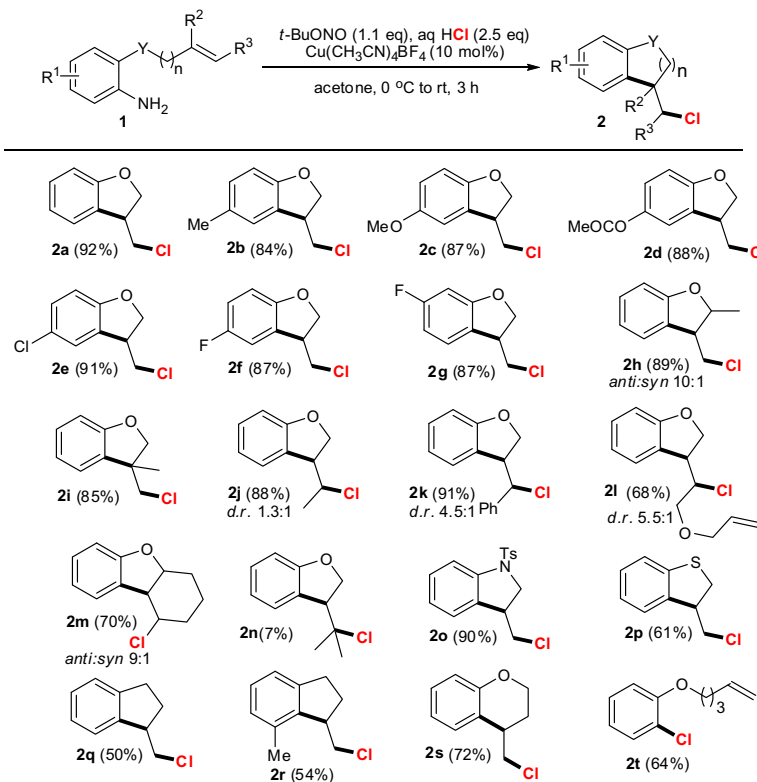
^c N.P.: no product, while **1a** was all consumed to the corresponding diazonium salt.

radical cyclization protocol employing widely available aqueous HCl or HBr as the halogen sources and bench-stable aryl amines as starting materials (Fig. 1d). This methodology featured with easy-handle protocol and cheap halogen sources. Key results for the reaction optimization are summarized in Table 1.

At the outset, we carried out the reaction without any metal catalyst, and no desired product was formed (entry 1, Table 1). We then tried the reaction in the standard Meerwein arylation condition with CuCl₂ as the catalyst. Disappointingly, no expected cyclization product was formed (entry 2, Table 1). However, we were delighted to find that CuCl was capable of catalyzing the reaction to give the desired product, albeit in a low yield of 24% (entry 3, Table 1). Several other copper(I) salts or iron salts were further tested, but showed negative catalytic reactivity in this reaction (entries 4–7, Table 1). It is worth noting that *n*-Bu₄NI which performed well as a SET reagent^{7,8} was not a suitable initiator for carbochlorination, affording the carboiodination product only (entry 8, Table 1). The reaction did not proceed in CH₂Cl₂ or CH₃OH (entry 9 and 10, Table 1), probably due to the poor solubility of diazonium salt intermediates in these solvents. Moderate yield was obtained in DMSO (entry 11, Table 1). To our delight, the yield of **2a** was improved dramatically when switching to acetone as the solvent (entry 12, Table 1). Increasing the amount of aq HCl to 2.5 equiv resulted in an obviously higher yield (86%, entry 13, Table 1), while a further increase (3.0 equiv) gave a slightly lower yield of 74% (entry 14, Table 1). Delightedly, Cu(CH₃CN)₄BF₄ was proved to be the superior catalyst with 92% yield (entry 15, Table 1).

Having established the optimal condition (entry 15, Table 1), we evaluated the scope and limitations of this carbochlorination. A variety of aryl amines have been explored as the starting materials for this transformation, and the results are listed in Scheme 1.

The reaction scope with the substituted 2-allyloxyaniline (**1**) was first investigated. A variety of substituents/functional groups on the aromatic moiety, ranging from the electron-donating groups (**2b–2d**, Scheme 1) to electron-withdrawing groups (**2e–2g**, Scheme 1), remained intact during the reaction and generally the expected cyclic carbochlorination products were obtained in good to excellent yields. Notably, the substrate with the methoxyl group, which was not synthetically efficient in the reported radical



Scheme 1. Radical carbochlorination.

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