

Zwitterionic-Salt-Catalyzed Site-Selective Monobromination of Arenes

Xiaodong Xiong,[†][©] Fei Tan,[†] and Ying-Yeung Yeung^{*}[©]

Department of Chemistry, The Chinese University of Hong Kong, Shatin, NT, Hong Kong (China)

(5) Supporting Information

ABSTRACT: A zwitterionic-salt-catalyzed electrophilic monobromination of arenes with high regioselectivity has been developed. Under mild reaction conditions, a wide range of monobrominated aromatic compounds can be obtained in excellent yields. The reaction can be operated using an extremely low catalyst loading (0.05 mol %) with the inexpensive brominating agent *N*-bromosuccinimide. The



versatility of this catalytic protocol has been demonstrated by the scale-up reaction with a 0.01 mol % catalyst loading to provide the selectively halogenated compound in quantitative yield.

A ryl halides are very important building blocks and have been widely employed in the production of pharmaceuticals, agrochemicals, dyes, and functional materials.¹ The development of efficient methods for the preparation of aryl halides has received continuous attention from synthetic chemists. Among the existing methods, a common approach to prepare aryl halides is the direct C–H halogenation of aryl compounds using molecular halogen sources because of the low cost. This approach can be executed by the direct addition of molecular halogens or through the oxidation of halides to generate molecular halogens in situ.⁴ However, molecular halogens are not easy to handle, and typically the reactions suffer from poor regioselectivity, uncontrollable multiple halogenations, harsh reaction conditions, and a tedious workup process.²

N-Haloamide reagents (e.g., *N*-bromosuccinimide, NBS), which are safer alternatives to molecular halogen sources, have frequently been employed in electrophilic halogenations.³ Since the electrophilicity of *N*-haloamide reagents is typically weak, significant efforts have been devoted to the development of catalysts such as metal Lewis acid and Brønsted acid catalysts to activate the weakly electrophilic halogens in *N*-haloamide reagents.^{5,7} More recently, Lewis basic organocatalysts have emerged as a new class of catalytic systems in the electrophilic halogenation of aryl compounds that provide a greener alternative to the metal catalyst systems.⁶ While remarkable progress has been achieved in this research area, a relatively high catalyst loading is generally required in most cases.²

Zwitterions are an emerging class of organocatalysts that have been utilized in catalyzing some organic transformations.⁸ One of the interesting systems involved the use of sulfur-based zwitterionic organocatalysts, as reported by Ishihara.^{8g} As a part of our continuing efforts toward organocatalytic halogenation reactions,⁹ we described an efficient synthesis of medium-ring lactones through sulfur-based zwitterionic organocatalytic halocyclization using **1a** as the catalyst (Scheme 1, eq 1).^{8f} Herein, we are pleased to disclose our recent success in

Scheme 1. Zwitterionic-Salt-Catalyzed Electrophilic Brominations



applying the sulfur-based zwitterionic organocatalyst 1a in the site-selective monobromination of arenes. The inexpensive halogen source NBS was employed, and the reaction could be operated with an extremely low catalyst loading (Scheme 1, eq 2).

At the outset of our investigation, bromination of anisole (2a) with NBS was studied using various zwitterionic catalysts 1 at 25 °C (Table 1). To our delight, *para*-bromination of 2a proceeded smoothly with the application of just a 0.05 mol % loading of zwitterion 1a as the catalyst, giving the desired product 3a in appreciable conversion (entry 2). More importantly, compound 3a was found to be the only product in the reaction, and no overbromination was observed. A similar result was observed when 4-pyrrolidinopyridine-derived zwitterion 1b was used as the catalyst (entry 3). Zwitterionic organocatalysts that have different geometry (1c) and electronic demands (1d-h) were examined, revealing the

Received: June 21, 2017



Table 1. Optimization of the Reaction Conditions^a

^{*a*}Reactions were carried out with **2a** (0.5 mmol), catalyst **1** (0.00025 mmol), and NBS (0.525 mmol) in dichloromethane (1 mL) for 12 h at 25 °C in the absence of light. ^{*b*}Conversions were measured by ¹H NMR analysis, and the yields were determined by using mesitylene as an internal standard. ^{*c*}For all reactions, only the *para*-brominated product **3a** was observed. ^{*d*}The reaction was performed at 0 °C. ^{*c*}Yield with a reaction time of 36 h.

superior performance of catalyst **1a** (entries 4–9). Similar efficiency was observed when the reaction was conducted at a lower temperature (entry 10). Complete conversion was achieved when the reaction time was prolonged (entry 11). However, employing other halogen sources such as *N*-fluorobenzenesulfonimide, *N*-chlorosuccinimide, and *N*-iodo-succinimide gave sluggish reactions.

After the optimized conditions were established, a variety of substrates were examined, and the results are shown in Scheme 2. Gratifyingly, the halogenation of arenes containing electrondonating substituents such as alkoxy (2a, 2b) and benzyloxy (2c) proceeded smoothly to give the corresponding *para*brominated products 3a-c in excellent yields. In addition, 1,2and 1,3-disubstituted and 1,3,5-trisubstituted substrates 2d-jalso gave the corresponding products 3d-j with monobromination at the *para* position with respect to the alkoxy substituent.

Particularly, bromination of the sterically hindered isopropyl substrate 2i could still give 3i in excellent yield. For the 1,4disubstituted substrate 2k, the monobromination took place at the *ortho* position with respect to the methoxy group exclusively to give product 3k. Naphthyl substrates 2l-n were found to work equally well, giving 3l-n in excellent yields. Other than the oxygen-substituted substrates, anilines were also found to be compatible with this catalytic protocol. Acetyl, benzyl, pivaloyl, and Boc anilines 2o-r readily underwent the catalytic monobromination to furnish 3o-r. Similar to the alkoxyarenes, the disubstituted phenyl system 2s could be monobrominated with excellent site selectivity. Morpholine-

Scheme 2. Scope of Zwitterion 1a-Catalyzed Bromination^a



^{*a*}Reactions were carried out with substrate 2 (0.5 mmol), catalyst 1a (0.00025 mmol), and NBS (0.525 mmol) in CH₂Cl₂ (1 mL) at 25 °C for 36 h in the absence of light. Isolated yields are shown. ^{*b*}The reaction was conducted at 0 °C. ^{*c*}CH₂Cl₂ (5 mL) was used as the solvent. ^{*d*}The reaction was conducted at -40 °C for 72 h.

and quinoline-containing **2t** and **2u** were well-tolerated under the reaction conditions to yield the brominated compounds **3t** and **3u**, respectively. Halogenated anthracenes are useful building blocks for organoelectronic materials, but halogenation of anthracene often suffers from uncontrollable multiple halogenation with poor site selectivity.¹⁰ Nonetheless, with the zwitterionic catalytic system (under careful control of the reaction temperature), monobrominated anthracene **3v** could be obtained smoothly. Toluene, xylene, and mesitylene were tested, but unfortunately, the reactions were sluggish.

It is notable that the present bromination could be easily scaled up and the catalyst loading could be further reduced: the bromination of **2a** and **2q** on a 25 mmol scale was complete in 36 h with only 0.01 mol % zwitterion **1a**. This advantage makes the present method more attractive for large-scale production in organic synthesis (Scheme 3).



Further experimentation indicated that achieving controllable monobromination is not trivial. For instance, the use of conventional Brønsted acid, Lewis acid, or Lewis base catalysts together with NBS exhibited moderate site selectivity in the bromination of 2a and gave a mixture of brominated products 3a and 3a' (Table 2, entries 2–4). When 2a was treated with

Table 2. Bromination of 2a with Different Catalysts^a

OMe 2a	catalyst (0.05 mol %) <u>NBS (1.05 equiv)</u> CH ₂ Cl ₂ , 25 °C, 36 h	Br 3a	+ OMe Br 3a'
entry	catalyst	Br source	2a:3a:3a' ratio ^b
1	none	NBS	97:3:0
2	conc. HCl	NBS	4:86:10
3	FeCl ₃	NBS	7:86:7
4	Ph ₃ PS	NBS	9:88:3
5	none	Br ₂	0:79:21
6	1a	NBS	0:100:0

^{*a*}Reactions were carried out with substrate **2a** (0.5 mmol), catalyst (0.05 mol %), and Br source (0.525 mmol) in CH_2Cl_2 (1 mL) at 25 °C for 36 h in the absence of light. ^{*b*}The ratios were determined by GC–MS analysis.

molecular bromine in the absence of catalyst, a significant amount of 3a' was observed (Table 2, entry 5). In sharp contrast, in the presence of zwitterionic catalyst 1a, clean conversion of 2a was observed, and the monobrominated product 3a was obtained exclusively (Table 2, entry 6).

While careful control of the stoichiometry of the halogen source is usually necessary to avoid multiple halogenation of arenes, this zwitterion catalytic protocol appears to be very selective in performing monobromination even in the presence of an excess amount of halogenation source. For example, the zwitterion 1a-catalyzed bromination of 2a with 10 equiv of NBS still gave 3a exclusively, while a mixture of mono- and dibrominated products 3a and 4a were obtained with other catalytic systems (Table 3, entries 1-3). A significant amount

Table 3. Bromination of 2a with an Excess Amount of the Halogen Source^a

н∕	OMe 2a	catalyst (1 mol %) <u>NBS (10 equiv)</u> <u>CH₂Cl₂ 25 °C, 32 h</u>	Br 3a	Br OMe + Br Br	Br OMe Br 5a	
	entry	catalyst	Br source	3a:4a	: 5a ratio ^b	
	1	1a	NBS	10	0:0:0	
	2	Ph ₃ PS	NBS	83	3:17:0	
	3	FeCl ₃	NBS	93	3:7:0	
	4	_	Br ₂	0:	0:24:76	

^{*a*}Reactions were carried out with anisole (2a) (0.5 mmol), catalyst (1 mol %), and the Br source (5.0 mmol) in dichloromethane (1 mL) at 25 °C for 32 h in the absence of light. ^{*b*}The ratios were determined by GC–MS analysis.

of tribrominated product **5a** was also obtained if an excess amount of molecular bromine was applied (entry 4). These results further demonstrated the superior performance of zwitterion **1a** in controlling the monobromination.

Since zwitterion 1a is known to exist in equilibrium with its constitutional components N,N-dimethylaminopyridine (DMAP) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (6) in solution,^{8f} a series of control experiments were conducted to elucidate the active catalytic species (Table 4). The bromination of 2a was sluggish when no catalyst was applied (entry 1). When the individual component DMAP or isothiocyanate 6 was employed as the sole catalyst, only trace amounts of product 3a were detected after 12 h (entries 2 and 3). These results indicated that although zwitterion 1a can

Table 4. Control Experiments^a



"Reactions were carried out with anisole (2a) (0.5 mmol), catalyst (0.05 mol %), and NBS (0.525 mmol) in dichloromethane (1 mL) at 25 °C for 12 h in the absence of light. ^bDetermined by ¹H NMR analysis with mesitylene as the internal standard. ^cAn equimolar mixture of DMAP and 6 was used.

dissociate into DMAP and **6**, the active catalytic species 1a still plays the main role in promoting the reaction (entry 4). Moreover, similar catalytic performance was achieved through in situ generation of 1a by addition of a 1:1 mixture of DMAP and **6** to the reaction mixture (entry 5).

On the basis of the experimental results and our previous studies,^{8f} at this stage we believe that zwitterion 1a can react with NBS to form S–Br complex A or N–Br complex A' with the succinimide anion charged pair with the iminium cation (Scheme 4). We speculate that the π electrons of arene 2 might





react with the electrophilic Br in complex **A** to give intermediate **B**. Because of its close proximity, the basic succinimide anion could then readily deprotonate the acidic proton in the arene to give the desired monobrominated product **3** together with the regeneration of zwitterion **1a**. A more detailed study is on the way in order to elucidate a clearer mechanistic picture.

In summary, we have developed an efficient and practical catalytic protocol for the bromination of arenes using zwitterionic organocatalyst **1a**. The advantages of low catalyst loading, excellent regioselectivity, mild reaction conditions, and clean transformation make this catalytic protocol potentially useful in industry. Efforts to apply these zwitterionic catalysts to other reactions are underway.

Organic Letters

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b01899.

Experimental procedures and characterization data for all new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: yyyeung@cuhk.edu.hk.

ORCID 0

Xiaodong Xiong: 0000-0002-6357-7398 Ying-Yeung Yeung: 0000-0001-9881-5758 Author Contributions

[†]X.X. and F.T. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are thankful for the financial support from the Research Grant Council of the Hong Kong Special Administration Region (Project CUHK14315716), The Chinese University of Hong Kong Direct Grant (Project 4441628), and the Research Fellow Scheme (Project 4200486).

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