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Mechanistic study on iodine-catalyzed aromatic bromination of aryl ethers by *N*-Bromosuccinimide

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ABSTRACT

Although iodine-catalyzed reaction has rapid advances in recent years, examples on iodine-catalyzed bromination are rare and the mechanism of these reactions remains unclear. Herein, we reported an I_2-catalyzed aromatic bromination of aryl ethers by NBS and presented the details of the mechanistic study including kinetic study and the study of kinetic isotope effects. The study revealed that the reaction was actually catalyzed by IBr formed in the induction period, and the rate-determining step was the HBr-elimination of the Wheland intermediate assisted by IBr.

1. Introduction

N-Bromosuccinimide (NBS) is a highly useful reagent in organic synthesis. It can be used for organic transformations including radical[1] or electrophilic substitutions,[2] electrophilic additions,[3] oxidations,[4] and Hofmann rearrangement.[5] Due to the character of the succinimidyl N–Br bond, NBS is stable under mild conditions and can be activated by various catalysts or in proper reaction media according to the substrate type and the reaction type. Taking the substitution reaction for the example, NBS has been widely applied to the bromination of a wide range of aliphatic and aromatic hydrocarbons. For aromatic substrates, the electrophilic aromatic substitution by NBS can not only be catalyzed by Lewis acids,[6] Brönsted acids,[7] or Lewis bases,[8] but also affected by the reaction media[9] substantially (Fig. 1). Besides these methods, NBS can also be activated by photo-irradiation[10] or free radicals from the dissociation of radical initiators such as AIBN[11] and benzoyl peroxide[12] to generate bromine[13] or succinimidyl radicals[1b,14] as chain carriers for radical substitutions (Scheme 1A). However, if the free radical (e.g. an iodine radical) underwent Br-abstraction from NBS to produce an electrophilic reagent rather than the radical carriers, an electrophilic substitution on the aromatic ring might be initiated (Scheme 1B).

Iodine-catalyzed reaction has rapid advances in the recent years.[15] These reactions mainly utilized the redox property of iodine to mimic transition metals for C-C or C-heteroatom coupling via peroxide decomposition,[16] hypervalent iodine generation,[17] or heteroatom-iodine bond formation.[18] However, examples on iodine-catalyzed brominations are rare, though the first iodine-catalyzed bromination of aromatic compounds by Br_2 was reported one century ago.[19] In the 1950s, Tsuruta revisited this reaction by kinetic study and provoked that IBr was the key species promoting the rate-determining HBr-elimination from a 1:1 aromatic-bromine complex.[20] In 2000, Masnovi found that molecular iodine accelerated the aromatic bromination of 9-methylanthracene by NBS remarkably and attributed this effect to increasing the concentration of Br_2.[21] In 2006, Stavber reported I_2-catalyzed α-bromination of acetophenone by NBS, but did not give any explanation for the iodine effect.[22] Besides the above reports, molecular iodine was also found to catalyze hydroxybromination of activated alkenes and nucleophilic substitution of carboxylic acid derivatives, in which the authors considered iodine as a Lewis acid catalyst.[23] Interestingly, Chaikovskii's report on the reaction of NBS with I_2 for the synthesis of *N*-iodosuccinimide (NIS)[24] demonstrated the ability of the iodine radical for Br-abstraction from NBS.[25] Moreover, Stucky's discovery on iodine-catalyzed bromination of methane and oxidative dehydrogenation of propane by CH_2Br_2[26] further evidenced the high propensity of the iodine

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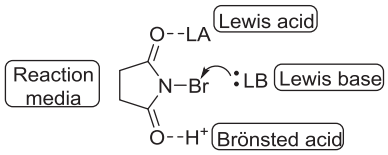
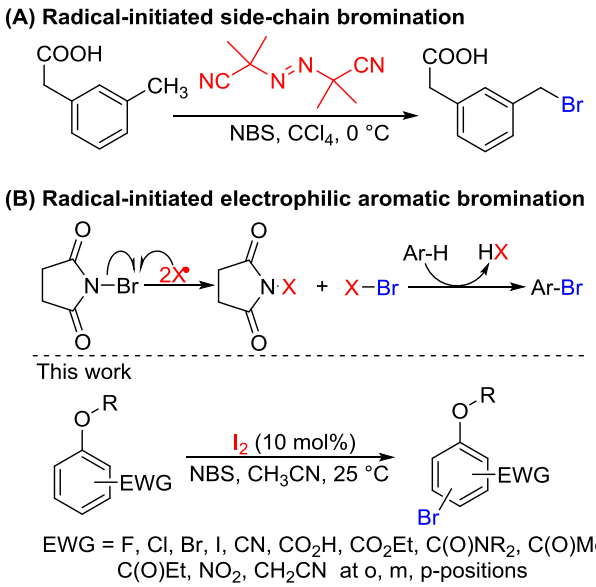


Fig. 1. NBS activation in electrophilic substitution.



Scheme 1. NBS activation by free radicals.

radical towards the bromine atom to generate IBr.

The mechanistic study on iodine-catalyzed bromination reactions would not only help us understand the interplay between iodine and bromine, but also give us implications for reaction design with iodine as the catalyst. In connection with our interest in reaction design and mechanistic study on iodine-catalyzed organic reactions, we herein reported a molecular iodine-catalyzed aromatic bromination of aryl ethers with NBS and presented the details of our mechanistic study on this reaction. The reaction exhibited high regioselectivity, broad substrate scope and good functional tolerance. The results of catalyst and solvent screening, kinetic study, kinetic isotope effects and others revealed that the I_2-catalyzed bromination reaction initially underwent a radical chain reaction to generate IBr and followed an IBr-catalyzed reaction to deliver the bromination products. Furthermore, the rate-determining step was identified as the HBr-elimination of the Wheland intermediated promoted by IBr according to the reaction order and kinetic isotope effects.

2. Results and discussion

2.1. Conditions screening and substrate scope

Choosing the aromatic bromination of *para*-chloroanisole **1a** by NBS as the model reaction, we at first conducted catalyst screening. As the reaction without any catalyst in CH_3CN at 25 °C did not give any product (entry 1, Table 1), several iodine reagents were then screened as the catalyst. In the presence of 10 mol% of I_2, the reaction after 12 h gave the *ortho*-brominated product **2a** in 95% yield (entry 2, Table 1). IBr exhibited as high activity as I_2 (entry 7, Table 1) and 2-iodoaniline showed lower activity (entry 6, Table 1), while TBAI and NIS had very poor activity (entries 3–5, Table 1). In order to further understand the behavior of the iodine catalyst in the reaction, the activity of some common catalysts for electrophilic bromination by NBS was examined for comparison under albeit the same conditions. To our surprise, the reaction catalyzed by both TsOH and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) only delivered a trace of **2a**, while the *i*Pr_2EtN-catalyzed reaction gave **2a** in only 11% yield after 12 h (entries 8–10, Table 1). Lewis acids such as $FeCl_3$, $AlCl_3$, and $BF_3{\cdot}OEt_2$ all catalyzed the reaction very smoothly (entries 12–14, Table 1), but these reactions were slightly slower than that catalyzed by the same amount of I_2 (entry 11, Table 1). The result above ruled out the possibility of the reaction as a Brönsted acid, Lewis acid, or Lewis base catalysis.

Next, diverse organic solvents were screened for the iodine-catalyzed reaction. The experimental data showed that the sequence of the yield after the same reaction time was as follow (entries 15–20, Table 1): CH_2Cl_2 > $CHCl_3$ > THF > DCE > MeOH > DMF. This solvent effect on the reaction rate suggested that the reaction pathway was neither a radical nor an ionic one, but probably a mixed one.

Then, other reaction factors were investigated. When the reaction temperature was increased to 35 °C, the reaction was faster and the desired product was isolated by flash chromatography in 95% yield in 6 h (entry 21, Table 1). However, the yield decreased considerably to 76% and 10% when the catalyst loading of I_2 was reduced to 4.5 mol% and 1 mol% (entries 22 and 23, Table 1). Futhermore, the reaction in the presence of 20 mol% of TEMPO only gave a trace of the product **2a** (entry 24, Table 1). And the reaction in a NMR tube without stirring was found to be much slower than that in a reaction flask with a magnetic stirring bar (entries 25 and 21, Table 1). The result once again indicated that the iodine-catalyzed reaction might include free radical steps.

After conditions screening on the reaction of *para*-chloroanisole **1a** with NBS, we continued to examine the substrate scope of the novel method under the standard conditions as follow: substrate (0.2 mmol), I_2 (10 mol%, 0.02 mmol), NBS (0.3 mmol), and CH_3CN (1 mL), 35 °C, 12 h. Firstly, a series of aryl ethers with diverse functional groups at *para*-positions were tested (Table 2). Not only anisoles, but also benzyl and *n*-hexyl aryl ethers were suitable substrates for this method. Electron-withdrawing chloro (**2a**), bromo (**2b**), fluoro (**2c**), ester (**2j**) and amide (**2k**) groups were well tolerated and the reaction of substrates with these functional groups furnished *ortho*-monobromination products in very excellent yield. Furthermore, aryl ethers with acyl (**1d-1h**) and carboxyl (**1i**) groups underwent *ortho*-monobromination smoothly. The formyl-substituted anisole (**1d**) is a challenging substrate as the oxidation/decarboxylative bromination can take place in the presence of NBS. However, this side-reaction was suppressed by using 1.0 equiv of NBS and conducting the reaction under N_2 atmosphere. More importantly, the application of the iodine-catalysis to the aromatic ketone substrates (**1e-1h**) led to aromatic bromination with high selectivity, while the reaction of these substrates catalyzed by TsOH or $BF_3{\cdot}OEt_2$ furnished α-bromination products as the major.

Secondly, the standard conditions were further applied to aryl ethers with substituents at *ortho* or *meta*-positions (Table 3). Interestingly, the reaction of both *ortho*- and *meta*-substituted substrates delivered *para*-monobromination compounds as the single products. And functionalities such as nitro (**4a**), cyano (**4b**, **4c**, **4n**), acyl (**4d**, **4j**), cyanomethyl (**4i**), halide (**4f-4h**, **4l**, **4m**) and ester (**4e**, **4k**) were tolerated to the conditions very well. It is worth noting that in the reaction of **3b** and **3i**, no benzylic hydrogen was substituted by NBS, which indicated that C–Br bond formation happened in an ionic process.

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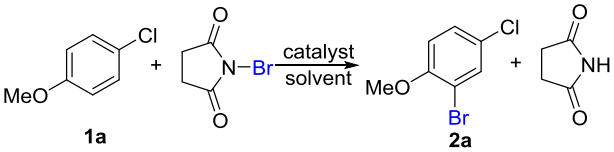
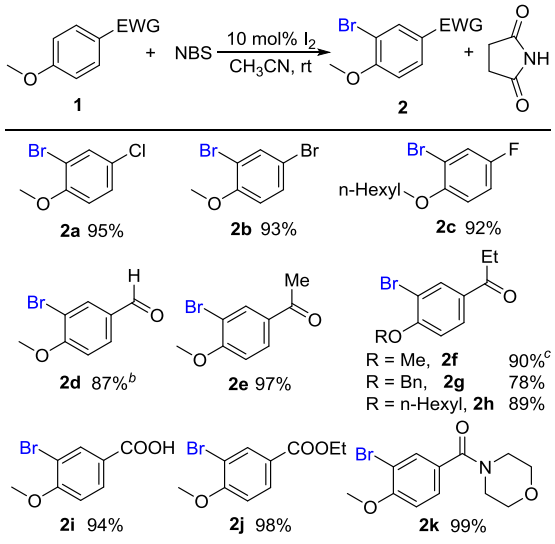
Table 1
Conditions screening on the bromination of *para*-chloroanisole **1a** with NBS.[a]



Entry	Catalyst (mol%)	NBS (equiv)	Solvent	Temperature (°C)	Time (h)	Yield[b]
1	–	1.5	CH_3CN	25	17	n.d.
2	I_2 (10)	1.5	CH_3CN	25	11	95%
3	TBAI (10)	1.5	CH_3CN	25	12	n.d.
4	NIS (10)	1.5	CH_3CN	25	12	trace
5	TBAI/NIS (10)	1.5	CH_3CN	25	12	trace
6	2-Iodoaniline (10)	1.5	CH_3CN	25	12	74%
7	IBr (10)	1.5	CH_3CN	25	11	100%
8	DMAP (10)	1.5	CH_3CN	25	12	n.d.
9	iPr_2EtN (10)	1.5	CH_3CN	25	12	11%
10	TsOH (10)	1.5	CH_3CN	25	12	1%
11	I_2 (10)	1.0	CH_3CN	25	6	94%
12	$FeCl_3$ (10)	1.0	CH_3CN	25	6	63%
13	$AlCl_3$ (10)	1.0	CH_3CN	25	6	90%
14	$BF_3{\cdot}OEt_2$ (10)	1.0	CH_3CN	25	6	82%
15	I_2 (10)	1.5	DMF	25	6	46%
16	I_2 (10)	1.5	CH_3OH	25	6	68%
17	I_2 (10)	1.5	THF	25	6	77%
18	I_2 (10)	1.5	DCE	25	6	71%
19	I_2 (10)	1.5	$CHCl_3$	25	6	84%
20	I_2 (10)	1.5	CH_2Cl_2	25	6	88%
21	I_2 (10)	1.5	CH_3CN	35	6	100% (95%)[c]
22	I_2 (4.5)	1.5	CH_3CN	35	6	76%
23	I_2 (1.0)	1.5	CH_3CN	35	6	10%
24[d]	I_2 (10)	1.5	CH_3CN	35	12	trace
25[e]	I_2 (10)	1.5	CH_3CN	35	7	72%

[a] Conditions: **1a** (0.2 mmol), NBS (0.2–0.3 mmol), catalyst (10 mol%), solvent (1 mL), 25–35 °C, stirring speed 740 rpm.
[b] GC yield with PhCl as the internal standard.
[c] Isolated yield.
[d] 20 mol% of TEMPO was added.
[e] The reaction was conducted in a NMR tube without stirring.

Table 2
Scope for *para*-substituted aryl ethers in *ortho*-bromination.[a]



[a]Conditions: **1** (0.2 mmol), NBS (0.3 mmol), and I_2 (10 mol%), CH_3CN (1 mL), 35 °C, 12 h. [b]1.0 equiv NBS, N_2.
[c] Reaction catalyzed by TsOH or $BF_3{\cdot}OEt_2$ afforded the α-bromination product.

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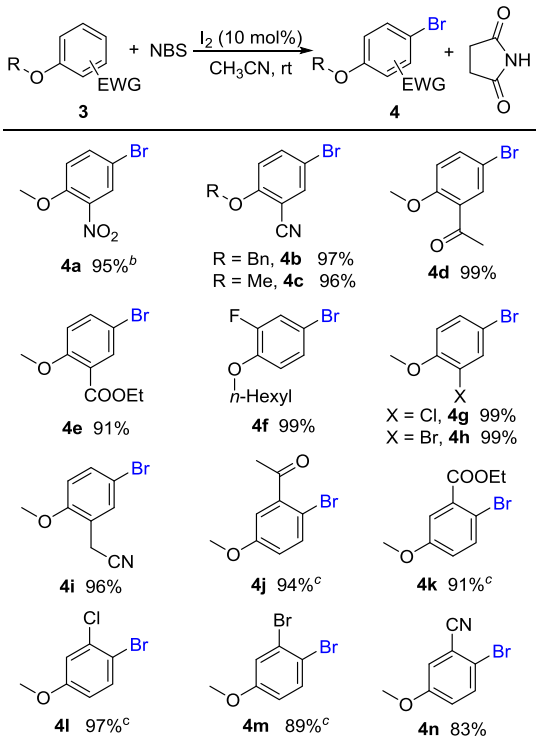
Table 3
Scope for *ortho* or *meta*-substituted aryl ethers in *para*-bromination.[a]



[a]Conditions: **3** (0.2 mmol), NBS (0.3 mmol), and I_2 (10 mol%), CH_3CN (1 mL), 35 °C, 12 h. [b]50 °C, 48 h. [c] 1.0 equiv NBS.

2.2. Mechanistic study

2.2.1. Kinetic profiles of the bromination reaction of *1a*

To further gain mechanistic insights to the iodine catalysis, we performed the study on reaction kinetics using the bromination reaction of *para*-chloroanisole **1a** with NBS as the model reaction. At first, the reaction of **1a** with 1.0 equiv of NBS in CH_3CN at 35 °C was conducted in the presence of 10 mol% of I_2. The kinetic profile of the product **2a** in the reaction was obtained by gas chromatographic analysis of the reaction mixture using PhCl as the internal standard (Fig. 2A). Surprisingly, a significant induction period (ca. 5 min) was detected in the I_2-catalyzed reaction. However, pretreatment of I_2 with NBS for 10 min before addition of **1a** led to the disappearance of the induction period (Fig. 2B). The result above indicated the actual catalyst in the reaction was not molecular iodine, but some species (probably IBr or Br_2) *in-situ* formed from in the induction period.

In order to uncover the real catalytic species, the reaction of **1a** with NBS in the presence of 10 mol% of IBr or Br_2 was next performed. It was found that the reaction catalyzed IBr showed a similar kinetic profile of **2a**, while Br_2 exhibited very poor activity as the catalyst (Fig. 2C). Further analysis of the kinetic data showed that a linear relation between the logarithm of 1/[**1a**] and the reaction time with a linearity of more than 0.99 was observed in both of the two reactions using I_2 and IBr (Fig. 2D).

Then, the reaction between I_2 and NBS was investigated by ^{13}C NMR and mass spectroscopic analysis. The NMR data showed that mixing I_2 and NBS in CD_3CN at room temperature for 1 h furnished NIS in about 90% yield, and mass spectroscopic data of the same sample proved that IBr was indeed formed as the by-product. According to the results above, we proposed that I_2 reacted with NBS slowly in the induction period to generate IBr, which acted as the actual catalyst after the induction period.

2.2.2. Determination of kinetic orders of *1a*, NBS and IBr

In order to gain more details about the mechanism of the iodine-catalyzed reaction, we continued to investigate the kinetic dependence of the reaction rate on each reagent. As the iodine-catalyzed reaction had an induction period, and IBr was considered as the actual catalyst of this reaction after the induction period, we chose the bromination reaction catalyzed by IBr as the model reaction for this study. The study used the initial-rate method to identify the initial reaction rate (V_0) of the reaction under different concentrations of **1a**, NBS and IBr (see the supporting information for details).

First, five reactions with different $[\mathbf{1a}]_0$ (0.1–0.3 mol/L) were conducted and the plot of $\log(1/V_0)$ *versus* $\log(1/[\mathbf{1a}]_0)$ was drawn based on the calculated initial rate (Fig. S5 and Table S2). Linear fitting of this plot resulted in a line with a linearity of 0.99 and a slope of 0.93, which indicated that the reaction rate had a 1st order dependence on [**1a**] (Fig. 3A). Second, similar reactions were also carried out with different initial concentrations of NBS (0.1–0.3 mol/L) (Fig. S6 and Table S3). Surprisingly, the reaction rate was non-dependent on [NBS] (Fig. 3B). This result proved that NBS was not involved in the rate-determining step. Third, the reactions with $[IBr]_0$ varying from 0.002 mol/L to 0.008 mol/L were performed (Fig. S7 and Table S4) and a 2nd dependence on [IBr] was identified (Fig. 3C). The 2nd order dependence might be interpreted that IBr not only played a role as an electrophile in the electrophilic addition step, but also acted as a promotor in the HX-elimination step, which was probably the rate-determining step.

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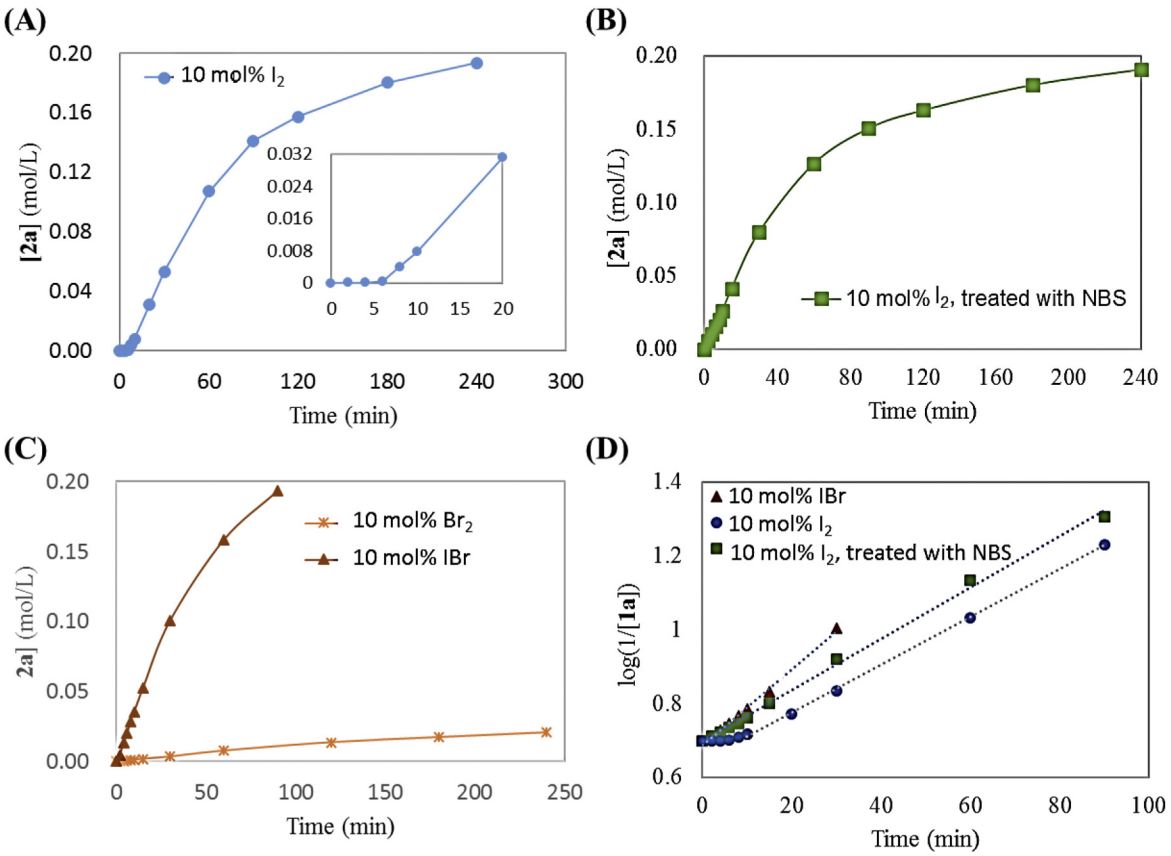

Fig. 2. Kinetic profiles of the bromination reaction of **1a** with NBS in the presence of I_2 (**A**), I_2 treated by NBS (**B**), Br_2 and IBr (**C**). Plots of the logarithm of 1/[**1a**] *versus* the reaction time (**D**). Conditions: [**1a**] = 0.2 mol/L, [NBS] = 0.2 mol/L, [I_2], [Br_2] or [IBr] = 0.02 mol/L, [PhCl] = 0.5 mol/L, V(CH_3CN) = 1.0 mL, 35 °C, stirred at 740 rpm.

Finally, the rate law of the IBr-catalyzed reaction was determined as shown in Fig. 4. And the observed rate constant was calculated as 29.707 S^{-1} mol^{-2} L^2 through linear fitting for the plot of V_0 versus [**1a**][IBr]^2.

2.2.3. Kinetic isotope effects

The bromination reaction catalyzed by IBr has two main steps: electrophilic addition of IBr to **1a**, and the elimination of the formed Wheland complex to deliver **2a** and other by-products. As C–H bond cleavage took place in the latter step, the study of kinetic isotope effects could provide direct information of the rate-determining steps of both I_2 and IBr-catalyzed reactions.

First, the intramolecular KIE experiment was conducted by doing the bromination reaction of the mono-deuterated substrate **1a**-D with NBS in the presence of 10 mol% of I_2 or IBr. ^{1}H NMR analysis of the reaction mixtures showed that the intramolecular KIE value was 1.44 for both I_2 and IBr catalyzed reactions (Fig. S10 and Scheme 2A). Second, the one-pot competition reaction of **1a** and bi-deuterated substrate **1a**-2D (1:1 ratio) with NBS in the presence of 10 mol% I_2 or IBr gave larger KIE values (1.86 for both I_2 and IBr catalysis) by ^{1}H NMR analysis of the reaction mixtures at about 10% conversion (Fig. S11 and Scheme 2B). Third, the parallel reactions of **1a** and bi-deuterated substrate **1a**-2D under the same conditions were performed using 4.5 mol% of I_2 or 3 mol% of IBr (Fig. S12). The intermolecular KIE values were derived as 1.43 and 1.68 respectively (Table S5 and Scheme 2C). Similar KIE values between I_2 and IBr catalyzed reactions supported that IBr might be actual catalyst in the I_2-catalyzed reaction. And the KIE values by different methods were obviously greater than those in the cases of typical secondary KIE, suggesting that a primary isotope effect existed in both I_2-catalyzed and IBr-catalyzed reactions. Therefore, the C–H bond cleavage (the HX-elimination step) was considered as the rate-determining step.

2.2.4. Plausible mechanism

According to the results of conditions screening, kinetic study, kinetic isotope effects and others, a plausible mechanism for the molecular iodine-catalyzed aromatic bromination was proposed (Scheme 3). The reaction began with the generation of IBr from I_2 and NBS. This transformation from I_2 and NBS to IBr took place in the induction period and was considered as a radical chain reaction (Scheme 3a, eqs 1–4) according to Chaikovskii's discovery that this reaction was much faster in CCl_4 than DCE.[24] It was further supported by our study of solvent effect that the I_2-catalyzed reaction was faster in DCE and CH_2Cl_2 than in CH_3OH and DMF (Table 1). Furthermore, a longer induction period detected in the reaction at room temperature (ca. 30 min) than at 35 °C (ca. 5 min) was in accord with the hypothesis.

After the induction period, the bromination reaction was supposed to be actually catalyzed by IBr according to the similar kinetic behavior between I_2 and IBr-catalyzed bromination reactions. Early work by Militzer[25] demonstrated that IBr was a competent electrophile for aromatic bromination, and this work showed that the bromination by IBr delivered I_2 and HBr rather than HI as the by-products, suggesting that IBr might play a key role in the elimination step. The same effect of IBr in the elimination step was also observed in the I_2-catalyzed aromatic bromination of arenes with Br_2.[20] According to the precedent work and the result of our kinetic study, a catalytic cycle (Fig. S9 and Scheme 3b, eqs 5–8) with a rate-determining HBr-elimination assisted by IBr (eq 6) was proposed.

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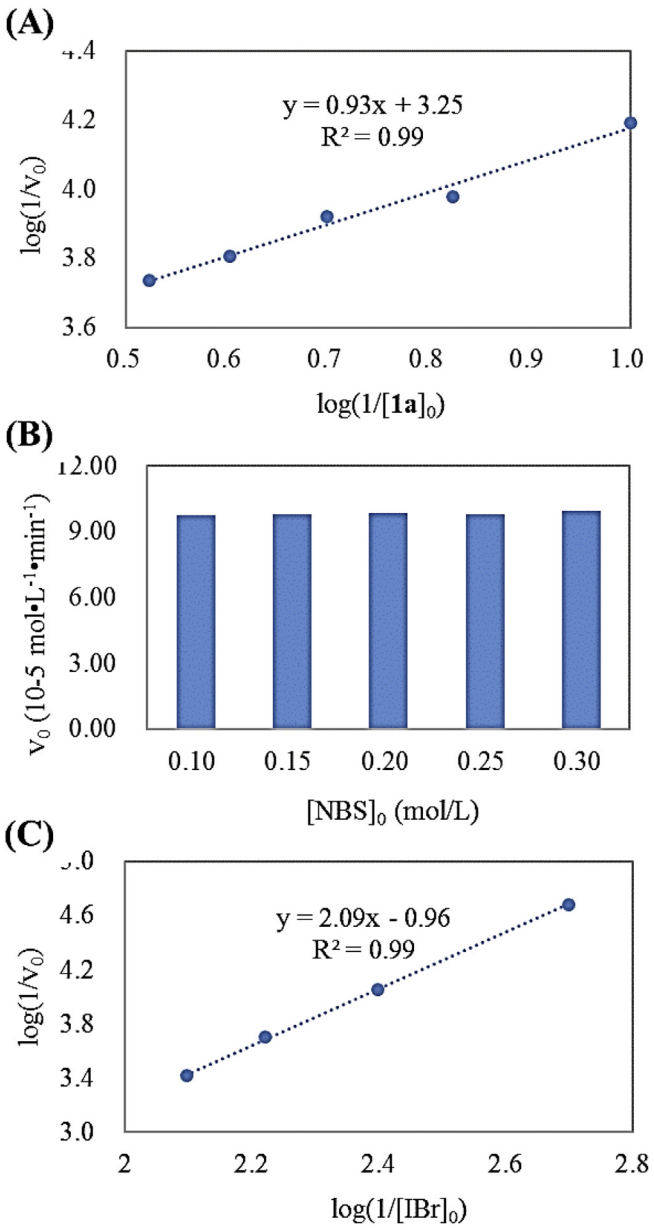
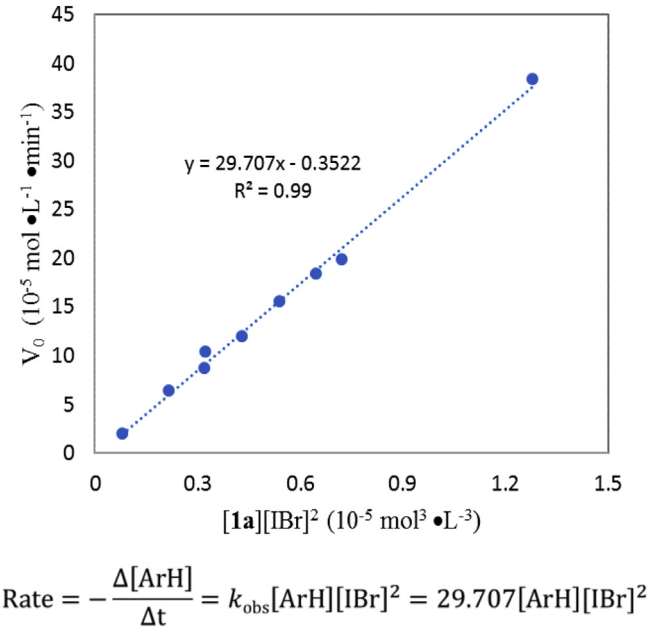


Fig. 3. Determination of kinetic orders in **1a**, NBS, and IBr. V_0 was the reaction rate determined by the initial-rate method. Conditions for (A): $[\mathbf{1a}]_0$ = 0.10–0.30 mol/L, $[NBS]_0$ = 0.20 mol/L, $[IBr]_0$ = 0.00464 mol/L, [PhCl] = 0.5 mol/L; for (B): $[\mathbf{1a}]_0$ = 0.20 mol/L, $[NBS]_0$ = 0.10–0.30 mol/L, $[IBr]_0$ = 0.00421 mol/L, [PhCl] = 0.5 mol/L; for (C): $[\mathbf{1a}]_0$ = 0.2 mol/L, $[NBS]_0$ = 0.2 mol/L, $[IBr]_0$ = 0.002–0.008 mol/L, [PhCl] = 0.5 mol/L; V(CH_3CN) = 1.0 mL, 35 °C, stirred at 740 rpm.

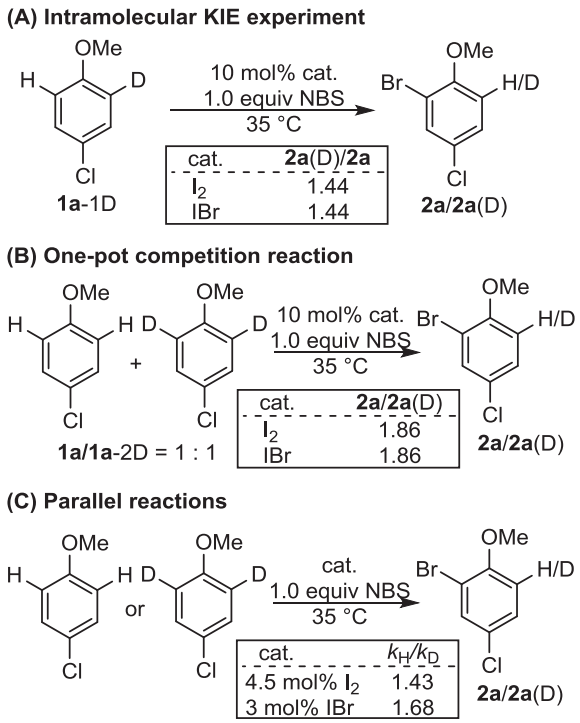
Electrophilic addition of IBr to the aromatic ring (eq 5) delivered a Wheland complex, which underwent HBr-elimination assisted by IBr to give the brominated product, HBr and I_2 (eq 6).

Then the regeneration of IBr from HBr, I_2, NBS and other compounds seemed very complicated. Among all possible transformations, the nucleophilic substitution of NBS by HBr to furnish Br_2 (eq 7)[27] was considered as the most facile one. And the formed Br_2 could react with I_2 rapidly to regenerate IBr for the next catalytic cycle (eq 8) as no induction period was detected when a mixture of 5 mol% I_2 and 5 mol% Br_2 was used as the catalyst in the bromination of **1a** (Fig. S3). However, the reaction between HBr and the initially formed NIS provided an alternative way to generate IBr (eq 9).[28] But this pathway led to the decrease in the concentration



$$\text{Rate} = -\frac{\Delta[\text{ArH}]}{\Delta t} = k_{obs}[\text{ArH}][\text{IBr}]^2 = 29.707[\text{ArH}][\text{IBr}]^2$$

Fig. 4. The rate law of the IBr-catalyzed aromatic bromination.



Scheme 2. Kinetic isotope effects in the bromination of **1a** in the presence of I_2 or IBr.

of IBr, which might account for the different reaction rates of two reactions catalyzed by the same amounts of I_2 and IBr (Fig. 2B and C). By comparing the initial rates of the reactions catalyzed by 10 mol% of I_2 and IBr, it was estimated that the I2-catalyzed reaction was actually catalyzed by 8.6 mol% of IBr.

3. Conclusion

In conclusion, we have developed an I_2-catalyzed aromatic

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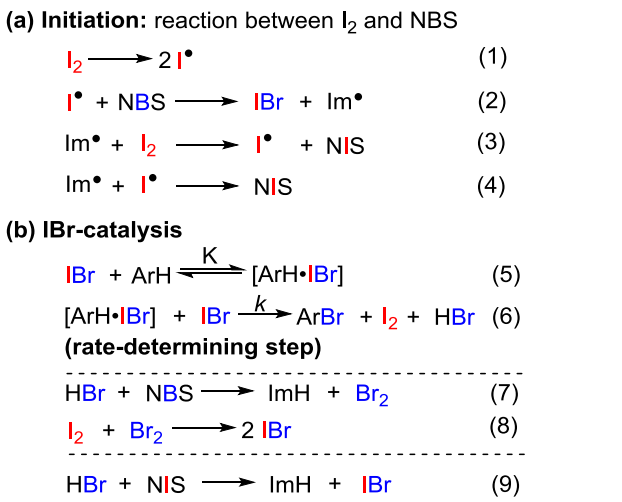

Scheme 3. Plausible mechanism for the I_2-catalyzed aromatic bromination.

bromination of aryl ethers by NBS. The method was applicable to a wide array of aryl ethers with diverse electron-withdrawing groups at *ortho*, *meta*, or *para*-positions and the reaction exhibited single regiosiomers in 78–99% yield. The result of catalyst and solvent screening, kinetic study, kinetic isotope effects and others helped us disclose the mechanism of this reaction. It began with a radical chain reaction to generate IBr, and went on with an IBr-catalyzed reaction to deliver the bromination product. The new catalytic cycle included elementary steps such as electrophilic addition of IBr to the aromatic compound, HBr-elimination of the formed Wheland intermediate promoted by IBr, nucleophilic substitution reaction between HBr and NBS to produce Br_2, and IBr formation from I_2 and Br_2. The application of this method in organic synthesis and the implications of mechanistic study for reaction design is underway.

4. Experimental section

4.1. General information and methods

4.1.1. Materials and instruments

Solvents, starting materials, catalysts (including iodine reagents, Lewis acids, protic acids, and amines) were purchased from Chemical companies and used without further purification. Chromatographic purification was conducted with technical grade solvents (petroleum ether, dichloromethane and ethyl acetate) and silica gel 40–63 μm. TLC was performed on silica gel 60 F_{254} TLC glass plates and visualized with UV light (254 nm). ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer in $CDCl_3$, DMSO-d_6, acetone-d_6 or CD_3CN. Chemical shifts were referenced relative to residual solvent signal ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR; DMSO-d_6: 2.50 ppm for ^{1}H NMR, 39.52 ppm for ^{13}C NMR; acetone-d_6: 2.05 ppm for ^{1}H NMR, 29.84 ppm for ^{13}C NMR; CD_3CN: 1.94 ppm for ^{1}H NMR, 1.32 ppm for ^{13}C NMR). Infrared spectra were recorded on a Brucker Alpha-FTIR, which could be used to obtain FTIR transmission spectra in the range of 500–4000 cm^{-1} and were reported as cm^{-1} (w = weak, m = medium, s = strong). HRMS were performed on a mass spectrometer (APCI-MS). Melting points were measured with micro melting point apparatus.

4.1.2. Methods for mechanistic study

For kinetic study, all the reactions were set with PhCl (0.5 mol/L) as the internal standard in 5-mL vials, which were placed inside the holes of a preheated aluminium block at 35 °C and stirred at the speed of 740 rpm. The reactions were monitored by gas chromatographic analysis to calculate the concentrations of the starting material (**1a**) and the product (**2a**). The initial reaction rate (V_0) was obtained by linear fitting for the plot of [**2a**] versus the reaction time when the conversion was less than 10%. The kinetic order of each reagent was derived by linear fitting for the plot of $\log(1/V_0)$ *versus* $\log(1/[S]_0)$ (S is **1a**, NBS or IBr).

4.2. General procedure for conditions screening

To a reaction tube charged with NBS (1.5 equiv, 0.3 mmol), catalyst (10 mol%, 0.02 mmol) and a solvent (1.0 mL), was added *para*-chloroanisole **1a** (0.2 mmol). After being stirred at room temperature for 6–12 h in dark, the reaction was quenched by saturated aqueous solution of $Na_2S_2O_3$ (2 mL). The resulting mixture was extracted by ethyl acetate (3 × 5 mL). The combined organic extracts were washed by brine (10 mL), dried over Na_2SO_4 and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was submitted to gas chromatographic analysis. The pure product was obtained by flash chromatographic purification on a silica gel column with petroleum ether/dichloromethane (5:1) as the eluent.

4.3. General procedure for the I_2-catalyzed aromatic bromination of aryl ethers with NBS

To a reaction tube charged with NBS (1.5 equiv, 0.3 mmol), catalyst (10 mol%, 0.02 mmol) and CH_3CN (1.0 mL), was added *para*-chloroanisole **1a** (0.2 mmol). After being stirred at room temperature for 12 h in dark, the reaction was quenched by saturated aq. solution of $Na_2S_2O_3$ (2 mL). The resulting mixture was extracted by ethyl acetate (3 × 5 mL). The combined organic extracts were washed by brine (10 mL), dried over Na_2SO_4 and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography on a silica gel column with petroleum ether/dichloromethane (5:1) as the eluent to give

4.3.1. 2-Bromo-4-chloroanisole (*2a*)

42.0 mg, 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 2.4 Hz, 1H), 7.24 (dd, J = 8.6, 2.3 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 3.88 (s, 3H). The NMR data is in good agreement with that reported in the literature.[29]

4.3.2. 2,4-Dibromoanisole (*2b*)

49.4 mg, 93% yield from the reaction of 4-bromoanisole with NBS. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.67 (d, J = 2.3 Hz, 1H), 7.38 (dd, J = 8.8, 2.3 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 3.88 (s, 3H). The NMR data is in good agreement with that reported in the literature.[30]

4.3.3. 2-Bromo-4-fluoro-1-(hexyloxy)benzene (*2c*)

50.6 mg, 92% yield. Liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, J = 7.8, 2.9 Hz, 1H), 6.96 (td, J = 8.4, 2.9 Hz, 1H), 6.82 (dd, J = 9.0, 4.8 Hz, 1H), 3.97 (t, J = 6.5 Hz, 2H), 1.90–1.75 (m, 2H), 1.53–1.45 (m, 2H), 1.39–1.30 (m, 4H), 0.91 (t, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (d, J = 242.5 Hz), 152.3 (d, J = 2.7 Hz), 120.5 (d, J = 25.7 Hz), 114.7 (d, J = 22.4 Hz), 113.8 (d, J = 8.4 Hz), 112.5 (d, J = 9.8 Hz), 70.1, 31.7, 29.2, 25.8, 22.7, 14.2. IR (neat) 2929(s), 2857(w), 1591(w), 1493(s), 1470(m), 1391(w), 1260(s), 1191(s), 1040(w), 861(w), 799(w). HRMS (APCI) calcd for $C_{12}H_{16}BrFO^+$ $[M]^+$ 274.0363; found 274.0365.

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*4.3.4. 3-Bromo-4-methoxybenzaldehyde (**2d**)*

37.4 mg, 87% yield from the reaction of **1d** with 1.0 equiv **NBS** under N_2 atmosphere. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 8.09 (d, J = 1.9 Hz, 1H), 7.83 (dd, J = 8.5, 1.9 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 3.99 (s, 3H). The NMR data is in good agreement with that reported in the literature.[31]

*4.3.5. 1-(3-Bromo-4-methoxyphenyl)ethanone (**2e**)*

44.4 mg, 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.92 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 8.6 Hz, 1H), 3.97 (s, 3H), 2.56 (s, 3H). The NMR data is in good agreement with that reported in the literature.[32]

*4.3.6. 1-(3-Bromo-4-methoxyphenyl)-1-propanone (**2f**)*

43.7 mg, 90% yield. White solid; mp. 98–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 2.1 Hz, 1H), 7.93 (dd, J = 8.6, 2.1 Hz, 1H), 6.93 (d, J = 8.6 Hz, 1H), 3.96 (s, 3H), 2.94 (q, J = 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5, 159.5, 133.7, 131.1, 129.2, 112.0, 111.2, 56.6, 31.6, 8.4. IR (neat) 2971(w), 2931(w), 1676(s), 1591(s), 1405(m), 1254(s), 1189(s), 1009(w), 795(w), 673(w). HRMS (APCI) calcd for $C_{10}H_{12}BrO_2^+$ $[M+H]^+$ 243.0015; found 243.0014.

*4.3.7. 1-(4-(Benzyloxy)-3-bromophenyl)-1-propanone (**2g**)*

49.8 mg, 78% yield. White solid; mp. 91–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 1.8 Hz, 1H), 7.88 (dd, J = 8.6, 1.8 Hz, 1H), 7.53–7.30 (m, 5H), 6.96 (d, J = 8.6 Hz, 1H), 5.23 (s, 2H), 2.93 (q, J = 7.2 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 158.6, 135.8, 133.7, 131.3, 129.0, 128.8, 128.3, 127.0, 112.8, 112.6, 71.0, 31.6, 8.4. IR (neat) 2955(w), 2855(w), 1676(s), 1591(m), 1499(w), 1452(w), 1405(w), 1254(s), 1203(s), 1046(w), 1016(w), 797(w), 726(w), 679(w). HRMS (APCI) calcd for $C_{16}H_{16}BrO_2^+$ $[M+H]^+$ 319.0328; found 319.0322.

*4.3.8. 1-(3-Bromo-4-(hexyloxy)phenyl) -1-propanone (**2h**)*

55.7 mg, 89% yield. White solid; mp. 37–38 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 1.9 Hz, 1H), 7.89 (dd, J = 8.6, 1.9 Hz, 1H), 6.90 (d, J = 8.6 Hz, 1H), 4.09 (t, J = 6.5 Hz, 2H), 2.93 (q, J = 7.2 Hz, 2H), 1.91–1.80 (m, 2H), 1.56–1.46 (m, 2H), 1.39–1.32 (m, 4H), 1.21 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 6.8 Hz, 3H). 13C NMR (101 MHz, $CDCl_3$) δ 198.5, 159.2, 133.7, 130.8, 129.1, 112.4, 112.0, 69.5, 31.6 (two peaks overlap), 29.0, 25.7, 23.0, 14.1, 8.4. IR (neat) 2935(w), 2859(w), 1678(s), 1593(m), 1499(m), 1405(w), 1254(s), 1205(s), 1046(w), 1016(w), 797(w), 728(w), 679(w). HRMS (APCI) calcd for $C_{15}H_{22}BrO_2^+$ $[M+H]^+$ 313.0798; found 313.0794.

*4.3.9. 3-Bromo-4-methoxybenzoic acid (**2i**)*

43.4 mg, 94% yield. White solid; mp. 219–221 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, J = 2.1 Hz, 1H), 7.95 (dd, J = 8.6, 2.1 Hz, 1H), 7.21 (d, J = 8.7 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.9, 158.9, 133.8, 130.7, 124.3, 112.3, 110.4, 56.7. IR (neat) 2926(w), 2847(w), 1664(s), 1593(m), 1501(w), 1430(w), 1273(s), 1250(s), 1126(w), 1054(m), 899(w), 763(m). HRMS (APCI) calcd for $C_8H_6BrO_3^-$ $[M-H]^-$ 228.9506; found 228.9501.

*4.3.10. Ethyl 3-bromo-4-methoxybenzoate (**2j**)*

50.8 mg, 98% yield. White solid; mp. 70–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 2.1 Hz, 1H), 7.98 (dd, J = 8.6, 2.1 Hz, 1H), 6.91 (d, J = 8.6 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 159.5, 134.8, 130.7, 124.3, 111.5, 111.1, 61.2, 56.5, 14.5. IR (neat) 2924(w), 2845(w), 1705(s), 1599(m), 1497(m), 1362(m), 1268(s), 1246(s), 1126(s), 1016(m), 901(w), 842(w), 763(s). HRMS (APCI) calcd for $C_{10}H_{12}BrO_3^+$ $[M+H]^+$ 258.9964; found 258.9963.

*4.3.11. (3-Bromo-4-methoxyphenyl) (morpholino)methanone (**2k**)*

59.4 mg, 99% yield. White solid; mp. 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 2.1 Hz, 1H), 7.37 (dd, J = 8.4, 2.1 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 3.92 (s, 3H), 3.72–3.60 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 157.3, 132.8, 128.8, 128.3, 111.9, 111.6, 67.0 (two peaks overlap), 56.5. IR (neat) 2924(s), 2857(w), 1705(s), 1599(s), 1497(w), 1362(w), 1271(s), 1250(s), 1111(s), 1014(s), 901(w), 844(w), 757(w). HRMS (APCI) calcd for $C_{12}H_{15}BrNO_3^+$ $[M+H]^+$ 300.0230; found 300.0225.

*4.3.12. 4-Bromo-2-nitroanisole (**4a**)*

44.0 mg, 95% yield from the reaction of **3a** with NBS at 50 °C for 48 h. White solid; mp. 84–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.64 (d, J = 8.9 Hz, 1H), 6.99 (d, J = 8.9 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 137.0 (two peaks overlap), 128.5, 115.3, 112.0, 56.9. IR (neat) 2922(m), 2853(w), 1601(m), 1513(s), 1468(w), 1342(m), 1264(s), 1154(w), 1101(w), 1009(s), 875(m), 814(s), 528(w). HRMS (APCI) calcd for $C_7H_7BrNO_3^+$ $[M+H]^+$ 231.9526; found 230.9524.

*4.3.13. 2-(Benzyloxy)-5-bromobenzonitrile (**4b**)*

55.9 mg, 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 2.5 Hz, 1H), 7.57 (dd, J = 9.0, 2.5 Hz, 1H), 7.48–7.31 (m, 5H), 6.88 (d, J = 9.0 Hz, 1H), 5.20 (s, 2H). The NMR data is in good agreement with that reported in the literature.[33]

4.3.14. 5-Bromo-2-(methyloxy)benzonitrile (4c)

40.7 mg, 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 2.4 Hz, 1H), 7.63 (dd, J = 8.9, 2.5 Hz, 1H), 6.87 (d, J = 8.9 Hz, 1H), 3.93 (s, 3H). The NMR data is in good agreement with that reported in the literature.[34]

*4.3.15. 5′-Bromo-2′-methoxyacetophenone (**4d**)*

45.3 mg, 99% yield. White solid, mp. 35–37 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 2.6 Hz, 1H), 7.54 (dd, J = 8.8, 2.6 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 3.90 (s, 3H), 2.59 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 158.1, 136.2, 133.1, 129.8, 113.7, 113.3, 56.0, 31.9. IR(neat) 2916 (w), 2846 (w), 1672 (s), 1586 (m), 1478 (s), 1393 (s), 1354 (m), 1268 (s), 1221 (s), 1178 (w), 1144 (w), 1020 (m), 899 (w), 807 (m), 718 (w), 626 (w), 565 (w), 522 (w) HRMS (APCI) calcd for $C_9H_{10}O_2Br^+$ $[M+H]^+$ 228.9859; found 228.9857.

*4.3.16. Ethyl 5-bromo-2-methoxybenzoate (**4e**)*

47.1 mg, 91% yield. Liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 2.6 Hz, 1H), 7.54 (dd, J = 8.9, 2.6 Hz, 1H), 6.86 (d, J = 8.9 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 158.4, 136.0, 134.2, 122.3, 114.1, 112.4, 61.3, 56.4, 14.4. IR(neat) 2979 (w), 2840 (w), 1731 (s), 1592 (m), 1488 (s), 1403 (w), 1364 (w), 1297 (m), 1274 (m), 1099 (m), 1079 (m), 1023 (m), 813 (m), 675 (w), 626 (w), 530 (w). HRMS (APCI) for $C_8H_6O_2Br^+$ $[M+H]^+$ 212.9546; found 212.9544.

*4.3.17. 4-Bromo-2-fluoro-1-(hexyloxy)benzene (**4f**)*

54.4 mg, 99% yield. Liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, J = 10.6, 2.4 Hz, 1H), 7.19–7.13 (m, 1H), 6.82 (t, J = 8.7 Hz, 1H), 3.99 (t, J = 6.6 Hz, 2H), 1.86–1.73 (m, 2H), 1.52–1.41 (m, 2H), 1.39–1.29 (m, 4H), 0.91 (t, J = 9.2, 4.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8 (d, J = 250.6 Hz), 146.8 (d, J = 10.5 Hz), 127.3 (d, J = 4.0 Hz), 119.8 (d, J = 21.4 Hz), 116.1 (d, J = 2.4 Hz), 111.9 (d, J = 8.3 Hz), 69.8, 31.7, 29.2, 25.7, 22.7, 14.2. IR (neat) 2930 (w), 2859 (w), 1582 (w), 1505 (s), 1409 (w), 1305 (m), 1266 (m), 1207 (m), 1129 (m), 1019 (m), 876 (m), 858 (m), 799 (m), 638 (w), 575 (w). HRMS (APCI) for $C_{12}H_{16}BrFO^+$ $[M]^+$ 274.0363; found 274.0363.

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*4.3.18. 4-Bromo-2-chloroanisole (**4g**)*

43.8 mg, 99% yield. White solid; mp. 68–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 2.4 Hz, 1H), 7.33 (dd, J = 8.8, 2.4 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 154.5, 132.8, 130.7, 123.8, 113.4, 112.6, 56.4. IR(neat)3022 (w), 2930 (m), 1578 (m), 1480 (s), 1456 (s), 1291 (s), 1062 (s), 1017 (s), 875 (m), 803 (s), 705 (m), 620 (w), 552 (w). HRMS (APCI) calcd for $C_7H_6OClBr^+$ $[M]^+$ 219.9285; found 219.9292.

*4.3.19. 2,4-Dibromoanisole (**4h**)*

52.6 mg, 99% yield from the reaction 2-bromoanisole **3h** with NBS. The NMR spectroscopic data is the same as **2b**.

*4.3.20. 2-(5-Bromo-2-methoxyphenyl)acetonitrile (**4i**)*

43.4 mg, 96% yield. White solid; mp. 59–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 2.4 Hz, 1H), 7.42 (dd, J = 8.7, 2.4 Hz, 1H), 6.77 (d, J = 8.7 Hz, 1H), 3.85 (s, 3H), 3.66 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 132.4, 132.1, 120.9, 117.5, 113.0, 112.3, 55.9, 18.6. IR(neat) 2975 (w), 2944 (w), 2842 (w), 2247 (w), 1592 (m), 1490 (s), 1409 (m), 1325 (m), 1284 (m), 1256 (s), 1121 (s), 1023 (s), 864 (m), 817 (m), 622 (m), 530 (w). HRMS (APCI) for $C_9H_8ONBr^+$ $[M]^+$ 224.9784; found 224.9783.

*4.3.21. 2′-Bromo-5′-methoxyacetophenone (**4j**)*

43.0 mg, 94% yield from the reaction of **3j** with 1.0 equiv NBS. Liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 3.1 Hz, 1H), 6.85 (dd, J = 8.8, 3.1 Hz, 1H), 3.81 (s, 3H), 2.63 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.4, 159.0, 142.4, 134.7, 118.0, 114.3, 109.2, 55.8, 30.4. IR(neat) 2936 (w), 2840 (w), 1702 (s), 1592 (m), 1568 (m), 1470 (s), 1403 (m), 1354 (m), 1313 (m), 1286 (s), 1219 (m), 1044 (m), 817 (m), 699 (w), 638 (w), 599 (w). HRMS (APCI) calcd for $C_9H_{10}O_2Br^+$ $[M+H]^+$ 228.9859; found 228.9858.

*4.3.22. Ethyl 2-bromo-5-methoxybenzoate (**4k**)*

47.1 mg, 91% yield from the reaction of **3k** with 1.0 equiv NBS under the standard conditions. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 3.1 Hz, 1H), 6.87 (dd, J = 8.8, 3.1 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H). The NMR data is in good agreement with that reported in the literature.[35]

*4.3.23. 2-Bromo-4-chloroanisole (**4l**)*

43.0 mg, 97% yield from the reaction of **3l** with 1.0 equiv NBS under the standard conditions. Liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.9 Hz, 1H), 7.00 (d, J = 2.9 Hz, 1H), 6.69 (dd, J = 8.9, 2.9 Hz, 1H), 3.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 135.0, 134.0, 115.9, 114.6, 113.0, 55.8. IR (neat) 2931(w), 2851(w), 1589(m), 1472(s), 1438(w), 1287(s), 1230(w), 1109(w), 1042(s), 861(w), 801(w), 608(w). HRMS (APCI) calcd for $C_7H_7BrClO^+$ $[M+H]^+$ 220.9385; found 219.9283.

*4.3.24. 3,4-Dibromoanisole (**4m**)*

47.3 mg, 89% yield from the reaction of **3m** with 1.0 equiv NBS under the standard conditions. Liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.9 Hz, 1H), 7.17 (d, J = 2.9 Hz, 1H), 6.74 (dd, J = 8.9, 2.9 Hz, 1H), 3.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 133.9, 125.1, 119.1, 115.4, 115.3, 55.9. IR (neat) 2934 (w), 2834 (w), 1586 (s), 1562 (w), 1472 (s), 1437 (w), 1287 (m), 1260 (w), 1227 (m), 1182 (w), 1103 (m), 1038 (m), 1007 (w), 848 (m), 672 (w), 603 (m), 571 (w). HRMS (APCI) for $C_7H_6OBr_2^+$ $[M]^+$ 263.8780; found 263.8779.

*4.3.25. 2-Bromo-5-(methyloxy)benzonitrile (**4n**)*

35.2 mg, 83% yield from the reaction of **3n** with NBS under the standard conditions. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.9 Hz, 1H), 7.15 (d, J = 2.8 Hz, 1H), 7.00 (dd, J = 9.0, 2.8 Hz, 1H), 3.83 (s, 3H). The NMR data is in good agreement with that reported in the literature.[36]

4.4. General procedure for kinetic study

For each reaction, to the solution of NBS, **1a** and PhCl in CH_3CN (being heated at 35 °C and stirred at 740 rpm) was added the stock solution of I_2 or IBr. Then timing started immediately. 50 μL of the reaction mixture was sampled at the interval from 2 min to 60 min. Each sample was quenched with $Na_2S_2O_3$ aqueous solution and extracted by CH_2Cl_2 (500 μL). Then about 300 μL of the organic extracts was transferred to a GC sample vial for gas chromatographic analysis.

4.5. Kinetic isotope effects

*4.5.1. Synthesis of mono-deuterated substrate (**1a**-1D)*

To the cold solution of **1a** (10 mmol, 1.43 g) in dry THF (5 mL) at −78 °C was added *n*BuLi (1.2 equiv, 5.45 mL, 2.2 M in Et_2O) dropwise. Then the mixture was warmed up to room temperature and stirred for 1 h. D_2O (1.5 equiv, 270 μL) was added to the reaction mixture dropwise and the resulting mixture was stirred for 20 min. The reaction mixture was filtered through Celite, and washed by petroleum ether. The filtrate was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was then distilled under vacuum to give **1a**-1D as a colorless liquid (496 mg, 35% yield).[37]

*4.5.2. Synthesis of bi-deuterated substrate (**1a**-2D)*

To the cold solution of **1a-**1D (1.0 mmol, 143 mg) in dry THF (5 mL) at −78 °C was added *n*BuLi (1.2 equiv, 5.45 mL, 2.2 M in Et_2O) dropwise. Then the mixture was warmed up to room temperature and stirred for 1 h. D_2O (1.5 equiv, 270 μL) was added to the reaction mixture dropwise and the resulting mixture was stirred for 20 min. The reaction mixture was filtered through Celite, and washed by petroleum ether. The filtrate was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was distilled under vacuum to give **1a**-2D as a colorless liquid (72.3 mg, 50% yield).[37]

4.5.3. Intramolecular KIE experiments

The mixture of **1a-**1D (0.1 mmol, 14.3 mg), NBS (0.15 mmol, 25.8 mg), I_2 (0.01 mmol) or IBr (0.01 mmol) and CH_3CN (0.5 mL) was stirred at 35 °C. The reaction was monitored by gas chromatographic analysis. The reaction mixture was quenched by NaS_2O_3 aqueous solution and extracted by Et_2O. The organic phase was washed with brine, dried over sodium sulfate and concentrated. The residue was dissolved in acetone-d_6 for ^{1}H NMR analysis. The intramolecular KIE values were calculated based on the ratio of **2a**(D) to **2a**. For the I_2-catalyzed reaction, the intramolecular KIE value was 1.44 at 50% conversion and 100% conversion of **1a**-1D. And the intramolecular value for the IBr-catalyzed reaction was 1.44 at 76% conversion and 100% conversion of **1a**-1D.

4.5.4. One-pot competition experiments

The mixture of **1a** (0.05 mmol, 7.65 mg) and **1a**-2D (0.05 mmol, 7.65 mg), NBS (0.15 mmol, 25.9 mg), I_2 (0.01 mmol) or IBr (0.01 mmol) and CH_3CN (0.5 mL) was stirred at 35 °C. The reaction was monitored by gas chromatographic analysis. When the conversion was around 10%, the reaction mixture was quenched by NaS_2O_3 aqueous solution and extracted by Et_2O. The organic phase was washed with brine, dried over sodium sulfate and concentrated. The residue was dissolved in $CDCl_3$ for ^{1}H NMR analysis. The KIE values were calculated based on the ratio of **2a** to **2a**(D). For the I_2-catalyzed reaction, the KIE value was 1.86 at 10% conversion. And the KIE value for the IBr-catalyzed reaction was 1.86 at 10% conversion.

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4.5.5. Parallel reactions

The mixture of **1a** (0.1 mmol, 14.3 mg) or **1a**-2D (0.1 mmol, 14.3 mg), NBS (0.15 mmol, 25.9 mg), I_2 (0.0045 mmol) or IBr (0.003 mmol), CH_3CN (0.5 mL) and PhCl (0.25 mmol) was stirred at 35 °C. The reaction was monitored by gas chromatographic analysis and the initial rates (v_H and v_D) were derived according to linear fitting for the plot of [**2a**] versus the reaction time when the conversion was lower than 10%. The KIE values were calculated based on the ratio of V_0(**1a**) to V_0(**1a**-2D). For the I_2-catalyzed reaction, the KIE value was 1.43 at 10% conversion. And the KIE value for the IBr-catalyzed reaction was 1.68 at 10% conversion.

Notes

The authors declare no competing financial interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2017.10.073.

References

1. (a) Adam J, Gosselain PA, Goldfinger P. *Nature*. 1953;171:704–705;
(b) Bloomfield GF. *J Chem Soc*. 1944:114–120.
2. (a) Roberts JC, Roffey P. *J Chem Soc C*. 1966:160–162;
(b) Goldberg Y, Alper H. *J Org Chem*. 1993;58:3072–3075;
(c) Ando W, Tsumaki H. *Synthesis*. 1982;1982:263–264;
(d) Van Tuyen N, Kesteleyn B, De Kimpe N. *Tetrahedron*. 2002;58:121–127.
3. (a) Guss CO, Rosenthal R. *J Am Chem Soc*. 1955;77:2549–2551;
(b) Dalton DR, Jones DC. *Tetrahedron Lett*. 1967;8:2875–2877;
(c) Dalton DR, Dutta VP, Jones DC. *J Am Chem Soc*. 1968;90:5498–5501.
4. (a) Dunstan S, Henbest HB. *J Chem Soc*. 1957:4905–4908;
(b) Prugh JD, McCarthy WC. *Tetrahedron Lett*. 1966;7:1351–1356;
(c) Pinnick HW, Lajis NH. *J Org Chem*. 1978;43:371–372;
(d) Beebe TR, Boyd L, Fonkeng SB, et al. *J Org Chem*. 1995;60:6602–6603;
(e) Uzagare MC, Padiya KJ, Salunkhe MM, Sanghvi YS. *Bioorg Med Chem Lett*. 2003;13:3537–3540;
(f) Mayhoub AS, Talukdar A, Cushman M. *J Org Chem*. 2010;75:3507–3510;
(g) Tripathi CB, Mukherjee S. *J Org Chem*. 2012;77:1592–1598;
(h) Guha S, Rajeshkumar V, Kotha SS, Sekar G. *Org Lett*. 2015;17:406–409.
5. (a) Senanayake CH, Fredenburgh LE, Reamer RA, Larsen RD, Verhoeven TR, Reider PJ. *J Am Chem Soc*. 1994;116:7947–7948;
(b) Huang X, Keillor W. *Tetrahedron Lett*. 1997;38:313–316;
(c) Huang X, Seid M, Keillor JW. *J Org Chem*. 1997;62:7495–7496.
6. For selected references on electrophilic bromination with NBS catalyzed by Lewis acids, see: (a) Surya Prakash GK, Mathew T, Hoole D, et al. *J Am Chem Soc*. 2004;126:15770–15776;
(b) Zhang Y, Shibatomi K, Yamamoto H. *Synlett*. 2005:2837–2842;
(c) Mo F, Yan JM, Qiu D, Li F, Zhang Y, Wang J. *Angew Chem Int Ed*. 2010;49:2028–2832;
(d) Qiu D, Mo F, Zheng Z, Zhang Y, Wang J. *Org Lett*. 2010;12:5474–5477;
(e) Mostafa MAB, Calder EDD, Racys DT, Sutherland A. *Chem Eur J*. 2017;23:1044–1047.
7. For selected references on electrophilic bromination with NBS catalyzed by Brönsted acids, see: (a) Castanet A-S, Colobert F, Broutin P-E. *Tetrahedron Lett*. 2002;43:5047–5048;
(b) Yu G, Mason HJ, Wu X, Endo M, Douglas J, Macora JE. *Tetrahedron Lett*. 2001;42:3247–3249;
(c) Oberhauser T. *J Org Chem*. 1997;62:4504–4506.
8. For recent references on Lewis base-catalyzed electrophilic bromination with NBS: (a) Maddox SM, Nalbandian CJ, Smith DE, Gustafson JL. *Org Lett*. 2015;17:1042–1045;
(b) Xiong X, Yeung Y-Y. *Angew Chem Int Ed*. 2016;55:16101–16105.
9. (a) Pingali SRK, Madhav M, Jursic BS. *Tetrahedron Lett*. 2010;51:1383–1385;
(b) Shirinian VZ, Lonshakov DV, Kachala VV, et al. *J Org Chem*. 2012;77:8112–8123;
(c) Carreno MC, Ruano JLG, Sanz G, Toledo MA, Urbano A. *J Org Chem*. 1995;60:5328–5331;
(d) Kano T, Tanaka Y, Osawa K, Yurino T, Maruoka K. *J Org Chem*. 2008;73:7387–7389.
10. (a) Cantillo D, De Frutos O, Rincon JA, Mateos C, Kappe CO. *J Org Chem*. 2014;79:223–229;
(b) Podgorsek A, Stavber S, Zupan M, Iskra J. *Tetrahedron Lett*. 2006;47:1097–1099;
(c) Dessolin J, Biot C, Davioud-Charvet E. *J Org Chem*. 2001;66:5616–5619.
11. (a) Zhang P, Liu R, Cook JM. *Tetrahedron Lett*. 1995;36:3103–3106;
(b) Suarez D, Laval G, Tu S-M, et al. *Synthesis*. 2009;2009:1807–1810;
(c) Lee HS, Spraggon G, Schultz PG, Wang F. *J Am Chem Soc*. 2009;131:2481–2483;
(d) Horvath A, Nussbaumer P, Wolff B, Billich A. *J Med Chem*. 2004;47:4268–4276.
12. (a) Deshpande AM, Natu AA, Argade NP. *J Org Chem*. 1998;63:9557–9558;
(b) Khatuya H. *Tetrahedron Lett*. 2001;42:2643–2644;
(c) Jang YJ, Jun JH, Swamy KMK, et al. *Bull Korean Chem Soc*. 2005;26:2041–2403.
13. (a) Incremona JH, Martin JC. *J Am Chem Soc*. 1970;92:627–634;
(b) Kim SS, Lee CS, Kim CC, Kim HJ. *J Phys Org Chem*. 1990;3:803–806;
(c) Day JC, Katsaros MG, Kocher WD, Scott AE, Skell PS. *J Am Chem Soc*. 1978;100:1950–1951.
14. Dauben Jr HJ, McCoy LL. *J Am Chem Soc*. 1959;81:4863–4873.
15. For selected recent reviews, see: (a) Parvatkar PT, Parameswaran PS, Tilve SG. *Chem Eur J*. 2012;18:5460–5489;
(d) Ren YM, Cai C, Yang RC. *RSC Adv*. 2013;3:7182–7204;
(e) Samanta R, Matcha K, Antonchick AP. *Eur J Org Chem*. 2013;2013:5769–5804;
(f) Dong D-Q, Hao S-H, Wang Z-L, Chen C. *Org Biomol Chem*. 2014;12:4278–4289;
(g) Wu XF, Gong JL, Qi X. *Org Biomol Chem*. 2014;12:5807–5817;
(h) Liu D, Lei A. *Chem Asian J*. 2015;10:806–823.
16. (a) Liu Z, Zhang J, Chen S, Shi E, Xu Y, Wan X. *Angew Chem Int Ed*. 2012;51:3231–3235;
(b) Mai W-P, Wang H-H, Li Z-C, et al. *Chem Commun*. 2012;48:10117–10119;
(c) Tan B, Toda N, Barbas CF. *Angew Chem Int Ed*. 2012;51:12538–12541.
17. (a) Dhineshkumar J, Lamani M, Alagiri K, Prabhu KR. *Org Lett*. 2013;15:1092–1095;
(b) Ito M, Kubo H, Itani I, Morimoto K, Dohi T, Kita Y. *J Am Chem Soc*. 2013;135:14078–14081;
(c) Xue Q, Xie J, Li H, Cheng Y, Zhu C. *Chem Commun*. 2013;49:3700–3702.
18. (a) Rai P, Srivastava M, Singh J, Singh J. *RSC Adv*. 2014;4:779–783;
(b) Dhineshkumar J, Prabhu KR. *Org Lett*. 2013;15:6062–6065;
(c) Hiebel M-A, Berteina-Raboin S. *Green Chem*. 2015;17:937–944;
(d) Kitamura T, Muta K, Kuriki S. *Tetrahedron Lett*. 2013;54:6118–6120;
(e) Yan R, Kang X, Zhou X, et al. *J Org Chem*. 2014;79:465–470.
19. Braner L. *Z Phys Chem*. 1902;41:514–543.
20. (a) Tsuruta T, Sasaki K-I, Furukawa J. *J Am Chem Soc*. 1952;74:5995–5998;
(b) Tsuruta T, Sasaki K-I, Furukawa J. *J Am Chem Soc*. 1954;76:994–998.
21. Duan S, Turk J, Speigle J, Corbin J, Masnovi J, Baker RJ. *J Org Chem*. 2000;65:3005–3009.
22. Pravst I, Zupan M, Stavber S. *Tetrahedron Lett*. 2006;47:4707–4710.
23. For I_2-catalyzed hydroxybromination of activated alkenes with NBS, see: (a) Lodh RS, Borah AJ, Phukan P. *Ind J Chem Sec B*. 2014;53:1425–1429. For I_2-catalyzed nucleophilic substitutions of carbonyl compounds with amines, see:;
(b) Panguluri NR, Narendra N, Sureshbabu VV. *Ind J Chem Sec B*. 2014;53:1430–1435;
(c) Varala R, Nuvula S, Adapa SR. *J Org Chem*. 2006;71:8283–8286;
24 For a reference on the reaction between NBS and I_2 to synthesize NIS, see: Chaikovskii VK, Skorokhodov VI, Filimonov VD *Russ J Org Chem*. 2001;37:1503–1504. This paper showed that the reaction of NBS with I_2 was much faster in CCl_4 than in DCE. Therefore, the reaction pathway that bromine abstraction of NBS by iodine radicals to generate NIS and IBr was proposed.
25. For an early reference on electrophilic aromatic brominations with IBr, see: Militzer W *J Am Chem Soc*. 1938;60:256–257.
26. For a reference on bromination of methane with CH_2Br_2 in the presence of I_2, see: (a) Ding K, Metiu H, Stucky GD. *ACS Catal*. 2013;3:474–477. For a reference on oxidative dehydrogenation of propane in the presence of I_2, see:;
(b) Ding K, Metiu H, Stucky GD. *ChemCatChem*. 2013;5:1906–1910;
(c) Ding K, Zhang A, Stucky GD. *ACS Catal*. 2012;2:1049–1056.
27. Ganguly NC, De P, Dutta S. *Synthesis*. 2005;2005:1103–1108.
28. Eberson L, Finkelstein M, Folkesson B, et al. *J Org Chem*. 1986;51:4400–4403.
29. Hamashima Y, Suzuki T, Takano H, Shimura Y, Sodeoka M. *J Am Chem Soc*. 2005;127:10164–10165.
30. Hamamoto H, Hattori S, Takemaru K, Miki Y. *Synlett*. 2011;11:1563–1566.
31. Tsoukala A, Liguori L, Occhipinti G, Bjørsvik H. *Tetrahedron Lett*. 2009;50:831–833.
32. Kong Y, Wang K, Edler MC, et al. *Bioorg Med Chem*. 2010;18:971–977.
33. Zhang P, Zou MF, Rodriguez AL, Conn PJ, Newman AH. *Bioorg Med Chem*. 2010;18:3026–3035.
34. Anbarasan P, Neumann HL, Beller M. *Chem Eur J*. 2011;17:4217–4222.
35. Matos MC, Murphy PV. *J Org Chem*. 2007;72:1803–1806.
36. Malashikhin SA, Baldridge KK, Finney NS. *Org Lett*. 2010;12:940–943.
37. Eloi A, Rose-Munch F, Jonathan D, Tranchier J-P, Rose E. *Organometallics*. 2006;25:4554–4559.