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COMMUNICATION

Environmentally Benign Indole-Catalyzed Position-Selective Halogenation of Thioarenes and Other Aromatics†‡

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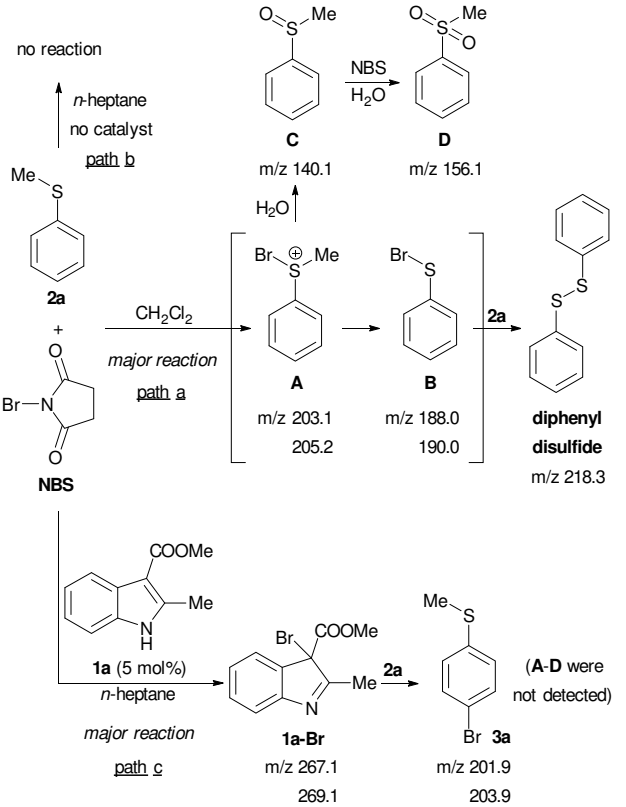
Halogenated aromatic compounds are the cores of many pharmaceutical, agricultural and chemical products but they are commonly prepared using electrophilic halogenation reactions in non-green chlorinated solvents under harsh conditions. A separate problem happens in the aromatic halogenation of thioarenes because they readily undergo oxidative side-reactions. Herein we report an environmentally benign electrophilic bromination of aromatics using an indole-catalytic protocol, which is suitable for a wide range of substrates including thioarenes.

Halogenated arenes are important to the pharmaceutical, agricultural, chemical, and material sciences. In addition, they are important synthetic intermediates for metal-mediated aryl-coupling chemistry.[1-6] Thus, development of new synthetic methods to introduce halogens into arenes is of great significance.[1-9]

Electrophilic halogenation is a common method to produce halogen-containing arenes. *N*-haloamides are frequently employed in the electrophilic halogenation processes because they are easy to handle as compared with the toxic and highly corrosive molecular halogens. However, in many cases environmentally unfriendly solvents such as chlorinated solvents are necessary for high efficiency (due to the poor solubility of the polar *N*-haloamide reagents) and selectivity. In addition, conventional aromatic electrophilic halogenations frequently encounter difficulty in controlling regioselectivity.[10-13] Furthermore, these reactions generally require harsh reaction conditions such as highly acidic solutions,[11] high reaction temperatures, or high catalyst loadings.[11-13] Halogenation of thioarenes with *N*-haloamides often encounter a separated type of challenge since thioarenes readily undergo oxidative reactions to give disulfide compounds and sulfoxides.[14-18] Herein, we are pleased to disclose our recent success in using structurally re-engineered super-lipophilic indoles for the position-selective mono-halogenation of arenes in the environmentally friendly solvent heptane. In particular, this newly developed catalytic protocol was found to be highly efficient in suppressing the disulfide formation in the halogenation of thioarenes. The scope was found to be broad and the products could be isolated under column-free condition.

The investigation began with the evaluation of a sample containing thioanisole (**2a**) and *N*-bromosuccinimide (NBS) in dichloromethane using GCMS (Scheme 1, path a). Strong



Scheme 1. Reaction between thioanisole (**2a**) and NBS analysed by GCMS.

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signals that correspond to the sulfonium bromide species **A** (*m/z* 203.1, 205.2), the S-Br species **B** (*m/z* 188.0, 190.0), and diphenyl disulfide (*m/z* 218.3) were detected (Scheme 1, path a). However, minor aromatic halogenation product was observed. We believe that the putative sulfonium bromide species **A** could be formed through the nucleophilic attack of the Lewis basic sulfide in **2a** to NBS.[14,19-23] A possible pathway to the formation diphenyl disulfide could undergo through the nucleophilic attack of the sulfide in species **B** by a molecule of **2a** followed by demethylation.[14,15] At the same time, two weak signals that correspond to sulfone **C** (m/z 140.1) and sulfoxide **D** (m/z 156.1) were observed and these compounds could be formed through the nucleophilic attack of species **A** by moisture.[16-18]

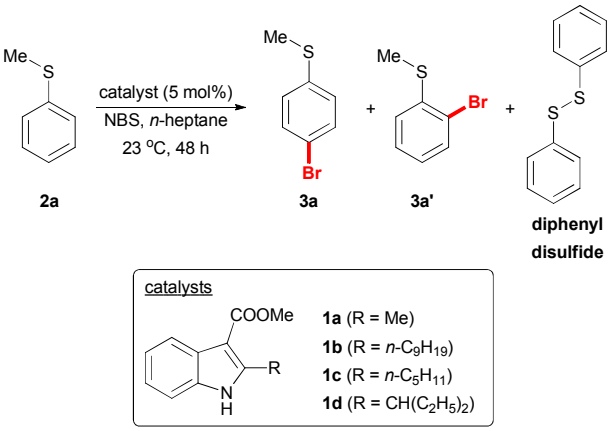
Recently, we have introduced a new concept of using lipophilic indole **1a** as an organocatalyst in electrophilic halogenation in non-polar green solvents through a solid-liquid phase transfer mechanism and have demonstrated that the catalytic protocol is suitable for a range of electrophilic halocyclization reactions.[24] Since the charged sulfonium bromide species **A** could be the active species for the formation of the undesired oxidative products, we hypothesized that conducting the reaction in lipophilic media could shut down the channel towards the oxidized products through suppressing the formation of species **A**.

To test the hypothesis, the aromatic bromination of thioanisole (**2a**) was performed in *n*-heptane. No reaction was observed in the absence of catalyst (Scheme 1, path b and Table 1, entry 1). On the other hand, we were delighted to realize that **3a** was the exclusive product when the reaction was conducted in *n*-heptane in the presence of 5 mol % of indole catalyst **1a** in the GCMS analysis (Scheme 1, path c). Although the yield of **3a** was moderate (38%), the reaction returned with a high *para*-selectivity and no oxidized products were detected (Table 1, entry 2). The reaction efficiency was not satisfactory, potentially due to the moderate solubility of the indole catalyst. We then decided to incorporate a lipophilic side chain to the indole catalyst system aiming at improving the reaction efficiency through the increase in solubility.

Thus, a series of indole catalysts **1** with various alkyl substituents were prepared according to a modified literature procedure.[25] As illustrated in Figure 1, the solubility of **1a** was moderate in *n*-heptane (Figure 1a and 1b). In contrast, indole **1b** that has a *n*-nonanyl side chain at the C(2) position appeared as a pale yellow oil and it was found to be miscible with *n*-heptane even the temperature was reduced to –28 °C (Figure 1c and 1d).

Next, the performance of the newly prepared indoles **1** was evaluated. To our delight, catalyst **1b** exhibited superior performance in driving the reaction to completion to give the desired product **3a** in 87% isolated yield (Table 1, entry 3). More importantly, excellent *para*/*ortho*-selectivity was obtained and no diphenyl disulfide side product was detected. Indole catalyst **1c** that has a relatively shorter hydrocarbon also gave comparable performance (entry 4). On the other

Table 1 Bromination of thioanisole (**2a**) with NBS



Entry[a]	Catalyst	Unreacted **2a** (%)[b]	**3a** (%)[b]	**3a'** (%)[b]	$(PhS)_2$ (%)[b]
1	-	100	0	0	0
2	**1a**	60	38	2	0
3	**1b**	0	98	2	0
4	**1c**	0	99	1	0
5	**1d**	15	83	2	0
6[c]	Ph_3PS	18	50	5	27
7[c]	HCl	10	46	13	31
8[c]	$FeCl_3$	6	64	5	5[d]

[a] Reactions were conducted using thioanisole (**2a**) (1 mmol), NBS (1.05 mmol) in *n*-heptane (2 mL) at 23 °C for 48 h in the absence of light. NBS was purified via recrystallization. [b] Determined by GC–MS. [c] CH_2Cl_2 was used as the solvent. [d] c.a. 20% of sulfoxide products was detected.

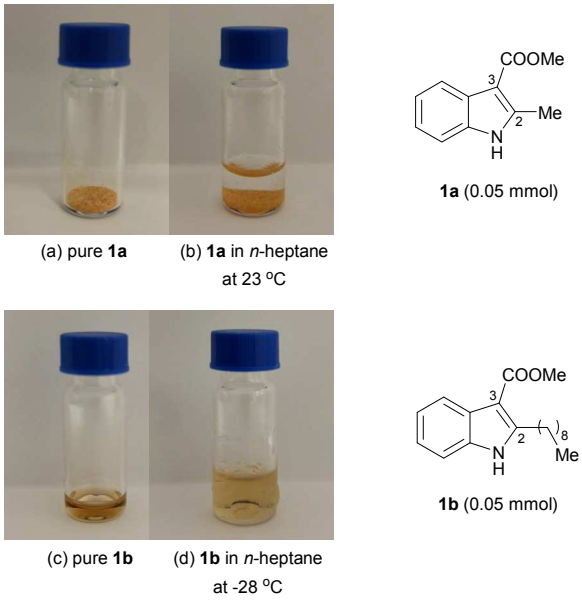


Fig 1 Comparison of the solubility of indole catalysts **1a** and **1b**.

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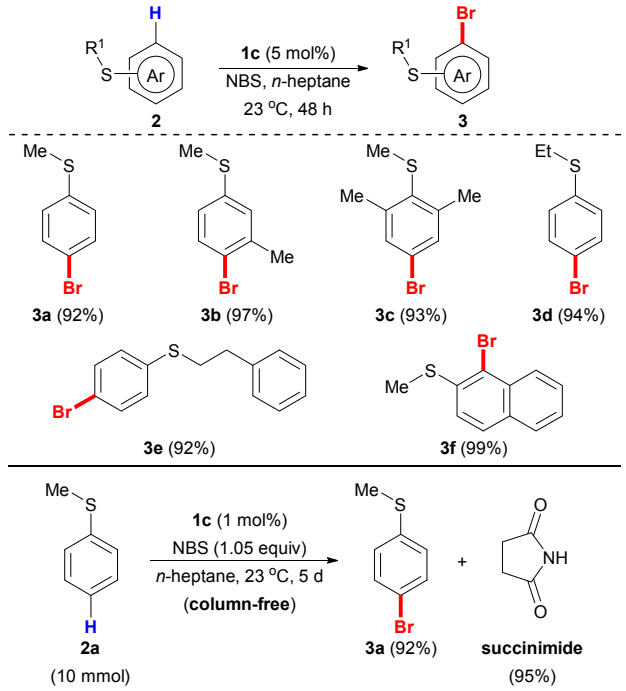
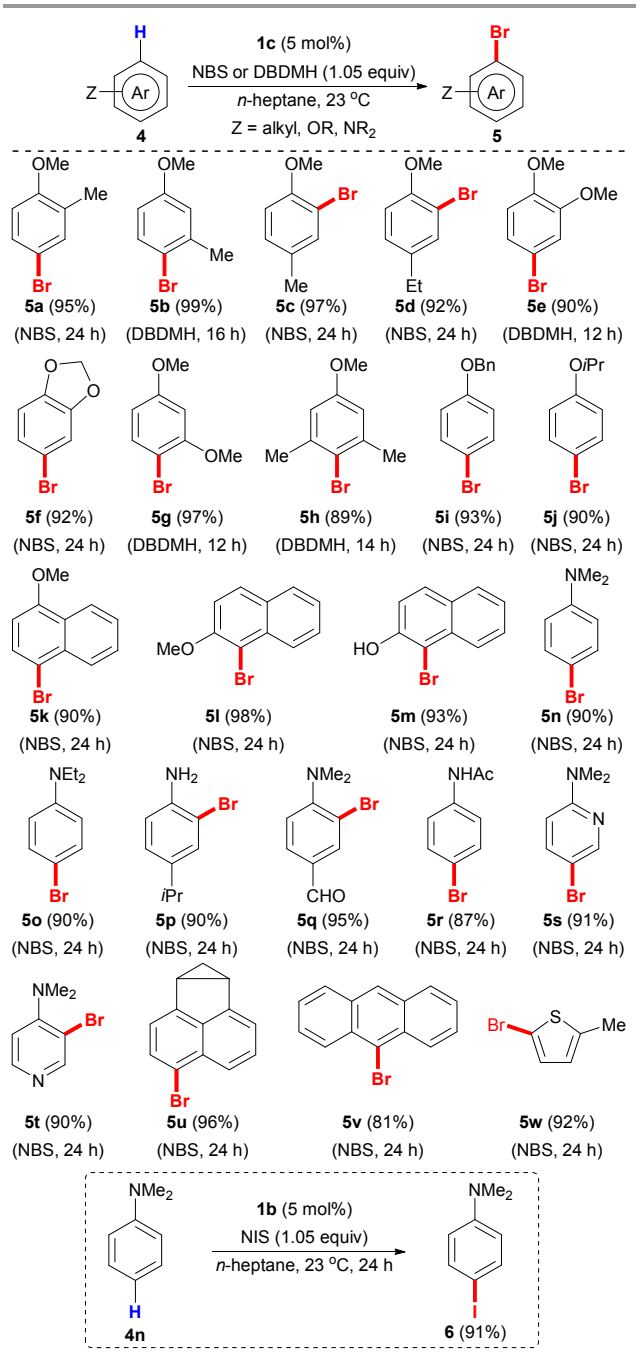
hand, the reaction efficiency was slightly reduced when indole catalyst **1d** was used, attributable to the relatively bulkier branching hydrocarbon substituent (entry 5). We have also investigated the reaction using some common catalysts for halogenation including Lewis base (Ph_3PS), Lewis acid ($FeCl_3$), and Brønsted acid (HCl) in dichloromethane. Although the reactions proceeded with moderate efficiency, poor *para*/*ortho*-selectivity together with significant amount of diphenyl disulfide side product were observed (entries 6–8). Indole catalyst **1c** was then used in the substrate scope study.

Other aryl thioethers **2** were then examined and the results are shown in Scheme 2. In general, excellent selectivity and chemical yield of the desired products **3** were observed. Again, no disulfide by-product was detected in all these cases. Other than S-methyl substrates, **2d** and **2e** that have different S-alkyl substituents were also found to be compatible with this catalytic protocol. Naphthalene thioether **2f** also gave the corresponding C(1) brominated product **3f** in excellent yield. We were also delighted to realize that the sulfides were not oxidized in all these cases. Since the halogen carrier succinimide is insoluble in *n*-heptane, we intended to purify the product under column-free condition. Thus, the reaction of **2a** was conducted using 1 mol % of indole **1c** (Scheme 2). Upon completion, the reaction was filtered and the succinimide residue was washed with *n*-heptane to yield the desired product **3a** in 92% yield with purities of up to 99% (as determined by ^{1}H NMR) together with the recovery of 95% of succinimide. It is worth-mentioning that the reaction was performed at 10 mmol scale and the reaction performance was satisfactory.



Scheme 2. Indole-catalyzed bromination of thioethers **2** in *n*-heptane.

Other arenes were also examined using the catalytic protocol (Scheme 3). A broad range of aromatic substrates was



Scheme 3. Indole-catalyzed bromination of aromatics.

found to be compatible and clean conversion was observed in all these cases. In general, anisole-type substrates **4** with substituents at the *ortho*-, *meta*-, or *para*-position reacted smoothly, giving the brominated products **5** in good yields and excellent position-selectivity (Scheme 3, **5a**–**5h**). Anisoles, such as 3-methylanisole (**4b**) and 1,3-dimethoxybenzene (**4g**), were brominated with excellent regioselectivities and good yields

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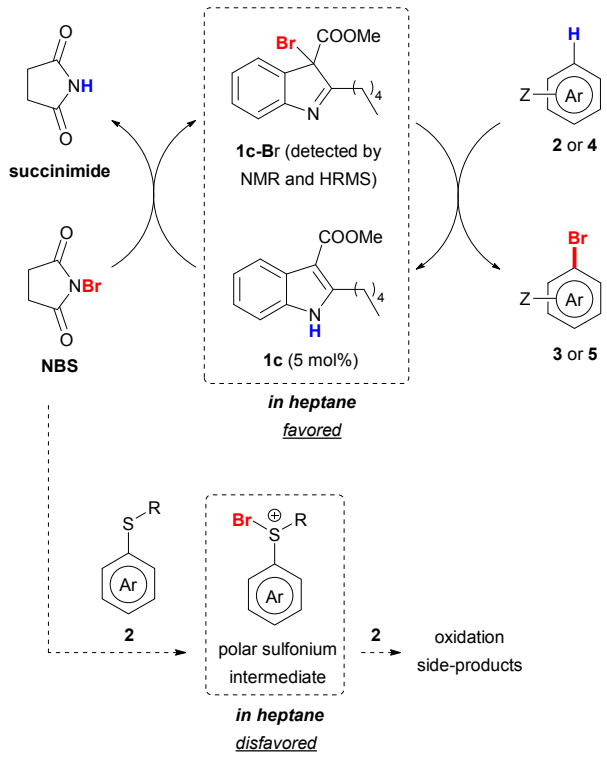
using 5 mol% of **1c** as the catalyst and 1.05 equivalent of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as the bromine source. *para*-Substituted anisoles **4c** and **4d** produced *ortho*-brominated anisoles **5c** and **5d**, respectively, in excellent yields. Benzyl phenyl ether (**4i**) and isopropyl phenyl ether (**4j**) were converted into the corresponding mono-bromides **5i** and **5j** in excellent *para*-selectivity (> 99:1 *p*/*o* ratio). Naphthenyl methyl ethers **4k** and **4l** worked equally well as the anisole-type substrates. The unprotected 2-naphthol (**4m**) could be brominated to give **5m** in 93% isolated yield.

Substituted anilines were also examined and the corresponding mono-brominated compounds could be furnished in high efficiency and selectivity (Scheme 3, **5n**–**5r**). The aldehyde-containing substrate **4q**, which is sensitive towards oxidation condition, was found to be compatible with the catalytic protocol and the product **5q** was obtained in 95% yield. Amino-pyridines **4s** and **4t** could readily be converted into **5s** and **5t** under the optimized reaction conditions. Polycyclic compounds were studied as well. The cyclopropane-containing bicyclic system 7,7a-dihydro-6b*H*-cyclopropa[*a*] acenaphthylene (**4u**) could be mono-brominated to give **5u** with the cyclopropane remained intact. Anthracene (**4v**) underwent mono-bromination smoothly to give **5v** in good yield and excellent regioselectivity. We were also delighted to realize that the heterocyclic compound 5-Bromo-2-methylthiophene (**5w**) was obtained in good yield and regioselectivity from 2-methylthiophene (**4w**). The catalytic protocol was found to be applicable to the preparation of iodinated arene. For instance, reaction of dimethylaniline (**4n**) with *N*-iodosuccinimide (NIS, 1.05 equiv) catalyzed by indole **1b** smoothly achieved *p*-iodo-*N,N*-dimethylaniline (**6**) in 91% yield in *n*-heptane at 23°C.

The proposed catalytic cycle for the aromatic bromination is shown in Scheme 4. We suspect that the reaction might begin with the halogen exchange between the soluble indole catalyst **1c** and the insoluble *N*-bromoamide to give the corresponding lipophilic 3-bromoindole species **1c-Br** through a solid-liquid phase-transfer mechanism,[24] which was evidenced by physical analysis using NMR and ESI high-resolution mass spectrometry (HRMS).[26] We believe that the Br in species **1c-Br** is highly active towards electrophilic bromination as a result of the loss of aromaticity in the conversion of **1c** to **1c-Br**. Species **1c-Br** could then deliver the Br to the arenes **2** or **4** in the lipophilic media, giving in the brominated products **3** or **5** in high efficiency. A possible explanation for the driving force of the reaction could be due to the resuming of the aromaticity of indole **1c** after delivering the Br to the substrates. Unlike many other halogenation protocols that rely on the polarized or charged halogen species,[27-29] the current reaction system involves the neutral brominating species **1c-Br** in non-polar media, which could execute the halogenation under mild and virtually neutral conditions, and could avoid the formation of side products through supressing the formation of the polar sulfonium intermediate (Scheme 4).



Scheme 4. Proposed catalytic cycle.

Conclusions

In summary, good yields and excellent regioselectivities were achieved in the bromination of aromatics using indole-based organocatalysts in the lipophilic media heptane. Mechanistic studies revealed that the putative active species 3-bromoindole could be formed through a solid-liquid phase-transfer mechanism. The catalytic protocol is compatible with a wide range of arenes. In particular, the formation of oxidative side products in the halogenation of thioarenes can effectively be suppressed in the lipophilic reaction media. The bromination scheme introduced in this report does not require the use of hazardous substances, such as halogenated solvents, which conforms with the principles of green chemistry. Moreover, easy purification of the halogenated products could be realized without the need for column chromatography. These make this approach an environmentally friendly and sustainable pathway for the synthesis of valuable bromoarenes. Efforts are now underway to apply green solid-liquid phase-transfer organocatalysts to other classes of reactions.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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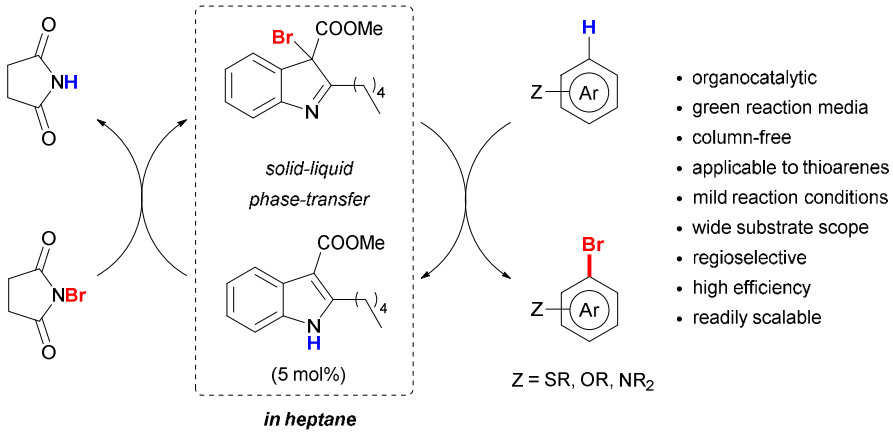

Position-selective halogenation of thioarenes and a wide range of aromatics using highly lipophilic indole organocatalyst has been developed.