Aromatization modulates the activity of small organic molecules as promoters for carbon–halogen bond activation†

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The combination of small organic molecules and a base serves as a unique system for the activation carbon–halogen bonds in haloarenes by single electron transfer (SET). However, most of the molecules employed as promoters only allow for the activation of aryl iodides, and efficient activation of aryl bromides and chlorides under this mode is still rather challenging. Herein, we report the discovery of a structurally simple yet powerful promoter molecule, indoline, which exhibits unusually high activity in promoting the activation of haloarenes by SET. In the presence of t-BuOK and a trace amount of oxygen, indoline promotes the formation of aryl radicals not only from aryl iodides and bromides, but also from unactivated aryl chlorides (e.g., chlorobenzene) under relatively mild conditions. Mechanistic studies reveal the molecular basis for its high activity, for which the aromatization process plays a key role in modulating the electron transfer process.

Introduction

Aryl halides constitute an important category of intermediates in organic chemistry, and the activation of carbon–halogen (C–X) bonds in aryl halides plays a significant role in organic synthesis. In addition to stoichiometric metalation or transition-metal catalysis for C–X bond activation, in recent years the development of small-organic-molecule-promoted C–X bond activation has attracted great attention. A series of small organic molecules, such as 1,10-phenanthrolines, 1,2-diamines, 1,2-diols and N-methylanilines, were found to promote the activation of haloarene in the presence of a base, producing a reactive aryl radical intermediate which undergoes substitution processes (referred to as base-promoted homolytic aromatic substitution, BHAS). Careful mechanistic studies revealed that the promoter is transformed into a "super electron donor" under the reaction conditions, which then initiates the cleavage of the C–X bond by single electron transfer (SET) to the haloarene substrate (Scheme 1a). This process represents a new mode of carbon–halogen bond activation, which enables a series of synthetic methods utilizing haloarenes as starting materials in a transition-metal-free manner.

Despite these achievements, efficient activation of relatively inert C–X bonds in the BHAS reaction remains a major challenge. To date, most promoters could merely activate iodoarenes, and only a few could activate bromoarenes. The activation of the C–Cl bond in unactivated chloroarenes is still rather challenging. This is due to the stepwise C–Br/C–Cl bond activation process with a slow C–X cleavage step, as well as the increasing difficulty for bromo- and chloroarene activation with respect to both reduction potential and bond strength (Scheme 1b). Herein, we report the discovery of a highly active promoter, indoline, based on the structural modification of existing promoters for carbon–halogen bond activation. It ranked among the most active small molecule promoters to date, which enables the activation of bromo- and chloroarenes.
and more attractively, a series of single electron reduction reactions traditionally carried out using alkali metal reductants.

**Results and discussion**

Our previous study showed that, N-methylaniline serves as an efficient promoter for the activation of iodoarenes in the presence of t-BuOK, where N-methylanilide anion acts as an electron donor. However, attempts to enable the activation of bromoarene 1a by structural tuning of the N-methylaniline promoter proved unsuccessful (Scheme 2a). Although electron-rich anilines exhibited slightly better activities (2a–e), the results were far from satisfactory, and the attachment of an additional aromatic ring to aniline (either as a substituent or as a fused cycle, 2f–h) with the aim to assist SET by stabilizing the formed N-centered radical, was also useless. With the hypothesis that ring strain might help to increase the activity, we attempted to use a cyclic aniline derivative, indoline (2i), as the promoter. To our surprise, the indoline/t-BuOK system exhibited great activity for activating iodo-, bromo- and even chloroarenes (Scheme 2b). A screen of substrates showed that the indoline/t-BuOK system is able to promote the BHAS reaction of a series of bromo- and chloroarenes, although chloroarenes are generally less reactive than bromoarenes (Scheme 2c).

**Scheme 2** Effect of the promoter structure on carbon–halogen bond activation.

Furthermore, compared with several of the most active organic promoters reported to date, indoline exhibited the highest activity under 80 °C (Fig. 1). The unprecedented high activity of indoline in the BHAS reaction attracted our interest and prompted us to elucidate its molecular basis.

First, we found that indole was generated in a high yield as the end-product in this indoline-promoted BHAS-type reaction. This transformation involves both oxidation and aromatization, which might be responsible for the observed SET-initiated C–X activation. Second, aniline-type promoters that were not able to form indole through aromatization were found to be much less active (Table 1). 3,3-Dimethylindoline (2j), tetrahydroquinoline (2k), and N-isobutylaniline (2l) were found to exhibit activity for iodoarene, but not for bromo- and chloroarenes. These results suggest that the activation of iodoarenes and bromo-/chloroarenes is rather different, and the aromatization process, rather than the ring-strain, plays a key role in the activation of more challenging C–X bonds.

**Table 1** Effect of promoter structure on activity

| Entry | Promoter | ArI (1b) | ArBr (1a) | ArCl (1c) |
|-------|----------|----------|-----------|-----------|
|       | Conv.    | Yield    | Conv.     | Yield     | Conv. |
| 1     | 95%      | 75%      | 19%       | 6%        | 10%   |
| 2     | 99%      | 73%      | 16%       | 7%        | 7%    |
| 3     | 76%      | 59%      | 16%       | 1%        | 10%   |

* Reaction conditions: haloarene 1 (0.5 mmol), promoter 2 (20 mol%), t-BuOK (1.5 mmol), 4 mL benzene, Ar atmosphere, 80 °C for 12 h. Conversions and yields were determined by gas chromatography.
Another observation also provided important clues for the initiation mechanism. The kinetic profile of the reaction revealed that the indoline-promoted BHAS reaction of 4-chloroanisole (1d) had a significant induction period under argon, whereas the reaction exhibited no induction period in the presence of O₂ (Fig. 2A). The generation of indole from indoline in these reactions followed the same trend. Injection of pure O₂ into the reaction system directly initiated the reaction, but led to a low final conversion (Fig. 2B). The control experiment also showed that under rigorous oxygen-free conditions, the reactions of chloro- and bromoarenes were almost completely suppressed, but the reaction of iodoarene could still proceed (Scheme 3). The transformation of indoline to indole proceeded without a haloarene substrate with trace O₂, but could not proceed under O₂-free conditions (Scheme 3).

The above experimental results indicate that the aromatization of indoline plays a critical role in the activation of chloro- and bromoarenes, and trace oxygen existing in the reaction system serves as a key factor to initiate the activation process. Based on this, the mechanism of carbon–halogen bond activation in the indoline-promoted BHAS reaction is proposed in Scheme 4. Deprotonation of indoline by t-BuOK led to anilide anion A, which serves as a weak electron donor. For iodoarenes, anion A could directly activate the C–I bond by SET, and radical intermediate B is formed simultaneously. Subsequent proton abstraction by t-BuOK affords intermediate C (equivalent to a radical anion), which acts as a better electron donor and is able to activate another iodoarene molecule. This process is similar to the initiation mechanism of the BHAS reaction promoted by N-methylaniline. On the other hand, for bromo-/chloroarenes, anion A is not able to act as a direct electron donor. Alternatively, in the presence of a trace amount of O₂, single electron oxidation of A takes place to generate B, which

![Scheme 4](image)

Scheme 4 Proposed initiation mechanism in the indoline-promoted BHAS reaction.

**Fig. 2** Kinetic profiles of the indoline-promoted BHAS reaction of 4-chloroanisole (1d) to produce biaryl 3a under Ar and in the presence of O₂ (A) and under Ar with injection of O₂ (B). Reaction conditions: 1d (1 mmol), indoline (40 mol%), t-BuOK (3 mmol), 8 mL benzene, 80 °C.
then affords C as a more efficient electron donor. Due to the slow C–X bond cleavage step, the electron transfer between C and the ArBr/ArCl substrate to form ArX⁻ and isoindole D is reversible. Under this circumstance, the isomerization of D to indole is rather important because the irreversible aromatization favors the electron transfer equilibrium and thus enables the activation of more challenging bromo-/chloroarenes. Thus, the proposed mechanism well rationalizes the superior activity of indoline over many aniline-type promoters, and clarifies the key role of trace O₂ in the initiation process.

This mechanism was further supported by the reaction employing 2-cyclopropylindoline (2m) as a probe (Scheme 5a). In the reactions of bromo- and chloroarenes 1a and 1c promoted by 2m, both 2-cyclopropylindole (5m) and 2-propylindole (5m’0) were observed as the end-product of indoline 2m. Under O₂-free conditions no reaction occurred and none of the end-products were formed. The formation of the ring-opening product 5m’ serves as key evidence for the existence of radical anion-type intermediate E in the reaction system (Scheme 5b). Once formed, radical anion E could undergo either SET to ArX to afford indole 5m, or cyclopropane ring-opening to produce the ring-opened radical F, which is then transformed to 5m’ by hydrogen atom transfer or reduction. In this kinetic competition scenario, the ratio of the two end-products is expected to be dependent on [ArX]. This was proven to be true by experiments performed with different [1a] (Fig. 3), which clearly indicate that intermediate E acts as the key electron donor in the SET-induced carbon–halogen activation.

DFT calculation was conducted to provide a quantitative understanding of the indoline-promoted C–X bond activation (Fig. 4). Starting from the deprotonated indoline Int-1 (equivalent to intermediate A), direct electron transfer to Ph is possible, though endergonic by 25.0 kcal mol⁻¹ in terms of Gibbs free energy, to produce phenyl radical and radical complex Int-2 (equivalent to intermediate B). Deprotonation of Int-2 at the C–H bond neighboring the N-centered radical via TS-1 is rather facile, according the radical anion complex Int-3 (equivalent to intermediate C). Though endergonic by 24.8 kcal mol⁻¹, the direct activation of Ph by anilide Int-1 is feasible. In contrast, for PhBr and PhCl direct electron transfer is not possible since the SET step is rather endergonic (~60 kcal mol⁻¹, see the ESI†). In such cases, trace oxygen reacts with Int-1 to afford radical complex Int-2 with a much more favorable free energy barrier, and Int-3 is subsequently generated by deprotonation.

As expected, complex Int-3 is a more efficient electron donor, enabling exergonic SET to Ph to form the phenyl radical and isoindole complex Int-4 (equivalent to intermediate D). The following aromatization process from Int-4 to Int-5 is also exergonic (by 18.6 kcal mol⁻¹). For the reaction of bromo-/chloroarenes, this aromatization process is of great
other reactions to modulate the electron transfer processes therein.

Conflicts of interest

The authors declare no competing financial interest.

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