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# A *para*-C-H functionalization of aniline derivatives via *in-situ* generated bulky hypervalent iodinium reagents

Chao Tian,[a] Xu Yao,[a] Weizhe Ji,[a] Qian Wang,[a] Guanghui An*[a,b] and Guangming Li*[a]

**Abstract:** A practical *para*-C-H functionalization of aniline derivatives has been developed using an *in-situ* generated bulky hypervalent iodinium reagent. *Para*-iodo, bromo, chloro, nitro, trifluormethyl aniline derivatives can be obtained efficiently, in many cases in 10 mins in a transition metal-free manner. Medicinal chemicals or intermediates can be purified without column chromatography or recrystallization, which significantly reduces the waste and simplifies the work-up process.

## Introduction

During the past decades, the *para*-selective C–H functionalization of arenes has attracted considerable attention owing to its utility in the construction of challenging and important structural motifs.[1] The groups of Gaunt[2] and Ritter[3] reported electronic controlled C-H functionalization at the *para*-position of electron-rich arenes (Scheme 1a). Maiti et al. have applied extended template strategies in the remote *para*-C-H olefination of arenes and phenols.[4] The groups of Itami[5] and Nakao[6] reported *para*-C-H borylation and alkylation using designed bulky iridium (I) catalysts and manipulation of steric effects. Zhao and Lan employed a ruthenium-catalyzed σ-activation strategy *via* strongly bound ruthenacycles for electronic activation of remote positions, and developed radical *para*-selective difluoromethylation.[7] Although great progress has been achieved, the scope of *para*-C-H functionalization process however is still limited.

Anilides, ubiquitous in pharmaceuticals and agrochemical compounds have been widely used as templates for C-H functionalization. *para*-Substituted anilides are important building blocks for many pharmaceutical agents, such as SB-245570 (antidepressive),[8] Apixaban (anticoagulant),[9] Rivaroxaban (antithrombotics),[10] and Cilostazol (antiplatelet)[11] (Figure 1). Electronic control strategies[12] and bidentate cyclometalates protocol[13,14] have been widely applied to the *para*-functionalization of 8-aminoquinolines (Scheme 1b).

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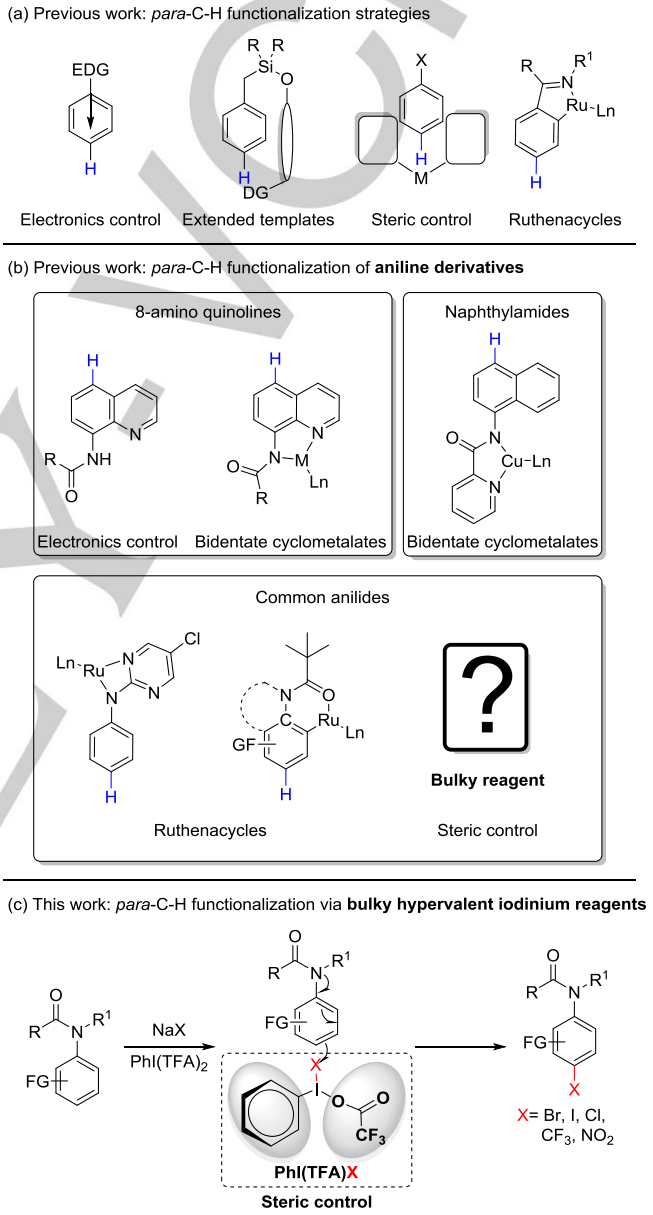



**Scheme 1.** Previous reports on *para*-selective catalytic C-H functionalization in the context of this work.

Coordinating activation strategy *via* bidentate cyclometalates has been utilized by Weng et al. in the *para*-C-H functionalization of naphthylamides.[15] However, owing to the lack of an *ortho* sterically hindering group, control of the regioselectivity for *para*-functionalization of common aniline derivatives is difficult, and only a few examples have been

reported.[12d,16] Consequently, a general protocol to install various *para*-substituents on anilides remains highly desirable. Recently, a ruthenium-catalyzed σ-activation strategy has been applied to *para*-selective alkylation and difluoromethylation of aniline derivatives by Frost's group[17] and Zhao and Lan et al.[18] Despite these progresses and works on C5-functionalization of 8-acylamino quinolines,[19] a general transition-metal-free[20] *para*-functionalziation of aniline derivatives with reduced toxicity has scarcely been reported. Herein, we disclose a general steric control strategy employing *in-situ* generated bulky hypervalent iodinium reagents[21] for the *para*-selective C-H functionalization of anilides to form C-X (X= Cl, Br, I), C-N or C-C bonds. The protocol uses readily available reagents in an environmentally benign solvent and proceeds in a transition-metal-free manner (Scheme 1c).[22] Medicinally related compounds can be obtained with a simple work-up procedure.

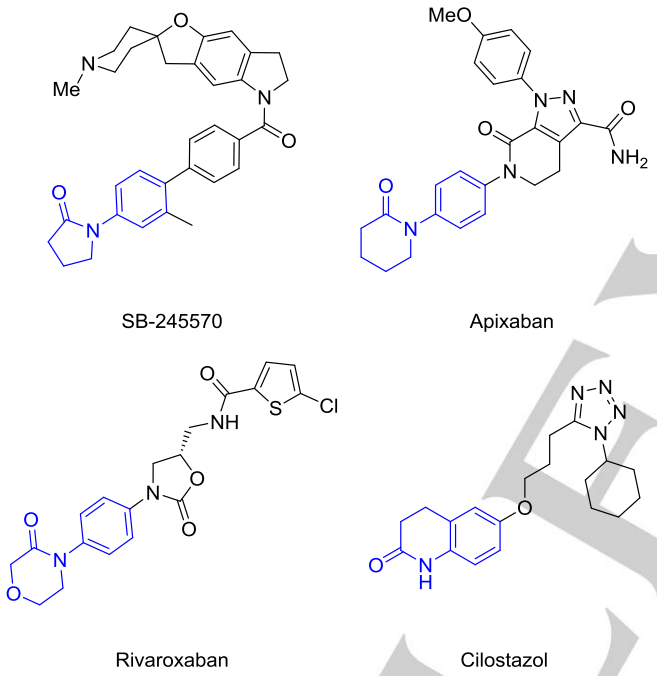
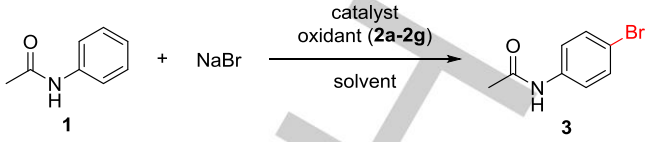



**Figure 1.** Representative bioactive *para*-substituted anilines.

## Results and Discussion

We selected a halogenation reaction for optimization experiments and commenced our studies with the *para*-halogenation of *N*-phenylacetamide with NaBr, employing various hypervalent iodinium reagents and other oxidants (Table 1, entries 1-7). In our hypothesis for the reaction, we envisioned that the hypervalent iodium reagent would afford the active species PhI(TFA)X (Scheme 1c) *via* ligand exchange and phenyliodo bis(trifluoroacetate) (PhI(TFA)$_2$) (**2g**) was reported to faciliate the process with a fast reaction rate.[21] Indeed, PhI(TFA)$_2$ (**2g**) exhibited the best efficiency among various hypervalent iodium reagents, producing **3** in 74% yield (Table 1,

**Table 1.** Optimization of *para*-bromination conditions.[a]

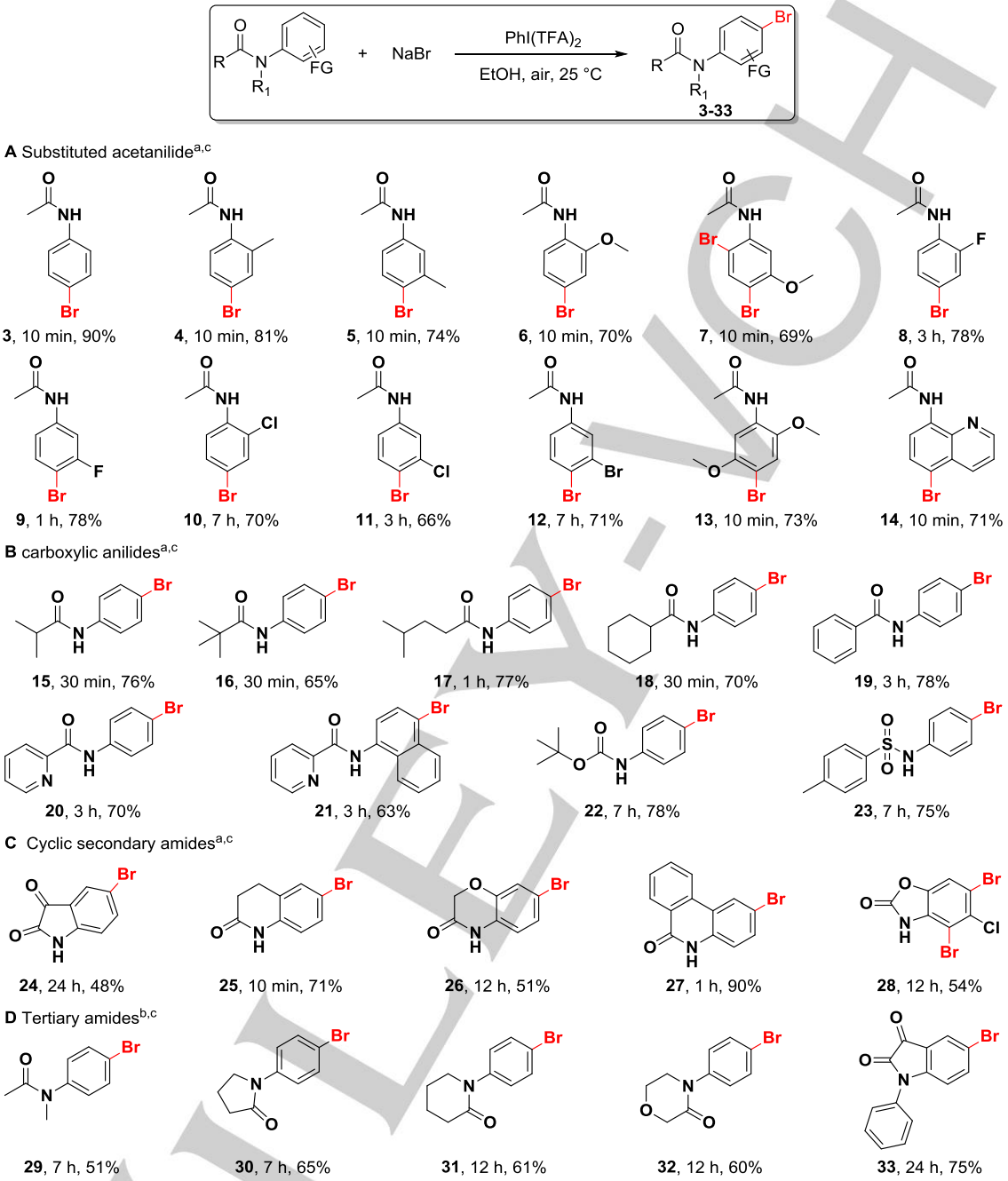



1 3

| Entry | Catalyst | Oxidant | Time | Yield [%][b] |
|---|---|---|---|---|
| 1 | $FeCl_3$ | $PhI(OAc)_2$ (**2a**) | 7 h | 30 |
| 2 | $FeCl_3$ | $PhI(OPiv)_2$ (**2b**) | 7 h | 35 |
| 3 | $FeCl_3$ | $PhI(OCOPh)_2$ (**2c**) | 7 h | 40 |
| 4 | $FeCl_3$ | DMP (**2d**) | 7 h | 32 |
| 5 | $FeCl_3$ | $Na_2S_2O_8$ (**2e**) | 7 h | trace |
| 6 | $FeCl_3$ | $K_2S_2O_8$ (**2f**) | 7 h | trace |
| 7 | $FeCl_3$ | $PhI(TFA)_2$ (**2g**) | 7 h | 74 |
| 8 | $FeCl_3$ | $PhI(TFA)_2$ (**2g**) | 7 h | 72[c] |
| 9 | $FeBr_3$ | $PhI(TFA)_2$ (**2g**) | 7 h | 61 |
| 10 | $CuCl_2$ | $PhI(TFA)_2$ (**2g**) | 7 h | 80 |
| 11 | none | $PhI(TFA)_2$ (**2g**) | 7 h | 80 |
| 12 | none | $PhI(TFA)_2$ (**2g**) | 7 h | 70[d] |
| 13 | none | $PhI(TFA)_2$ (**2g**) | 7 h | 89[e] |
| 14 | none | $PhI(TFA)_2$ (**2g**) | 2 h | 90[e] |
| 15 | none | $PhI(TFA)_2$ (**2g**) | 10 min | 90[e] |

[a] Unless otherwise specified, the reactions were carried out in the presence of **1** (0.2 mmol), NaBr (2 equiv), oxidant (1.5 equiv), catalyst (10 mol%), and MeOH (2 mL) at 25 °C under air. [b] Isolated yield. [c] 3 equiv $PhI(TFA)_2$ was added. [d] MeCN instead of MeOH. [e] EtOH instead of MeOH. DMP = Dess-Martin periodinane.

entry 7 vs entries 1-3). $Na_2S_2O_8$ and $K_2S_2O_8$ (Table 1, entries 5-6), which have been commonly used in C5-functionalization of 8-acylamino quinolines,[13a-e,14c-d] delivered no desired products. Moreover, the reaction failed in the absence of an oxidant, indicating that the hypervalent iodinium reagent is indispensable and crucial in the process. Increasing the amount of oxidants didn't elevate the reaction efficiency (Table 1, entry 8). A series of metal salts as catalysts were subjected to the halogenation conditions and showed no significant improvement in reaction efficiency (Table 1, entries 9-10; for details, see SI Table S1, entries 10-17). With these preliminary results (Scheme 1b), we speculated that the catalyst may not be necessary, and a catalyst-free reaction indeed was found to proceed smoothly without any loss of reactivity (Table 1, entries 9-10 *vs* entry 11). Thus, the reaction could not be an electrophilic aromatic substitution catalyzed by Lewis acids. Further screening of solvents revealed that the environmentally benign solvent, EtOH

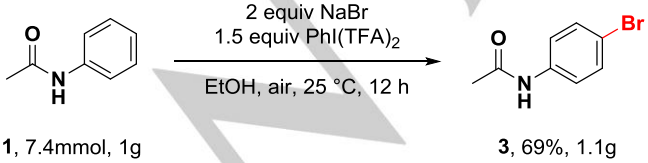



**Scheme 2.** Substrate scope with respect to bromination. [a] Reactions were carried out in the presence of anilides (0.2 mmol), NaBr (2 equiv), $PhI(TFA)_2$ (1.5 equiv), and EtOH (2 mL) at 25 °C under air. [b] Reactions were carried out in the presence of anilides (0.1 mmol), NaBr (4 equiv), $PhI(TFA)_2$ (3 equiv), and EtOH (2 mL) at 25 °C under air. [c] Isolated yield.

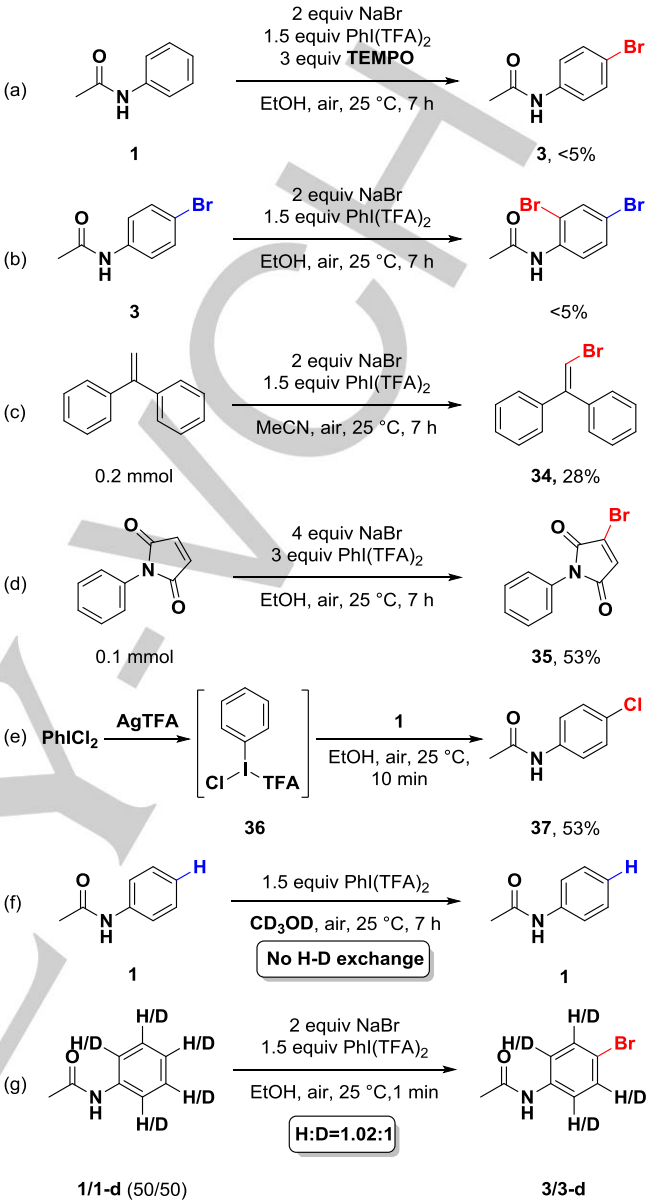
can promote the *para*-bromination producing higher chemical yields (Table 1, entry 13). Surprisingly, reaction is effectively complete within 10 minutes with 90% yield (Table 1, entry 15).

With the optimal conditions in hand, we explored the scope of *para*-C-H bromination with respect to substituted acetanilides (Scheme 2A). The method showed good tolerance to a broad scope of aniline derivatives with different substituents including methyl (**4**, **5**), methoxyl (**6**, **7**), F (**8**, **9**) Cl (**10**, **11**), Br (**12**), and a 2,5-methoxy compound (**13**). Electron-donating groups on the aromatic rings accelerate the reaction and most of the substituents at the *ortho*- or *meta*-position have little effect on the regioselectivity. Interestingly, *m*-methoxyacetanilide under-

goes a dibromination process, generating **7** in 69% yield. This may be attributed to the strong electron donating nature of methoxyl group. When the substrates with strong electron-withdrawing groups, $NO_2$ and CN, in *ortho*-position of aromatic ring were subjected to the reaction, the *para*-bromo products were not obtained. *N*-(quinolin-8-yl)acetamide, which was previously employed in a metal-catalyzed halogenation,[13j] was also viable under the current reaction conditions. A range of carboxylic anilides were examined (Scheme 2B). Aromatic carboxylic anilides require a longer reaction time. *N*-Phenylbenzamide[16i] and *N*-phenylpicolinamide[16k] which have been studied previously, afforded the corresponding products (**19-20**), and a previously reported substrate, *N*-(naphthalen-1-yl)picolinamide[15] was also compatible with these reaction conditions, delivering **21** in a satisfactory yield. In addition to carboxylic anilides, *N*-Boc aniline and *N*-sulfonylaniline also gave novel bromination products (**22-23**).[16i] We continued to explore the versatility of this protocol, examining the *para*-bromination of synthetically useful secondary anilides. As shown in Scheme 2C, a variety of building blocks related to pharmaceutical compounds,[23] such as indoline-2,3-dione, dihydroquinolinone and phenanthridin-6(*5H*)-one, underwent this *para*-selective reaction smoothly, delivering the corresponding *para*-bromo anilides (**24**-**27**) in moderate to good yields. Chlorzoxazone, a muscle relaxant also reacted under these conditions, affording a disubstituted product (**28**). The absence of any need for a catalyst in the reaction suggests that the N-H group was not required for coordination, and so tertiary amides may be accessible to the reaction. Hence, we subjected the normally unreactive *N*-methyl-*N*-phenylacetamide to the reaction (Scheme 2D), and obtained the *para*-brominated product (**29**). This had been reported only rarely in previous research,[16i] and suggests that an unsubstituted N−H group is not a prerequisite for this transformation. Given the importance of *para*-halogenated cyclic tertiary anilides as important precusors for various bioactive and medicinal compounds (Figure 1),[24] we were delighted to observe that the *para*-bromination proceeded with excellent positional selectivity and the purification of corresponding products required no column chromatography or recrystallization (**30-32**).[25] A single substituted brominated product (**33**) was obtained from 1-phenylindoline-2,3-dione, indicating that the fused ring structure in anilides such as oxindole was more likely to promote *para*-bromination than a tertiary cyclic anilide. The bromination of **1** was also successfully performed on a gram scale (7.4 mmol, 1 g) under the same reaction conditions, producing **3** in 69% yield (Scheme 3).

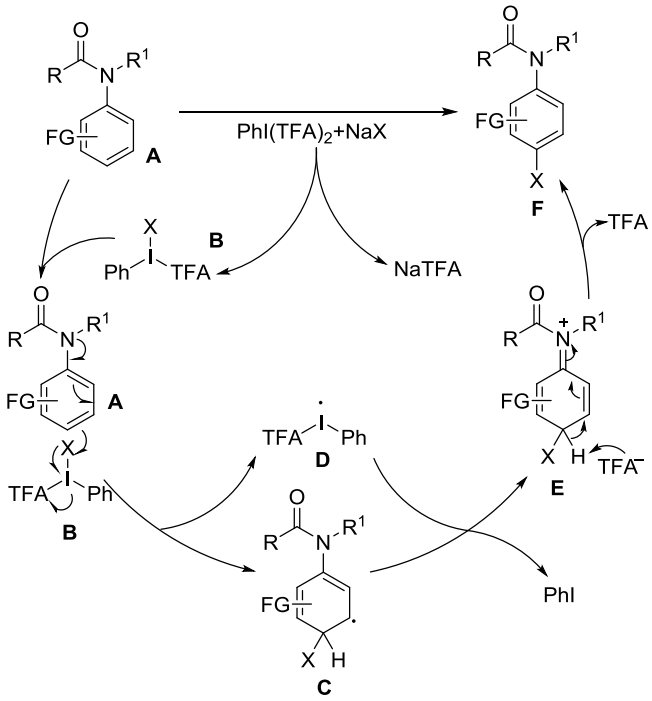



**Scheme 3.** Gram-scale synthesis.



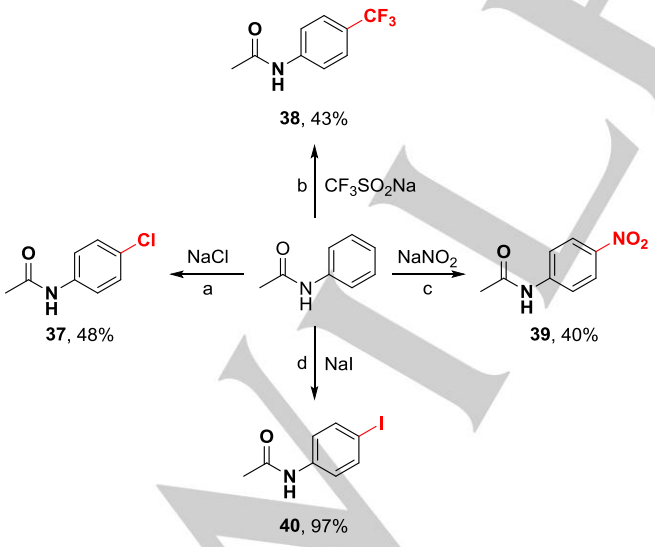

**Scheme 4.** Control Experiments.

To gain insights into the mechanism of the reaction, a series of control experiments were carried out (Scheme 4). The radical scavenger, 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), can readily inhibit the bromination process and allows 95% recovery of the starting materials, implying a single electron transfer (SET) process for the reaction (Scheme 4a). *Ortho*-bromination of compound **3** gave yields of less than 5% (Scheme 4b), indicating that the steric effect with an innate electronic nature could be the key factor governing the control of regioselectivity. The halogen radical was trapped using 1,1-diphenylethylene in the presence of NaBr, and the coupling product (**34**) was obtained in 28% yield (Scheme 4c). A similar radical coupling reaction was observed with 1-phenyl-*1H*-

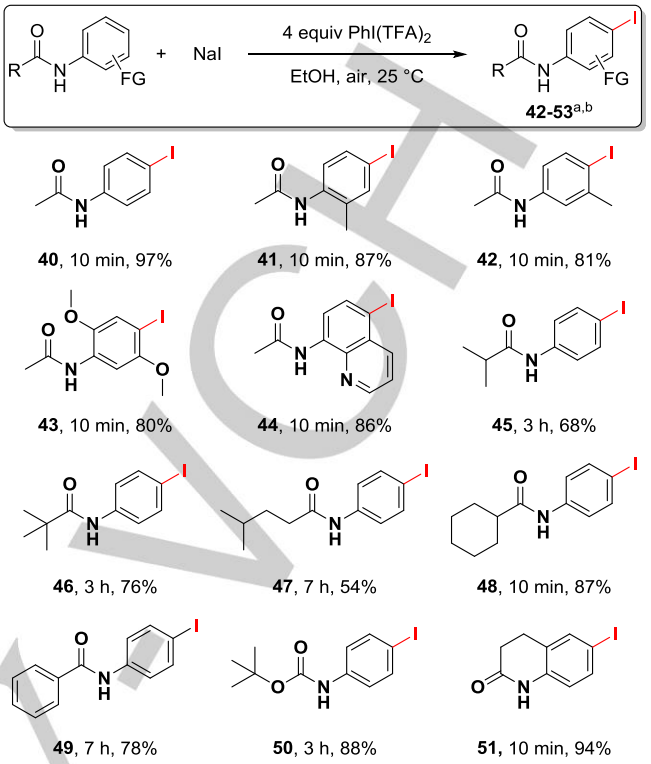



**Scheme 5.** Proposed Mechanism.

pyrrole-2,5-dione, providing a single product (**35**) (Scheme 4d). This compound (**35**) was utilized as conjugate acceptor for bioconjugation,[26] and precursor for synthesis of natural products[27] and electronic communication materials.[28] Interestingly, **35** could be purified without use of chromatography and recrystallization,[25] which further shows the value of this protocol. Further investigation into the origin of the bromo radical and the regioselectivity revealed that the proposed *in situ* generated intermediate (**36**) derived from dichlorophenyl-λ$^3$-iodane and AgTFA readily afforded the *para*-product (**37**) in a reasonable yield (Scheme 4e). Therefore, an *in situ* generated bulky hypervalent iodinium reagent could be responsible for the generation of bromo radical and the outcome in terms of the regioselectivity. In addition, no deuterium was incorporated into the recovered starting material when MeOH-$d_4$, was used as the solvent. This indicates that an irreversible C–H cleavage event occurred during the reaction (Scheme 4f).The kinetic isotope effect factor of 1.02 suggests that the C-H activation is not the rate-determining step (Scheme 4g). After completion of the reaction, iodobenzene was detected and acidity of reaction mixture had increased. Therefore, we rationalized that the intermediate **36** as a bulky halogen source would direct the attack on the *para*-position of anilides in a SET process.




**Scheme 6.** Versatile *para*-C−H functionalization of *N*-phenylacetamide. Conditions: (a) **1** (0.2 mmol), NaCl (2 equiv), PhI(TFA)$_2$ (1.5 equiv), and EtOH (2 mL), air, 25 °C, 1 h; (b) **1** (0.2 mmol), $CF_3SO_2Na$ (2 equiv), PhI(TFA)$_2$ (1.5 equiv), and MeCN (2 mL), air, 25 °C, 24 h; (c) **1** (0.1 mmol), $NaNO_2$ (4 equiv), PhI(TFA)$_2$ (3 equiv), and MeCN (2 mL), air, 25 °C, 7 h; (d) **1** (0.1 mmol), NaI (4 equiv), PhI(TFA)$_2$ (3 equiv), and EtOH (2 mL), air, 25 °C, 10 min.




**Scheme 7.** Substrate scope with respect to Iodination. [a] Reactions were carried out in the presence of anilides (0.1 mmol), NaI (4 equiv), PhI(TFA)$_2$ (3 equiv), and EtOH (2 mL) at 25 °C under air. [b] Isolated yield.

With this bulky hypervalent iodium reagent protocol formed *in situ*, other moieties, which previously were reported to be inaccessible to *para* C-H functionalization of anilides, can be successfully introduced to the *para* position. *Para*-chlorination and *para*-nitration were examined by reacting *N*-phenylacetamide with NaCl and $NaNO_2$ (Scheme 6), delivering **37** and **39**. *Para*-trifluoromethylation, which was mainly investigated on 8-amino quinoline derivatives,[12c] can be

successfuly achieved on anilides. These results not only demonstrate an easy route to *para*-substituted aniline derivatives under relatively mild conditions, but also support our proposed mechanism.

We found that iodinated products, which are widely used as coupling reagents, can also be obtained through this reaction (Scheme 7) and various carboxylic anilides can efficiently complete the *para*-iodination reaction. Interestingly, all iodoanilides can be obtained without chromatography or recrystallization. The heterocylic amide, *N*-(quinolin-8-yl)acetamide, can also participate in the reaction, affording **44** in 86% yield. *N*-Boc-*para*-iodo-anilides (**50**) can be readily accessed satisfactory yields by this protocol. Furthermore, a cyclic secondary amide was also tolerated in the reaction system (**51**).

## Conclusions

In summary, we have developed a general sterically controlled strategy *via in-situ* generated bulky hypervalent iodinium reagents to access various *para*-substituted aniline derivatives. The protocol can be performed by using a combination of readily available reagents and environmentally benign solvents in a manner free of transition metals. A variety of anilides, including challenging tertiary amides undergo this reaction smoothly. Products related to medicinal chemicals can be obtained without purification by column chromatography or recrystallization. A mechanistic investigation revealed that the *in situ* generated bulky hypervalent iodinium reagents together with the innate electronic nature of anilines work to control the regioselectivity.

## Experimental Section

**General information**

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. The reaction product was isolated by column chromatography on a silica gel (236–400 mesh) column using petroleum ether (PE) with a boiling range from 60 to 90 °C and EtOAc. $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectra were recorded on 400, 101, 376 MHz NMR spectrometers using DMSO or $CDCl_3$ as solvent. In addition, $^{1}H$ and $^{13}C$ NMR spectra used tetramethylsilane as the internal standard and the $^{19}F$ NMR spectra used trifluoroacetic acid as the internal standard. HRMS were made by means of ESI. Unless otherwise noted, all reagents were weighed and handled in air, and all reactions were carried out in air.

**General experimental procedure for the synthesis of compounds 3-7, and 13-14**

To a mixture of aniline derivatives (0.2 mmol, 1 equiv) and NaBr (0.4 mmol, 2 equiv) was added a solution in EtOH of $PhI(TFA)_2$ (0.3 mmol, 1.5 equiv) (2 mL) and the reaction mixture was stirred at 25 °C. After completion of reaction, the solvent was evaporated under reduced pressure and the residue was diluted with EtOAc, and washed with brine. The water phase was extracted with EtOAc (2 × 30 mL) and the combined organic phase was dried over $Na_2SO_4$. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel to give the pure product.

**General experimental procedure for the synthesis of compounds 8-12 and 15-27**

To a mixture of aniline derivatives (0.2 mmol, 1 equiv), NaBr (0.4 mmol, 2 equiv), and $PhI(TFA)_2$ (0.3 mmol, 1.5 equiv) in EtOH (2 mL) was added and reaction mixture was stirred at 25 °C. After completion of reaction, the solvent was evaporated under reduced pressure and the residue was diluted with EtOAc, and washed with brine. The aqueous phase was extracted with EtOAc (2 × 30 mL) and the combined organic phase was dried over $Na_2SO_4$. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel to give the pure product.

**Experimental procedure for the synthesis of 28**

Chlorzoxazone (0.2 mmol, 1 equiv) and $PhI(TFA)_2$ (0.3 mmol, 1.5 equiv) were dissolved in EtOH (2 mL) and stirred for 5 min. NaBr (0.4 mmol, 2 equiv) was added and reaction mixture was stirred at 25 °C for 12 h. After completion of reaction, the solvent was evaporated under reduced pressure and the residue was diluted with EtOAc, and washed with brine. The aqueous phase was extracted with EtOAc (2 × 30 mL) and the combined organic phase was dried over $Na_2SO_4$. The solvent was evaporated *in vacuo* and the residue was washed with petroleum ether, and then the product was obtained by filtration.

**General experimental procedure for the synthesis of compounds 29-33**

To a mixture of aniline derivatives (0.1 mmol, 1 equiv), NaBr (0.4 mmol, 4 equiv) was added a solution in EtOH of $PhI(TFA)_2$ (0.3 mmol, 3 equiv) (2 mL) and reaction mixture was stirred at 25 °C. After completion of reaction, the solvent was evaporated under reduced pressure and the residue was diluted with EtOAc, and washed with brine. The aqueous phase was extracted with EtOAc (2 × 30 mL) and the combined organic phase was dried over $Na_2SO_4$. The solvent was evaporated *in vacuo*, the residue was washed with petroleum ether, and the product was obtained by filtration.

**Experimental procedure for the synthesis of 37**

To a mixture of *N*-phenylacetamide (0.2 mmol, 1 equiv), NaCl (0.4 mmol, 2 equiv) was added a solution in EtOH of $PhI(TFA)_2$ (0.3 mmol, 1.5 equiv) (2 mL) and reaction mixture was stirred at 25 °C. After completion of reaction, the solvent was evaporated under reduced pressure and the residue was diluted with EtOAc, and washed with brine. The aqueous phase was extracted with EtOAc (2 × 30 mL) and the combined organic phase was dried over $Na_2SO_4$. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel to give the pure product.

**Experimental procedure for the synthesis of 38**

To a mixture of *N*-phenylacetamide (0.2 mmol, 1 equiv), $CF_3SO_2Na$ (0.4 mmol, 2 equiv) was added a solution in MeCN of $PhI(TFA)_2$ (0.3 mmol, 1.5 equiv) (2 mL) and the reaction mixture was stirred at 25 °C. After completion of reaction, the solvent was evaporated under reduced pressure and the residue was diluted with EtOAc, and washed with brine. The aqueous phase was extracted with EtOAc (2 × 30 mL) and the combined organic phase was dried over $Na_2SO_4$. The solvent was

evaporated *in vacuo* and the residue was purified by column chromatography on silica gel to give the pure product.

**Experimental procedure for the synthesis of 39**

To a mixture of *N*-phenylacetamide (0.2 mmol, 1 equiv), $NaNO_2$ (0.4 mmol, 4 equiv) was added a solution in MeCN of $PhI(TFA)_2$ (0.3 mmol, 3 equiv) (2 mL) and the reaction mixture was stirred at 25 °C. After completion of reaction, the solvent was evaporated under reduced pressure and the residue was diluted with EtOAc, and washed with brine. The water phase was extracted with EtOAc (2 × 30 mL) and the combined organic phase was dried over $Na_2SO_4$. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel to give the pure product.

**General experimental procedure for the synthesis of compounds 40-51**

To a mixture of aniline derivatives (0.1 mmol, 1 equiv), NaI (0.4 mmol, 4 equiv) was added a solution in EtOH of $PhI(TFA)_2$ (0.3 mmol, 3 equiv) (2 mL) and reaction mixture was stirred at 25 °C. After completion of reaction, the solvent was evaporated under reduced pressure and the residue was diluted with EtOAc, and washed with brine. The water phase was extracted with EtOAc (2 × 30 mL) and the combined organic phase was dried over $Na_2SO_4$. The solvent was evaporated *in vacuo* and the residue was washed with petroleum ether, and then the product was obtained by filtration.

**Gram-scale reaction**

To a mixture of *N*-phenylacetamide (7.4 mmol, 1 equiv), NaBr (14.8 mmol, 2 equiv), and $PhI(TFA)_2$ (11.1 mmol, 1.5 equiv) was added EtOH (74 mL) and reaction mixture was stirred at 25 °C. After completion of reaction, the solvent was evaporated under reduced pressure and the residue was diluted with EtOAc, and washed with brine. The water phase was extracted with EtOAc (3 × 30 mL) and the combined organic phase was dried over $Na_2SO_4$. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel to give the pure product.

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**Conflicts of interest**

There are no conflicts to declare.

**Keywords:** arenes • C-H activation • hypervalent iodinium reagents • reaction mechanisms • steric control

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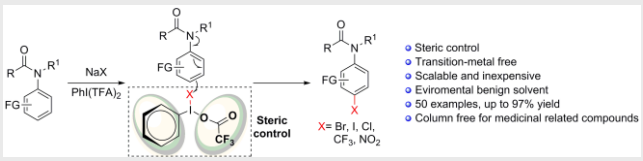


A general *para*-selective C-H functionalization was achieved via a steric control strategy. *Para*-iodo, bromo, chloro, nitro, and trifluormethyl aniline derivatives can be efficiently accessed *via in-situ* generated, bulky hypervalent iodinium reagents in as little as 10 min. Medicinal chemicals or intermediates can be purified without column chromatography or recrystallization, which significantly reduces the waste and simplifies the work-up.

**C-H functionalization***

*Chao Tian, Xu Yao, Weizhe Ji, Qian Wang, Associate Prof. Dr. Guanghui An* and Prof. Dr. Guangming Li**

***Page No. – Page No.***

**A *para*-C-H functionalization of aniline derivatives via *in-situ* generated bulky hypervalent iodinium reagents**