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Pd(II)-catalyzed *meta*-C–H bromination and chlorination of aniline and benzoic acid derivatives†

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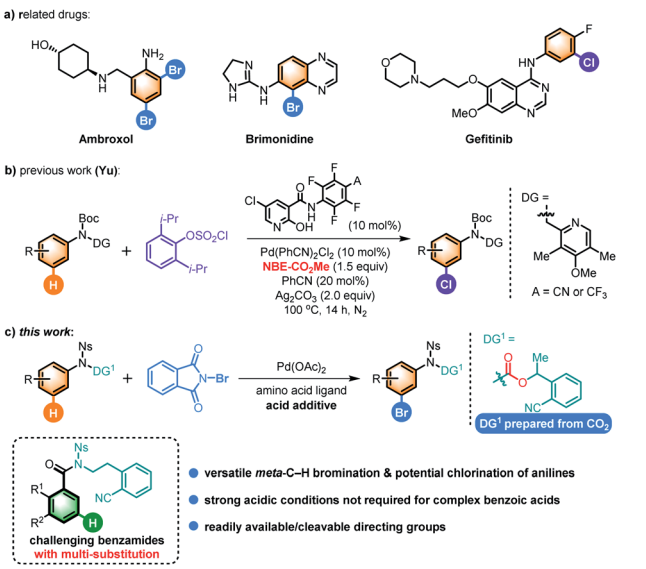
The classic electrophilic bromination leads to *ortho*- and *para*-bromination of anilines due to their electron-rich properties. Herein we report the development of an unprecedented Pd-catalyzed *meta*-C–H bromination of aniline derivatives using commercially available *N*-bromophthalimide (NBP), which overcomes the competing *ortho*/*para*-selectivity of electrophilic bromination of anilines. The addition of acid additives is crucial for the success of this reaction. A broad range of substrates with various substitution patterns can be tolerated in this reaction. Moreover, benzoic acid derivatives bearing complex substitution patterns are also viable with this mild bromination reaction, and *meta*-C–H chlorination is also feasible under similar reaction conditions. The ease of the directing group removal and subsequent diverse transformations of the brominated products demonstrate the application potential of this method and promise new opportunities for drug discovery.

Introduction

Aromatic bromides represent a class of highly important synthetic precursors in organic synthesis,[1] especially in their use for powerful cross-coupling reactions,[2] which has led to the pursuit of numerous methods for their synthesis.[1a–c] Moreover, many brominated aromatic derivatives, especially those of anilines, are often found as target molecules in pharmaceuticals (Scheme 1a), as well as in functional molecules and natural products.[1a,d] Classic methods for synthesis of brominated arenes, such as the Friedel–Crafts-type electrophilic bromination, often suffer from poor regioselectivity, harsh reaction conditions, long reaction time, tedious reaction procedures, or limited substrate scope.[1a,3] Moreover, although the fundamental reactivity pattern of anilines can provide predictable selectivity according to the electron-density distribution in the substrate and steric properties of the substituents in simple cases, it is difficult to access isomers that cannot be anticipated based on their fundamental reactivity. In addition, when there is more than one substituent with varied electronic or steric properties, the competition between these substituents in such complex systems may lead to a mixture of products that are difficult to isolate. Consequently, direct C–H bromination of anilines that overcomes the inherent site-selectivity, which is also applicable for anilines with multiple substituents, is extremely useful for producing valuable complex substituted aniline derivatives in a straightforward and unconventional manner.

Recently, transition metal-catalyzed C–H activation has emerged as one of the most promising methods for the synthesis of *ortho*- and *para*-C–H halogenated anilines.[1b,c,4,5] Notably, very limited, though elegant, protocols for producing



Scheme 1 Direct *meta*-C–H halogenation of anilines and benzoic acids.

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meta-C–H halogenated arenes have also been developed, mainly through the formation of cycloruthenated complex intermediates by Greaney,[6a] Huang,[6b] Ackermann,[6c,f] and others,[6] as well as by using a pyridyl-based *meta*-directing group (DG) with a Pd-catalyst by Yu[7a,b] and Dai[7c] groups. Recently, we have also developed *meta*-C–H iodination of hydrocinnamic acid *via* a formal metathesis reaction.[8a] However, the *meta*-C–H halogenation of anilines is still a formidable challenge since the conventional highly reactive sites are *ortho*/*para* positions. Although there have been several significant strategies disclosed for *meta*-C–H functionalization of arenes[9–28] and a few of them have been applied for aniline derivatives by the groups of Gaunt,[10] Yu,[11] Ackermann,[12] Phipps,[13a] Nakao,[14] and others[15] as well as our group,[16] to date, only a single[29] report on *meta*-C–H halogenation (*i.e.* chlorination) of aniline derivatives has been disclosed by the Yu group using a substituted pyridine as the DG for the initial *ortho*-C–H activation and modified norbornene as the mediator for subsequent *meta*-C–H chlorination (Scheme 1b).[11b] However, some substrates such as the simple aniline without a substituent did not work. Moreover, it is often observed in cross-coupling reactions that bromoarenes are more reactive than their chloroarene counterparts. Notably, the bromine atom generally forms stronger halogen bonding than chlorine, which is beneficial for drug discovery.[1d] Therefore, the development of a practical and complementary *meta*-C–H bromination reaction of anilines would be highly desirable.[30]

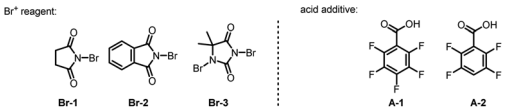
Herein, we disclose the first Pd(II)-catalyzed *meta*-C–H bromination of aniline derivatives using a readily cleavable nitrile-based DG, overcoming the competing *ortho*/*para*-selectivity of anilines (Scheme 1c). Moreover, this method can be modified to be compatible with benzoic acid derivatives[18f,20b,28] bearing complex substitution patterns, whose bromination *via* conventional methods generally requires harsh reaction conditions such as the addition of strong acid or high reaction temperature. In addition, *meta*-C–H chlorination was also found to be feasible. Finally, diverse transformations of the brominated anilines demonstrate the versatility of our methods and promise new opportunities for drug discovery.[1d,31]

Results and discussion

Our investigation was initiated by treating carbamate **1a**, which could be synthesized in one step from aniline, CO_2 and 2-(1-bromoethyl)benzonitrile under basic conditions developed in

Table 1 Optimization of reaction conditions[a]

Entry	Ligand	Br^+	Additive (equiv.)	Yield [%] (mono/di)	*para*-Br side product
1	*N*-Ac–Gly–OH	**Br-1**	—	23% (11/1)	3%
2	*N*-Ac–Gly–OH	**Br-2**	—	28% (8.3/1)	3%
3	*N*-Ac–Gly–OH	**Br-3**	—	—	8%
4	*N*-Ac–Gly–OH	**Br-2**	HOAc (0.5)	36% (6.2/1)	4%
5	*N*-Ac–Gly–OH	**Br-2**	TFA (0.5)	46% (2.8/1)	3%
6	*N*-Ac–Gly–OH	**Br-2**	PivOH (0.5)	40% (7.0/1)	4%
7	*N*-Ac–Gly–OH	**Br-2**	**A-1** (0.5)	50% (3.1/1)	2%
8	*N*-Ac–Gly–OH	**Br-2**	**A-2** (0.5)	50% (3.1/1)	2%
9	*N*-Ac–Gly–OH	**Br-2**	**A-1** (1)	66% (3.7/1)	2%
10	*N*-Ac–Gly–OH	**Br-2**	**A-1** (1.5)	70% (4.0/1)	2%
11	*N*-Ac–Gly–OH	**Br-2**	**A-1** (2)	75% (3.4/1)	3%
12	*N*-Ac–Gly–OH	**Br-2**	**A-1** (5)	89% (3.2/1)	4%
13	*N*-Ac–Gly–OH	**Br-2**	**A-1** (5)	N.D[b]	24%
14	*N*-Ac–β-Ala–OH	**Br-2**	**A-1** (5)	93% (2.2/1)	4%
15	*N*-TFA–Gly–OH	**Br-2**	**A-1** (5)	94% (2.8/1)	4%
16	*N*-TFA–β-Ala–OH	**Br-2**	**A-1** (5)	92% (2.4/1)	4%
17	***N*-Tf–β-Ala–OH**	**Br-2**	**A-1 (5)**	**93% (2.2/1)**[c]	**3%**
18	***N*-Tf–β-Ala–OH**	**Br-2**	**A-2 (5)**	**94% (1.8/1)**	3%
19	*N*-Tf–β-Ala–OH	**Br-2**	**A-2** (5)	90% (1/1.1)[c,d]	2%
20	*N*-Tf–β-Ala–OH	**Br-2**	**A-1** (5)	86% (4.1/1)[c,e]	2%
21	*N*-Tf–β-Ala–OH	**Br-2**	**A-1** (5)	89% (4.6/1)[c,f]	2%



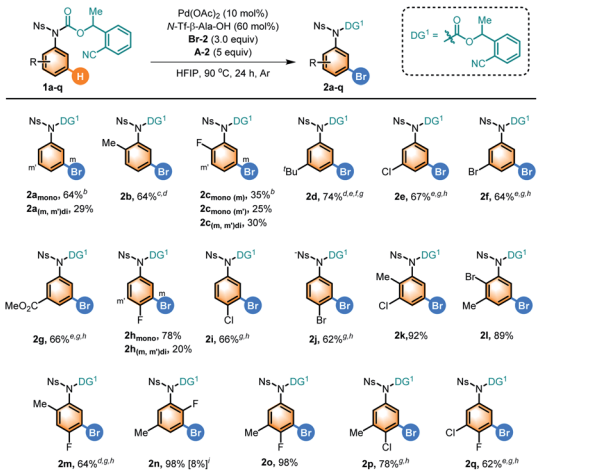
[a] Reaction conditions: **1a** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), ligand (60 mol%), Br^+ (03 mmol), additive, HFIP (1 mL), 90 °C, 24 h, Ar. Yield was determined by ^1H NMR with CH_2Br_2 as the internal standard. [b] Without $Pd(OAc)_2$. [c] Isolated yield. [d] **Br-2** (0.4 mmol), 100 °C, 48 h. [e] **Br-2** (0.2 mmol). [f] 12 h. N.D.: not detected.

our previous study on *meta*-C–H activation of anilines assisted by a nitrile-based DG,[16] with various brominating agents using palladium acetate as the catalyst and *N*-protected amino acid (*N*-Ac–Gly–OH) as the ligands in HFIP at 90 °C under argon. Selected optimization results are summarized in Table 1. To our delight, the reactions with commercially available *N*-bromosuccinimide (NBS, **Br-1**) or *N*-bromophthalimide (NBP, **Br-2**) led to *meta*-C–H brominated aniline **2a** in 23% and 28% combined yield of mono- and di-brominated anilines, respectively, with a trace of the *para*-C–H brominated aniline side product (entries 1 and 2), whereas 1,3-dibromo-5,5-dimethyl-imidazolidine-2,4-dione (**Br-3**) was ineffective and led to the formation of *para*-C–H brominated aniline (entry 3). To further improve the yield, acid additives such as acetic acid (HOAc), CF_3COOH (TFA) and pivalic acid (PivOH) were utilized and could improve the results evidently (entries 4–6). We were then pleased to find that addition of half an equivalent of pentafluorobenzoic acid (**A-1**) increased the yield of **2a** notably (entry 7). Tetrafluorobenzoic acid **A-2** was also used, and the same result was obtained (entry 8). Much to our delight, significant improvements in the yield were observed when the loading of **A-1** was increased gradually to five equivalents (entries 9–12). These low-cost electron-deficient polyfluorobenzoic acid additives might act as the activator of brominating reagents,[1a] while the costly silver carbonate activator was employed in the previous *meta*-C–H chlorination of aniline derivatives.[11b] It should be mentioned that polyfluorobenzoic acid might also act as a ligand to increase the electrophilicity and thus the reactivity of the Pd(II) catalyst.

Notably, without the addition of $Pd(OAc)_2$, not any *meta*-bromination products could be detected, whereas the *para*-bromination side product generated from the Friedel–Crafts-type electrophilic bromination was detected as the major product (entry 13). Moreover, only slight improvements in the desired products' overall yield were achieved by switching the *N*-protected amino acid ligands (entries 14–17). It should be mentioned that the use of 60% ligand is important for effective binding to the Pd center possibly due to the presence of excess of the acid additive. The optimal results that led to the highest catalytic turnover of the Pd catalyst were obtained using the *N*-Tf–β-Ala–OH ligand with **A-2** as the additive (entry 18). In addition, the proportion of the di-brominated product could be improved by adding 4 equivalents of **Br-2** and running the reaction for 48 hours at 100 °C (entry 19). Of note, the mono/di ratio could be increased greatly by either decreasing the loading of **Br-2** (entry 20) or shortening the reaction time (entry 21), though the overall yields were slightly lower (see the ESI† for more reaction conditions).

With the optimized reaction conditions in hand, we examined the scope of this *meta*-selective C–H bromination of anilines with a variety of substrates (Table 2). Substrates with methyl and fluoro groups at the *ortho*-position were well tolerated (**2b** and **2c**). The reactions also proceeded smoothly with various electron-donating and electron-withdrawing substituents at the *meta*-position (**2d–2g**). *para*-Substituted aniline carbamates bearing fluoro, chloro or bromo groups were also viable to deliver the desired bromination products in moderate

Table 2 The scope of *meta*-C–H bromination of aniline derivatives[a]

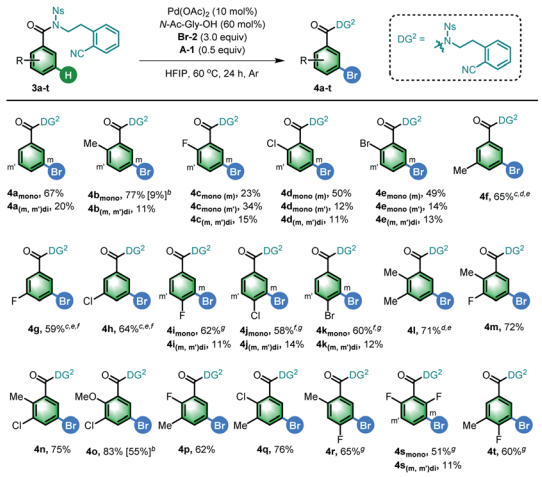


[a] Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), *N*-Tf–β-Ala–OH (0.06 mmol), **Br-2** (0.3 mmol), **A-2** (0.5 mmol), HFIP (1 mL), 24 h, 90 °C, Ar. Isolated yields. [b] **A-1** (0.5 mmol) instead of **A-2**. [c] *N*-TFA–β-Ala–OH (0.06 mmol) instead of *N*-Tf–β-Ala–OH. [d] HOAc (0.5 mmol) instead of **A-2**. [e] *N*-TFA–Gly–OH (0.06 mmol) instead of *N*-Tf–β-Ala–OH. [f] 60 °C. [g] 48 h. [h] 100 °C. [i] Yield in the square brackets is that of the *para*-brominated product from the reaction without using $Pd(OAc)_2$.

to good yields (**2h–2j**). Notably, the method was also applicable for several di-substituted anilines, providing a straightforward and unconventional method to access highly substituted aniline derivatives (**2k–2q**). Importantly, the direct generation of several di- and tri-halogenated anilines could be very interesting for drug discovery such as by providing more halogen bonding possibility (**2c**, **2e**, **2f**, and **2h–2q**).[1d] It should also be mentioned that the site-selectivity of the reaction was excellent, and other halogenation isomers were in trace amounts. Moreover, no C–H brominated products could be delivered for substituted anilines (**1b–1q**) under the optimized conditions without the Pd catalyst, except that substrate **1n** gave 8% of the *para*-brominated product.

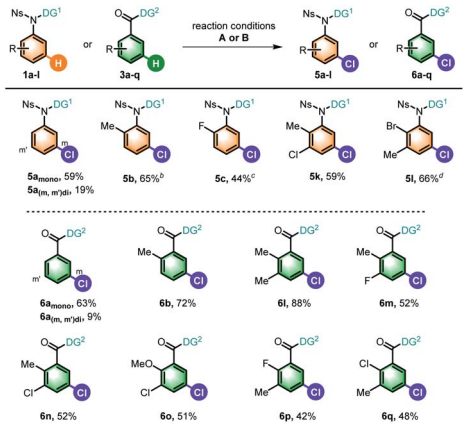
Following the successful bromination of aniline scaffolds, we moved on to investigate this method with benzoic acid derivatives attached with a nitrile-based DG that has been developed in our previous report on *meta*-C–H olefination of benzoic acids (Table 3).[20b] It should be noted that classic methods for bromination of benzoic acids often require harsh reaction conditions such as the addition of strong acid or high reaction temperature. After extensive modification of the reaction conditions (see ESI Table S1†), it was found that most of these benzoic acids afforded the best yields of the desired products with **A-1** as the optimal acid additive and *N*-Ac–Gly–OH as the ligand. Notably, no/trace product was obtained without using $Pd(OAc)_2$ for model substrate **3a** and most of the substrates, indicating that a Friedel–Crafts type bromination could hardly occur under the mild conditions. It was observed that substrates bearing both methyl and halogen groups at the *ortho*- and *para*-positions were well tolerated (**4b–4h**). *para*-Halogenated benzoic acids were also viable to deliver the

Table 3 The scope of *meta*-C–H bromination of benzoic acid derivatives[a]



[a] Reaction conditions: **3** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), *N*-Ac–Gly–OH (0.06 mmol), **Br-2** (0.3 mmol), **A-1** (0.05 mmol), HFIP (1 mL), 24 h, 60 °C, Ar. Isolated yields. No/trace product without $Pd(OAc)_2$, except **4b** and **4o**. [b] The yields in the square brackets are the ^1H NMR yields of reactions without using $Pd(OAc)_2$. [c] Chloranil (0.1 mmol) was added instead of **A-1**. [d] 16 h. [e] Without adding **A-1**. [f] 48 h. [g] *N*-Formyl–Gly–OH (0.06 mmol) instead of *N*-Ac–Gly–OH.

Table 4 The *meta*-C–H chlorination of aniline and benzoic acid derivatives[a]

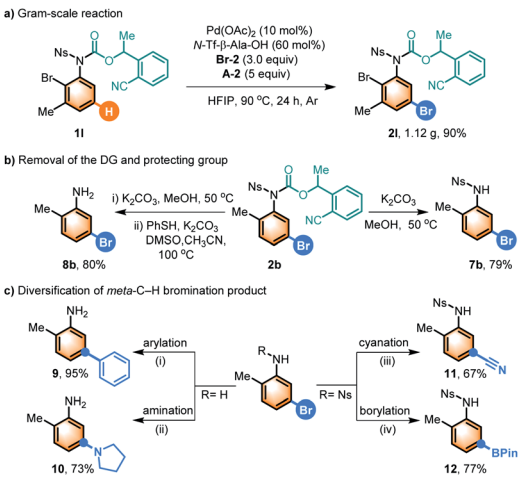


[a] Reaction conditions A: **1** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), *N*-TFA–β-Ala–OH (0.06 mmol), DCH (0.3 mmol), **A-2** (0.5 mmol), HFIP (1 mL), 48 h, 110 °C, Ar. Isolated yields. Reaction conditions B: **3** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), *N*-Ac–Gly–OH (0.06 mmol), DCH (0.3 mmol), **A-1** (0.1 mmol), HFIP (1 mL), 48 h, 90 °C, Ar. Isolated yields. [b] HOAc (0.5 mmol) instead of **A-2**. [c] *N*-TFA–Gly–OH (0.06 mmol) instead of *N*-TFA–β-Ala–OH. [d] *N*-Tf–β-Ala–OH (0.06 mmol) instead of *N*-TFA–β-Ala–OH. DCH = 1,3-dichloro-5,5-dimethylhydantoin.

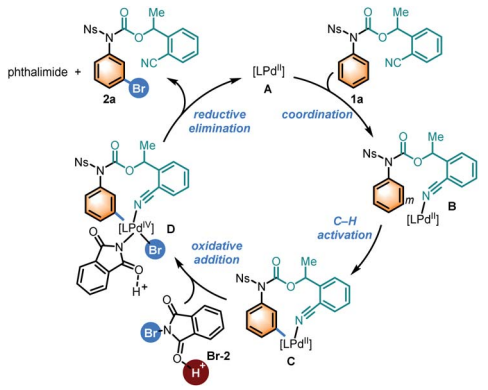
desired bromination products in good yields (**4i–4k**). Notably, this method was also suitable for *meta*-C–H brominating several challenging di-substituted benzoic acids (**4l–4t**), which may be useful for drug discovery. In these reactions, valuable products that may require several steps to synthesize by conventional methods were afforded in a straightforward and operationally simple manner. It should also be mentioned that the site-selectivity of this bromination was excellent, and only 9% of $\mathbf{4b_{mono}}$ and 55% of **4o** could be produced without $Pd(OAc)_2$, probably due to a higher tendency for **3b** and **3o** to undergo a Friedel–Crafts type reaction.

Since *meta*-chlorinated arenes are often found as important core structures in numerous drug molecules, we continued to explore the generality of chlorination of aniline and benzoic acid derivatives based on the optimized conditions for the above bromination reactions by using 1,3-dichloro-5,5-dimethylhydantoin (DCH) as the chlorinating reagent (Table 4), which led to limited scope of substrates with the current reaction conditions. The model aniline substrate afforded good overall yield of desired products (**5a**), and the mono-chlorinated product could be used as the substrate, for example, **2e** in Table 2, demonstrating the possibility of sequential *meta*-chlorination and bromination. The *ortho*-substituted anilines gave the *meta*-chlorinated products in moderate yields (**5b**, **5c**). Notably, di-substituted anilines were also viable in this reaction (**5k** and **5l**). We also selected benzoic acids as the testing compounds, and the scope is slightly better. Besides the simple substrate (**6a**), both mono (**6b**) and several di-substituted substrates (**6l–6q**) were viable substrates, giving moderate to good yields of desired products. It should be noted that no desired chlorinated product could be obtained for these substrates without $Pd(OAc)_2$. In addition, only low yield of iodinated products could be obtained with our aniline substrates using *N*-iodosuccinimide (NIS).

To demonstrate the utility of our *meta*-C–H bromination method, a gram-scale reaction was conducted, and the desired product **2l** was obtained in 90% yield (Scheme 2a). The carbamate DG and nosyl protecting group could be removed easily



Scheme 2 Synthetic elaborations. Reaction conditions: (i) **8b** (0.2 mmol), $Pd(OAc)_2$ (2 mol%), phenylboronic acid (1.5 equiv.), $(i\text{-Pr})_2NH$ (2.0 equiv.), H_2O (0.5 mL), 100 °C, 4 h, Ar. (ii) **8b** (1.5 mmol), CuI (10 mol%), L-proline (20 mol%), K_2CO_3 (2.0 equiv.), tetrahydropyrrole (1.5 equiv.), DMSO (1 mL), 90 °C, 29 h, Ar. (iii) **7b** (0.1 mmol), $Pd(PPh_3)_4$ (10 mol%), $Zn(CN)_2$ (2.0 equiv.), DMF (1 mL), 150 °C, 24 h, Ar. (iv) **7b** (0.1 mmol), B_2Pin_2 (1.2 equiv.), KOAc (3.0 equiv.), THF (6 mL), $PdCl_2(dppf)$–DCM (10 mol%), 80 °C, 24 h, Ar.



Scheme 3 Proposed catalytic cycle of *meta*-C–H bromination of aniline derivatives.

under mild conditions in good yields of **7b** and **8b**, respectively (Scheme 2b). The broad synthetic utility of the *meta*-C–H bromination reaction was then demonstrated by carrying out arylation, amination, cyanation, and borylation of **7b** and **8b**, respectively, using known established reaction conditions (Scheme 2c).

On the basis of the above results and previous studies,[9h,j,m] a plausible catalytic cycle is proposed in Scheme 3 for *meta*-C–H bromination of aniline derivative **1a**. Intermediate **B** is generated by coordination of substrate **1a** with Pd(II) species **A**, bringing the Pd(II) metal center close to the *meta*-C–H bond of the aromatic ring of aniline. Then chelation-assisted insertion of Pd(II) into the *meta*-C–H bond leads to complex **C**. Oxidative addition of **C** with brominating reagent **Br-2**, which might be activated by polyfluorobenzoic acid such as **A-1**, delivers a Pd(IV) intermediate **D**. It should be noted that polyfluorobenzoic acid might also act as a ligand to increase the electrophilicity of the Pd(II) catalyst. Finally, reductive elimination of **D** affords *meta*-brominated product **2a** and phthalimide after ligand exchange, liberating Pd(II) species **A** to re-enter the catalytic cycle.

Conclusions

In summary, we have developed the first Pd(II)-catalyzed *meta*-C–H bromination of aniline derivatives with commercially available *N*-bromophthalimide (NBP, **Br-2**) using the electron-deficient polyfluorobenzoic acid as the crucial additive. Moreover, a range of substituted benzoic acid derivatives are also viable, and *meta*-C–H chlorination is also promising under similar reaction conditions. Notably, many multiple-halogenated aniline and benzoic acid derivatives could be afforded by our methods, which is possibly interesting for medicinal chemistry. Finally, the DG can be removed under mild conditions, and the brominated products could be readily elaborated to various synthetically useful derivatives. We believe these results will find synthetic application for building up higher levels of structural complexity *via* halogenating arenes at unusual challenging positions.

Data availability

Experimental procedures, characterisation data, and NMR spectra for new compounds can be found in the ESI.†

Author contributions

H. Wang performed the experiments and developed the method. L. Fu and C. Zhou prepared some of the substrates and repeated some of the reactions. G. Li directed the project and wrote the manuscript with feedback from other authors.

Conflicts of interest

There are no conflicts to declare.

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