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ARTICLE

# Nickel-Catalyzed Regioselective C–H Halogenation of Electron-Deficient Arenes

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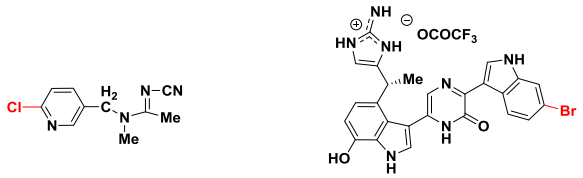
A straightforward Ni(II)-catalyzed general strategy was developed for the ortho-halogenation of the electron-deficient arenes with easily available halogenating reagents N-halosuccinimides (NXS; X=Br, Cl and I). The transformation was highly regioselective and accomplished with a wide scope and functional group tolerance. This discovery could be of great significance on the selective halogenation of amides, benzoic esters and other substances with guiding groups. Mechanistic investigations were also described.

## Introduction

Aryl halides are privileged structures ubiquitously found in numerous natural products and manufactured drugs[1]. They are also one of the most utilized organic intermediates in modern organic chemistry owing to its versatile characteristics[2]. For example (Scheme 1, **1** and **2**), acetamiprid **1** (a new pesticide), Dragmacidin D **2** (significant antibacterial activity).

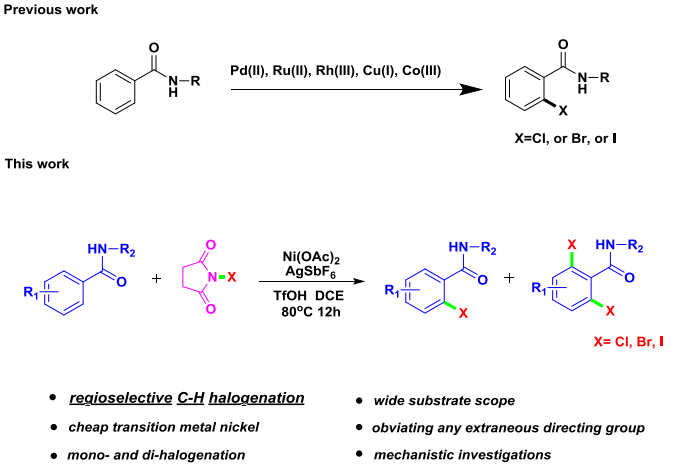



1 acetamiprid

2 Dragmacidin D

**Scheme 1.** Examples of natural products and drugs containing halide functional group.

As a consequence, the development of new methods to construct C–X (X=Br, Cl and I) bonds has received significant attention.[3] Over the past few decades, the catalytic systems of the transition metal including Pd[4a-4b,4h], Rh[4c-4e], Co[4f], Ru[4g], Cu[4j-4l], Ni[4n]catalyzed halogenations of C–H bonds in electron-deficient arenes have been well established. For example, a palladium(II)-catalyzed[4b] regio- and chemoselective C–H chlorination/bromination of electron-deficient arenes was reported by Rao's group in 2013, showing a highly efficient, atom-economic, and desirable method through a weak-coordination. Then, Glorius[4e] and co-workers described a versatile Rh(III)-catalyzed selective ortho-chlorination of amides. The reported protocols enable a perfectly regio-switchable and efficient direct chlorination. Furthermore, a Co(III)-catalyzed[4f] selective and efficient C–H activation halogenation was also established by Glorius's group, opening up new possibilities for the synthesis of aryl halides by cheap transition metal cobalt. All the previous developed methodologies were efficient and tolerated good functional compatibility. However, most of these methods rely on expensive transition metal catalysis. Apart from their expensive nature, they were generally limited by their scope or by being suitable for only one type of C–X bond formation. To the best of our knowledge, nickel catalyzed regioselective halogenation reaction of electron-deficient arenes without any extraneous directing group using easily available halogenating reagents N-halosuccinimides (NXS; X=Br, Cl and I) still poses a significant challenge.




**Scheme 2.** Previous Strategies for C-H Halogenations of Electron-Deficient Arenes.

Our group has developed a nickel-catalyzed cross-dehydrogenative coupling of α-C($sp^3$)–H bonds in N-methylamides with C($sp^3$)–H bonds in cyclic alkanes form C–C bonds.[5] So we next consider whether this system can be used in the formation of C–X(Br, Cl and I) bonds. Inspired by these,

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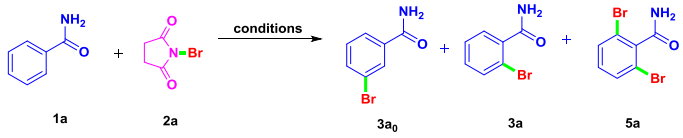
we herein demonstrated the first example of nickel-catalyzed regioselective C–H brominations, chlorinations and iodinations of electron-deficient arenes by using N-halosuccinimides (NXS; X=Br, Cl and I) as the halogenation reagent. Compared with previous research studies, this transformation (1) achieves regioselective C–H brominations, chlorinations and iodinations of electron-deficient arenes by using cheap transition metal Ni; (2) is compatible with wide substrate scope; (3) mechanistic investigations were described; (4) obviates prefunctionalisation of substrates, thus simplifying the experimental operation and avoiding the generation of by-product and waste.

## Results and discussion

**Table 1**. Optimization of the reaction conditions[a]

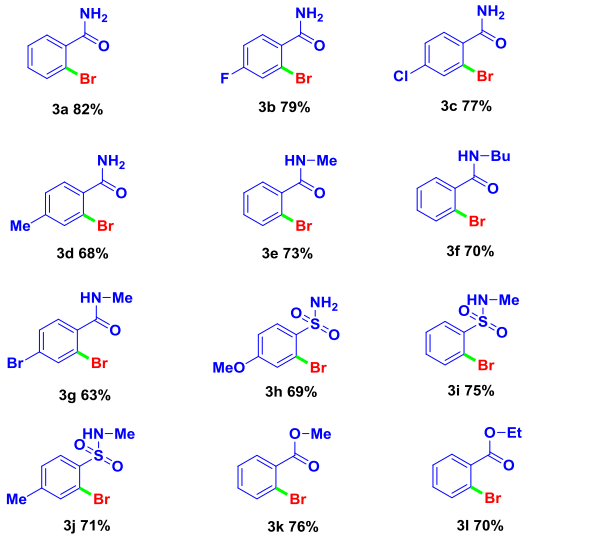



| Entry | Cat. | Ag salt | Additive | $3a_0$(%)[b] | 3a(%)[b] | 5a(%)[b] |
|---|---|---|---|---|---|---|
| 1 | - | - | - | 83 | 0 | 0 |
| 2 | $Ni(OAc)_2$ | - | - | 76 | 6 | 0 |
| 3 | $Ni(OAc)_2$ | $AgSbF_6$ | - | 55 | 19 | 0 |
| 4 | $Ni(OAc)_2$ | $AgSbF_6$ | HOAc | 19 | 58 | 0 |
| 5 | $NiCl_2$ | $AgSbF_6$ | HOAc | 23 | 50 | 0 |
| 6 | $Ni(acac)_2$ | $AgSbF_6$ | HOAc | 51 | 11 | 0 |
| 7 | $NiCl_2(PPh_3)_2$ | $AgSbF_6$ | HOAc | 64 | Trace | 0 |
| 8 | $Ni(OTf)_2$ | $AgSbF_6$ | HOAc | 57 | Trace | 0 |
| 9 | $Ni(OAc)_2$ | AgCl | HOAc | 34 | 28 | 0 |
| 10 | $Ni(OAc)_2$ | $Ag_2CO_3$ | HOAc | 30 | 32 | 0 |
| 11 | $Ni(OAc)_2$ | $Ag_2O$ | HOAc | 21 | 40 | 0 |
| 12 | $Ni(OAc)_2$ | AgOAc | HOAc | 20 | 43 | 0 |
| 13 | $Ni(OAc)_2$ | $AgSbF_6$ | PivOH | 18 | 57 | 0 |
| 14 | $Ni(OAc)_2$ | $AgSbF_6$ | TFA | 11 | 65 | Trace |
| 15 | $Ni(OAc)_2$ | $AgSbF_6$ | TsOH | 6 | 77 | Trace |
| **16** | **$Ni(OAc)_2$** | **$AgSbF_6$** | **TfOH** | **Trace** | **82** | **Trace** |
| 17[c] | $Ni(OAc)_2$ | $AgSbF_6$ | TfOH | 41 | 36 | 0 |
| 18[d] | $Ni(OAc)_2$ | $AgSbF_6$ | TfOH | 15 | 49 | 34 |
| 19[d],[e] | $Ni(OAc)_2$ | $AgSbF_6$ | TfOH | Trace | 29 | 63 |
| **20[d],[f]** | **$Ni(OAc)_2$** | **$AgSbF_6$** | **TfOH** | **0** | **7** | **75** |

[a]Reaction condition: **1a** (0.5 mmol), cat.(15% mmol), NBS (1.5 equiv), Ag salts (0.2 equiv), additives (0.5 equiv), DCE (1.5 mL), 80 °C, 12 h. [b]Isolated yield. [c] 60 °C. [d] NBS (2.5 equiv). [e] 24 h. [f] 36 h.

The optimization of the reaction conditions was performed using benzamide **1a** as model substrate and N-bromosuccinimide (NBS) as brominating source. The representative results were summarized in Table 1. Initially, only 6% yield product was observed in the presence of nickel salts in DCE at 80 °C (entry 2). Next, the adding of Ag salts afforded the mono ortho-brominated product **3a** in 19% yield (entry 3). The best yield was only 58% obtained with the presence of nickel salts, Ag salts and acid additive (entry 4). Based on the above results, we turned to investigate a number of Ni catalysts, including $NiCl_2$, $Ni(acac)_2$, $NiCl_2(PPh_3)_2$, $Ni(OTf)_2$ and $Ni(OAc)_2$ (entries 4–8). The results showed that $Ni(OAc)_2$ displayed the highest catalytic activity for the bromination reaction (entry 4). Then, we are also interested in the influence of different Ag salts on the yield (entries 9–12), we found that the reaction could proceed well by using $AgSbF_6$ and generate the ortho-bromination product in 58% yield. In addition, we explored the influence of acid additives on yield. To our delight, the ortho-bromination yield was increased to 82% by the addition of 0.5 equiv TfOH in the reaction system (entries 13–16). Unfortunately, lower temperature is not beneficial to the yield of ortho-bromination reaction (entries 17). Most importantly, increasing of the amount of N-bromosuccinimide (NBS) and prolonging the reaction time are beneficial to the increase of di-bromination product (entry 18-20).

**Table 2.** Screening of substrate scope in the ortho-bromination reaction of substituted amides.[a]

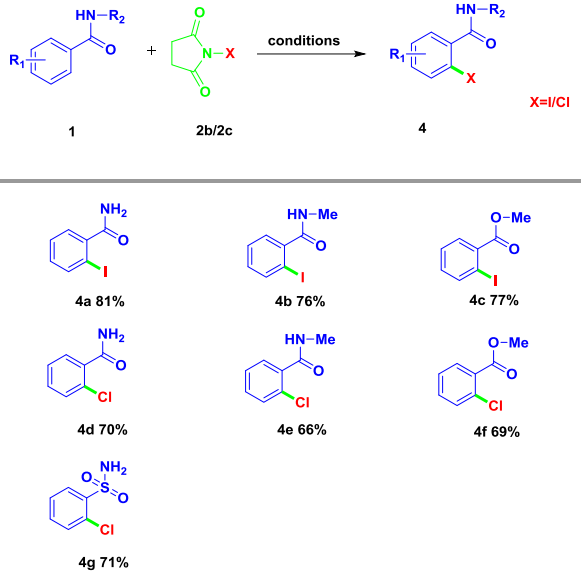




[a]Reaction condition: amides (0.5 mmol), cat.(15% mmol), NBS (1.5 equiv), Ag salts (0.2 equiv), additives (0.5 equiv), DCE (1.5 mL), 80 °C, 12 h.

With the optimized reaction conditions in hand, we then explored the substrate scope. As shown in Table 2, a wide range of electron-deficient arenes could afford the desired products in moderate to good yields. Benzamides containing electron-withdrawing groups, such as F and Cl **(3b–3c)**, underwent the bromination process well. benzamides bearing electron-donating substituents were tolerated well, furnishing **3d** in 68% yield. Meanwhile, various N-substituted amides (**3e-3g**) could produce the desired products in good yields. Moreover, we applied the optimal conditions to a series of sulfonamide (**3h**-**3j**). They underwent the reaction to give good yields of the corresponding products. Most importantly, benzoic esters were subjected to the reaction, bromination reaction could proceed smoothly **(3k-3l)**, which further expanded the substrate scope.

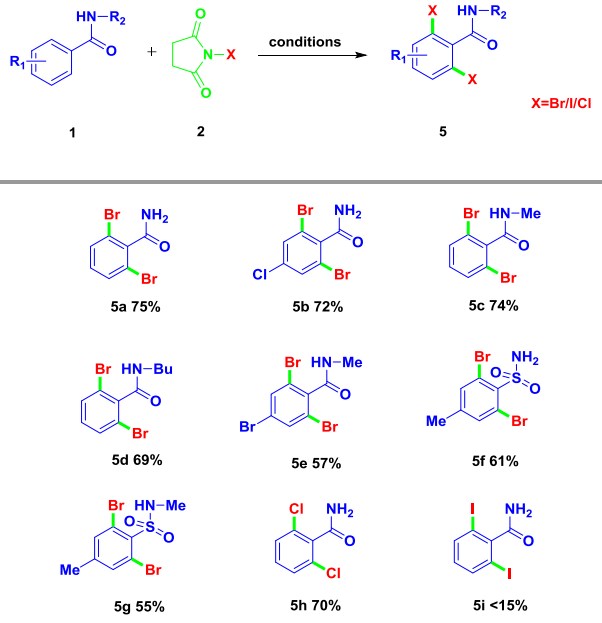
Encouraged by the above results, we investigated the use of this catalysis system for C-H iodination and chlorination (Table 3). Gratifyingly, these transformations showed excellent tolerance for various electron-deficient arenes such as benzoic esters, sulfonamides and benzamides. Furthermore, the di-halogenation reaction of substituted amides was investigated (Table 4). For the di-bromination reaction of NBS with benzamide (**5a**), 75% yield was obtained. Moreover, other substituted amides (**5b-5g**) could proceed smoothly in the di-bromination procedure. It is worth noting that NCS (**5h**) also reacted with amides to afford corresponding products in good yields (70%). Unfortunately, NIS (**5i**) can't couple with amides well in this procedure.

**Table 3.** Representative nickel-catalyzed C-H iodination and chlorination of various electron-deficient arenes

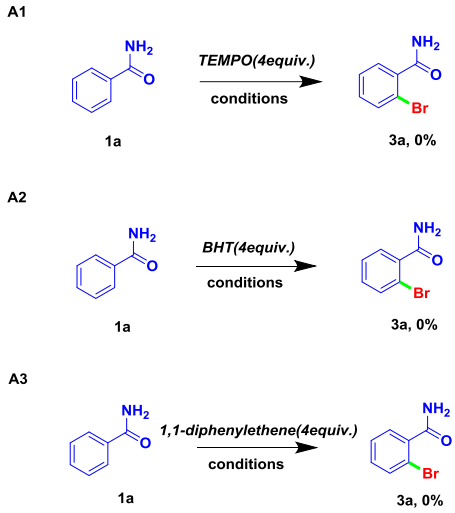



[a]Reaction condition: amides (0.5 mmol), cat.(15% mmol), NIS/NCS (1.5 equiv), Ag salts (0.2 equiv), additives (0.5 equiv), DCE (1.5 mL), 80 °C, 12 h.

**Table 4.** Representative examples in the di-halogenation reaction of substituted amides

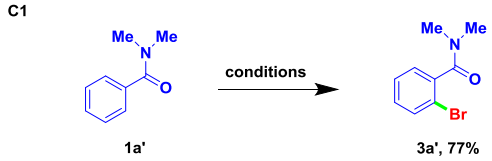



[a]Reaction condition: amides (0.5 mmol), cat.(15% mmol), NBS/NIS/NCS (2.5 equiv), Ag salts (0.2 equiv), additives (0.5 equiv), DCE (1.5 mL), 80 °C, 36 h.




Scheme 3. Control experiments.

To confirm the mechanism of this reaction, some control experiments were carried out. As is shown in Scheme 3, when 4 equivalents of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl), BHT (butylated hydroxytoluene) or 1,1-diphenylethene were added to the mono-bromination reaction as a radical scavenger, the coupling process was completely inhibited as expected (determined by GC-MS), indicating that the bromination might proceed through a radical pathway.




**Scheme 4**. Control experiments.

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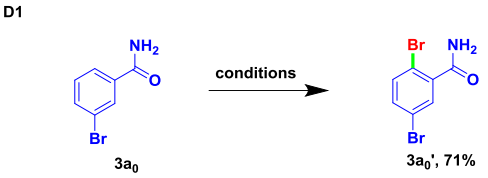
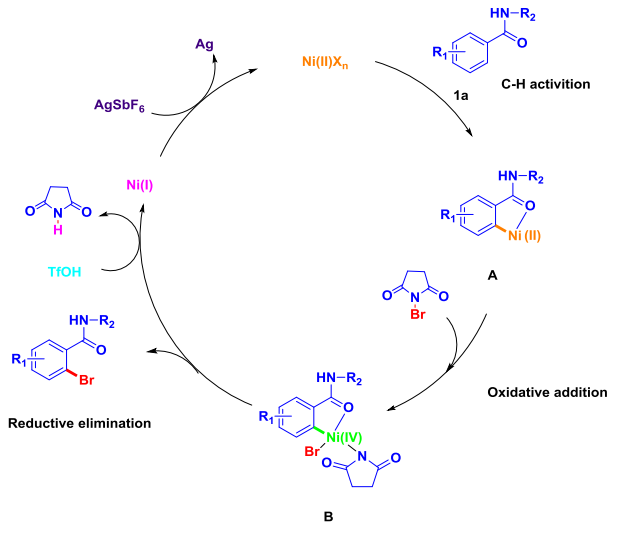



**Scheme 5**. Control experiments.

In order to further explore the reaction process, more necessary control experiments were made in Scheme 4 and Scheme 5. When we replaced **1a** with N-methyl-N-phenylacetamide under optimal conditions, this reaction proceeded well (determined by NMR **3a'**), showing benzamide NH didn't participate in coordination. On the other hand, when we changed the material from 1a to $3a_0$, the halogenation reaction could proceed smoothly (determined by NMR). Meta-selective bromination of benzamides proceeds without nickel catalyst is ordinary nature of chemistry. Ortho mono-bromination product is formed by the coordination of the metal, oxidant, additive and the directing group (see mechanism). Increase the amount of NBS and prolonging the reaction time will lead ortho di-bromination product[4b].

Based on our experimental results and previous reports[6] the plausible mechanism for this reaction was proposed and is displayed in Scheme 6. The first step is that chelate-directed C-H activation of the benzamide take place to form a five-membered cyclonickel (II) intermediate **A**[4m,6a-e], which underwent oxidative addition to generate the Ni(IV) species **B**[6f-6h]**.** Finally, the reductive elimination of intermediate **B** afforded coupling product, accompanying the generation of Ni(I) which is oxidized to regenerate Ni(II) species for the next cycle.




**Scheme 6.** Possible mechanism.

## Conclusions

In summary, a novel nickel(II)-catalyzed ortho-chlorination/bromination/iodination reaction has been developed for the synthesis of a series of arene halides from easily accessible electron-deficient arenes. In this procedure, regioselectivity and the control of selectivity by mono- and di-halogenation were achieved in a highly manner. This protocol is compatible with a broad range of substrates, not only various amides but also benzoic esters. This discovery could be also of great significance for the selective halogenation reaction of amides and other substances with guiding groups. Further studies in our laboratory are devoted to developing a milder method and performing a more detailed mechanistic investigation

## Experimental

### General experimental method

All compounds are characterized by $^1$H NMR, $^{13}$C NMR and MS. Analytical thin-layer chromatography is performed on glass plates precoated with silica gel impregnated with a fluorescent indicator (254 nm), and the plates are visualized by exposure to ultraviolet light. $^1$H NMR and $^{13}$C NMR spectra are recorded on an AVANCE 500 Bruker spectrometer operating at 500 MHz and 125 MHz in $CDCl_3$, respectively, and chemical shifts are reported in ppm.GC analyses are performed on an Agilent 7890A instrument (Column: Agilent 19091J-413:30 m × 320 μm × 0.25 μm, H, FID detection). GC-MS data was recorded on a 5975C Mass Selective Detector, coupled with a 7890A Gas Chromatograph (Agilent Technologies).

**General procedure for the synthesis of mono-bromination product:** To a mixture of benzamide (0.5 mmol) **1a**, $Ni(OAc)_2$ (15%mmol), $AgSbF_6$ (0.2 equiv), TfOH (0.5 equiv), and DCE (1.5ml) in a reaction tube was added N-bromosuccinimide (NBS) (1.5 equiv.). The reaction mixture was stirred at 80°C for 12h. The reaction mixture was extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the desired products **3a**.

**General procedure for the synthesis of di-bromination product:** To a mixture of benzamide (0.5 mmol) **1a**, $Ni(OAc)_2$ (15%mmol), $AgSbF_6$ (0.2 equiv), TfOH (0.5 equiv), and DCE (1.5ml) in a reaction tube was added N-bromosuccinimide (NBS) (2.5 equiv.). The reaction mixture was stirred at 80°C for 36h. The reaction mixture was extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the desired products **5a**.

The rest products were prepared by a similar procedure.

**2-bromobenzamide (3a):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **3a** as white solid (81.59mg, 82%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.73 – 7.63 (m, 2H), 7.46 – 7.41 (m, 1H), 7.38 – 7.33 (m, 1H), 6.16 (s, 1H), 6.02 (s, 1H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 168.1, 135.6, 132.6, 130.7, 129.0, 126.6, 118.2. GC-MS (EI) *m/z*: 199.

**2-bromo-4-fluorobenzamide (3b):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **3b** as white solid (85.72mg, 79%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.71 (dd, *J* = 8.7, 6.0 Hz, 1H), 7.37 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.14 – 7.08 (m, 1H), 6.16 (s, 1H), 6.03 (s, 1H). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.71 (dd, *J* = 8.7, 6.0 Hz, 1H), 7.37 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.14 – 7.08 (m, 1H), 6.14 (s, 1H), 6.04 (s, 1H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 167.1, 163.2, 131.7, 130.9, 120.1, 119.9, 114.1, 114.0. GC-MS (EI) *m/z*: 217.

**2-bromo-4-chlorobenzamide (3c):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **3c** as white solid (89.71mg, 77%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.68 – 7.58 (m, 2H), 7.38 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.15 (s, 1H), 6.00 (s, 1H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 167.2, 136.2, 133.9, 132.3, 130.1, 127.0, 118.8. GC-MS (EI) *m/z*: 233.

**2-bromo-4-methylbenzamide (3d):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **3d** as white solid (72.42mg, 68%). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.72 (s, 1H), 7.43 (s, 2H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.19 – 7.14 (m, 1H), 2.27 (s, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 168.5, 140.2, 135.8, 132.4, 127.9, 127.5, 118.0, 19.8. GC-MS (EI) *m/z*: 213.

**2-bromo-N-methylbenzamide (3e):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **3e** as white solid (77.75mg, 73%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.63 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.57 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.33 – 7.29 (m, 1H), 6.07 (s, 1H), 3.07 (d, *J* = 4.9 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 167.3, 136.9, 132.4, 130.2, 128.6, 126.6, 118.3, 25.8. GC-MS (EI) *m/z*: 213.

**2-bromo-N-(tert-butyl)benzamide (3f):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **3f** as white solid (89.25mg, 70%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.56 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.50 – 7.48 (m, 1H), 7.35 – 7.31 (m, 1H), 7.26 – 7.21 (m, 1H), 5.73 (s, 1H), 1.48 (s, 9H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 166.0, 138.1, 132.2, 130.8, 129.9, 128.3, 126.5, 51.3, 27.8. GC-MS (EI) *m/z*: 255.

**2,4-dibromo-N-methylbenzamide (3g):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **3g** as white solid (92.30mg, 63%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 1.8 Hz, 1H), 7.53 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 6.13 (s, 1H), 3.05 (d, *J* = 4.9 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 166.3, 135.7, 134.8, 133.0, 129.8, 123.5, 119.0, 25.8. GC-MS (EI) *m/z*: 293.

**2-bromo-4-methoxybenzenesulfonamide (3h):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **3h** as white solid (91.43mg, 69%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 2.3 Hz, 1H), 7.87 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 3.98 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 158.8, 133.8, 130.9, 126.6, 111.4, 110.4, 55.7. GC-MS (EI) *m/z*: 265.

**2-bromo-N-methylbenzenesulfonamide (3i):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **3i** as white solid (93.34mg, 75%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 8.20 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.79 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.60 – 7.29 (m, 3H), 2.66 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 136.6, 134.1, 132.8, 131.1, 126.9, 118.6, 28.3. GC-MS (EI) *m/z*: 249.

**2-bromo-N,4-dimethylbenzenesulfonamide (3j):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **3j** as white solid (93.37mg, 71%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 8.1 Hz, 1H), 7.56 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.28 – 7.26 (m, 1H), 2.60 (d, *J* = 5.4 Hz, 3H), 2.41 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 144.1, 134.5, 133.6, 131.1, 127.5, 118.4, 28.3, 20.1. GC-MS (EI) *m/z*: 263.

**methyl 2-bromobenzoate (3k):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **3k** as white solid (81.32mg, 76%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.77 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.64 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.38 – 7.27 (m, 2H), 3.92 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 165.6, 133.3, 131.6, 131.2, 130.3, 126.2, 120.6, 51.5. GC-MS (EI) *m/z*: 214.

**ethyl 2-bromobenzoate (3l):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **3l** as white solid (74.90mg, 70%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.78 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.65 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.40 – 7.28 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 165.3, 133.3, 131.6, 131.4, 130.2, 126.2, 120.5, 60.6, 13.2. GC-MS (EI) *m/z*: 228.

**2-iodobenzamide (4a):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **4a** as white solid (100.04mg, 81%). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.85 (d, *J* = 7.9 Hz, 1H), 7.80 (s, 1H), 7.49 (s, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.33 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.13 (td, *J* = 7.6, 1.8 Hz, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 170.1, 142.6, 138.6, 130.0, 127.4, 127.2, 92.6. GC-MS (EI) *m/z*: 247.

**2-iodo-N-methylbenzamide (4b):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **4b** as white solid (99.18mg, 76%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.92 – 7.77 (m, 1H), 7.48 – 7.32 (m, 2H), 7.10 (m, 1H), 5.77 (s, 1H), 3.03 (d, *J* = 4.9 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 169.1, 141.4, 138.9, 130.1, 127.2, 126.8, 91.5, 25.8. GC-MS (EI) *m/z*: 261.

**methyl 2-iodobenzoate (4c):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **4c** as white solid (100.87mg, 77%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.97 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.78 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.38 (td, *J* = 7.6, 1.1 Hz, 1H), 7.13 (td, *J* = 7.6, 1.8 Hz, 1H), 3.92 (s, 3H).$^{13}$C NMR (126 MHz, Chloroform-*d*) δ 165.9, 140.3, 134.1, 131.7, 130.0, 126.9, 93.1, 51.5. GC-MS (EI) *m/z*: 262.

**2-chlorobenzamide (4d):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **4d** as white solid (54.25mg, 70%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.85 – 7.74 (m, 1H), 7.57 – 7.32 (m, 3H), 6.69 (s, 1H), 6.46 (s, 1H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 167.5, 132.9, 130.8, 129.9, 129.6, 129.4, 126.2. GC-MS (EI) *m/z*: 155.

**2-chloro-N-methylbenzamide (4e):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **4e** as white solid (55.77mg, 66%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.67 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.41 – 7.32 (m, 3H), 6.24 (s, 1H), 3.03 (d, *J* = 4.9 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 166.2, 134.1, 130.3, 129.6, 129.2, 128.9, 126.1, 25.8. GC-MS (EI) *m/z*: 169.

**methyl 2-chlorobenzoate (4f):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **4f** as white solid (58.65mg, 69%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.82 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.42 (m, 2H), 7.30 (td, *J* = 7.5, 1.4 Hz, 1H), 3.93 (s, 3H).$^{13}$C NMR (126 MHz, Chloroform-*d*) δ 165.1, 132.7, 131.5, 130.4, 130.0, 129.1, 125.6, 51.4. GC-MS (EI) *m/z*: 170.

**2-chlorobenzenesulfonamide (4g):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **4g** as white solid (67.81mg, 71%). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.97 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.65 – 7.56 (m, 4H), 7.51 (td, *J* = 7.6, 1.5 Hz, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 140.5, 132.9, 131.0, 129.8, 128.4, 126.9. GC-MS (EI) *m/z*: 191.

**2,6-dibromobenzamide (5a):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **5a** as white solid (104.63mg, 75%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 8.1 Hz, 2H), 7.13 (t, *J* = 8.0 Hz, 1H), 5.94 (s, 1H), 5.73 (s, 1H). $^{13}$C NMR (126 MHz, DMSO-d6) δ 166.3, 135.5, 132.5, 128.9, 127.8. GC-MS (EI) *m/z*: 279.

**2,6-dibromo-4-chlorobenzamide (5b):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **5b** as white solid (112.32mg,72%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.58 (s, 2H), 6.02 (s, 1H), 5.77 (s, 1H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 166.2, 136.8, 135.3, 130.7, 119.3. GC-MS (EI) *m/z*: 312.

**2,6-dibromo-N-methylbenzamide (5c):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **5c** as white solid (108.41mg, 74%).$^1$H NMR (500 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.14 (t, *J* = 8.1 Hz, 1H), 5.79 (s, 1H), 3.09 (d, *J* = 4.9 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 166.1, 139.0, 130.8, 130.1, 119.5, 25.7. GC-MS (EI) *m/z*: 293.

**2,6-dibromo-N-(tert-butyl)benzamide (5d):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **5d** as white solid (115. 23mg, 69%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 1H), 5.48 (s, 1H), 1.49 (s, 9H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 164.2, 139.4, 130.8, 130.0, 119.5, 51.6, 27.7. GC-MS (EI) *m/z*: 344.

**2,4,6-tribromo-N-methylbenzamide (5e):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **5e** as white solid (105.74mg, 57%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.74 (s, 2H), 5.83 (s, 1H), 3.08 (d, *J* = 5.0 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 165.4, 137.9, 133.3, 122.8, 120.0, 25.7. GC-MS (EI) *m/z*: 371.

**2,6-dibromo-4-methylbenzenesulfonamide (5f):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **5f** as white solid (100.35mg, 61%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 8.28 (s, 1H), 7.61 (s, 1H), 5.18 (s, 2H), 2.45 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 143.8, 137.9, 135.5, 132.3, 21.8. GC-MS (EI) *m/z*: 329.

**2,6-dibromo-N,4-dimethylbenzenesulfonamide (5g):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **5g** as white solid (94.33mg, 55%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 8.27 (s, 1H), 7.60 (s, 1H), 5.03 (s, 1H), 2.64 (d, *J* = 5.4 Hz, 3H), 2.45 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 143.9, 135.6, 134.3, 123.2, 28.3, 21.8. GC-MS (EI) *m/z*: 343.

**2,6-dichlorobenzamide (5h):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **5h** as white solid (66.15mg, 70%). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.04 (s, 1H), 7.77 (s, 1H), 7.46 – 7.43 (m, 2H), 7.36 (dd, *J* = 8.9, 7.3 Hz, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 164.8, 136.5, 130.2, 130.1, 127.5. GC-MS (EI) *m/z*: 189.

**3-bromobenzamide (3a$_0$):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **3a$_0$** as white solid (82.59mg, 83%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 2.0 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.67 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 6.10 (s, 1H), 5.92 (s, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 165.8, 135.9, 133.4, 130.0, 129.7, 126.0, 121.1. GC-MS (EI) *m/z*: 199.

**2-bromo-N,N-dimethylbenzamide (3a'):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **3a'** as white solid (87.39mg, 77%). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.57 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.36 (m, 1H), 7.27 – 7.22 (m, 2H), 3.14 (s, 3H), 2.86 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 168.3, 137.9, 133.0, 131.7, 129.2, 126.7, 118.2, 37.2, 33.7. GC-MS (EI) *m/z*: 227.

**2,5-dibromobenzamide (3a$_0$'):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **3a$_0$'** as white solid (99.05mg, 71%).$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.99 (s, 1H), 7.72 (s, 1H), 7.54 – 7.52 (m, 2H), 7.51 (s, 1H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 171.9, 143.9, 136.8, 136.6, 135.6, 133.7, 133.5. GC-MS (EI) *m/z*: 279.

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## Conflicts of interest

There are no conflicts to declare.

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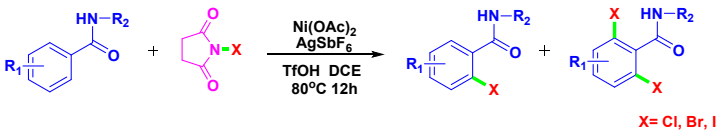


*regioselective C-H halogenation*

Graphical abstract