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A Practical Procedure for Regioselective Bromination of Anilines

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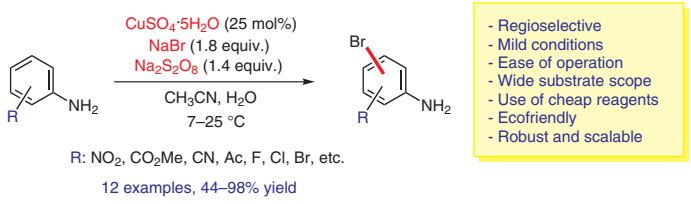

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Abstract A highly practical procedure for the preparation of bromoanilines by using copper-catalyzed oxidative bromination has been developed. Treatment of free anilines with readily available NaBr and $Na_2S_2O_8$ in the presence of a catalytic amount of $CuSO_4·5H_2O$ enabled regioselective bromination.

Key words anilines, bromination, catalysis, copper, halides, halogenation, oxidation

Aryl halides have gained much attention as important raw materials for invaluable compounds such as drugs and natural products.[1] Over the past few decades, C–H activation methodology that does not need a halogen atom as an activating group in the substrate has emerged as a powerful tool for making carbon–carbon and carbon–heteroatom bonds.[2] Despite the conceptually attractive features of that methodology, particularly for chemical industries, cross-coupling technology[3] employing aryl halides as starting materials has widely been used for producing functionalized aromatic compounds, thanks to the remarkable robustness and low cost of the substrates. In this context, the search for a more concise, economical, and environmentally viable procedure for producing aryl halides is still in great demand. Among the methods, particular attention has been focused on the bromination of free anilines because of their importance in the synthesis of nitrogen-containing heterocycles.[4] We report herein a novel and efficient synthesis of bromoanilines by means of copper-catalyzed oxidative bromination of free anilines.

Various methods for the bromination of free anilines by employing Br_2,[5a] HBr/DMSO,[5b] KBr/$NaBO_3$,[5c] [bmin]Br_3,[5d] NBS/TBAB,[5e] NBS-functionalized silica,[5f] NBS/ionic liquid,[5g] $CuBr_2$/ionic liquid,[5h] NaBr/cat. Pd/O_2,[5i] NBS/HFIP,[5j] KBr/$4Na_2SO_4·2H_2O_2$·NaCl,[5k] $CuBr_2$/TBAB,[5l] and TMSBr/PIFA[5m] have been reported. Among these, if atom economy and ecofriendliness are considered, oxidative bromination catalyzed by first-row transition metals, especially the copper-catalyzed process, is highly desirable. Although examples[5h,l] of this type of reaction have been reported, a stoichiometric amount of copper bromide ($CuBr_2$) was needed as the brominating reagent. To overcome this issue, Stahl and coworkers reported aerobic bromination by using a catalytic amount of $CuBr_2$.[6] However, this method requires a relatively higher temperature (60 °C) and examples with labile substrates such as unprotected anilines have not been reported.

Meanwhile, we have recently developed an efficient method for the azidation of free anilines by the use of a $CuSO_4·5H_2O/NaN_3/Na_2S_2O_8$ catalytic system.[7] Fascinated by the quite efficient nature of $Na_2S_2O_8$ as an oxidant, we came up with an idea to use a $CuSO_4·5H_2O/NaBr/Na_2S_2O_8$ system for the oxidative bromination of free anilines.

Initially, the bromination of 2-nitroaniline (**1a**) was tested as a typical example (Table 1). The possible product 4-bromo-2-nitoroaniline (**2a**) has been widely used as an important starting material for producing pharmaceuticals.[8] Treatment of **1a** with NaBr (1.2 equiv.) in the presence of $CuSO_4·5H_2O$ (25 mol%) and $Na_2S_2O_8$ (1.2 equiv.) in a mixture of CH_3CN and H_2O (2:1) at 7 °C for 4 h and at 25 °C for 18 h gave the desired 4-bromo-2-nitroaniline (**2a**) and the overbrominated 4,6-dibromo-2-nitroaniline (**3a**) (**2a**/**3a** = 94:6) with 36% assay yield of **2a** (Table 1, entry 1).

In sharp contrast to the above-mentioned azidation[7] using $CuSO_4·5H_2O/NaN_3/Na_2S_2O_8$, in which azidation proceeded *ortho* to the amino group, bromination occurred *para* to the amino group for the same anilines. This *para* selectivity might be accounted for by simple Friedel–Crafts-type electrophilic bromination rather than the reaction mediated by the copper–aniline complex.[7]

To enhance the conversion and prevent dibromination, the reaction was tested with increased amounts of NaBr and $Na_2S_2O_8$ (1.8 and 1.4 equiv., respectively) at the lower temperature (7 °C) (Table 1, entry 2). With this treatment, the ratio of **2a** and **3a** was remarkably improved to 100:0 and, if the temperature was maintained for 2 h, the conver-

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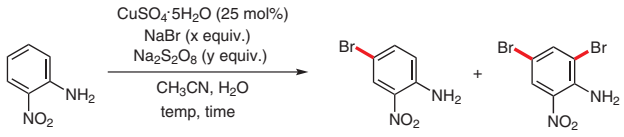
sion reached 63% (Table 1, entry 3). If, after that point in time, the mixture was stirred at 25 °C for a further 22 h, the desired product **2a** was obtained in 95% assay yield with excellent monobromination selectivity (**2a**/**3a** = 99.9:0.1; Table 1, entry 4). To prevent unfavorable dibromination, the reaction mixture was kept at 7 °C in the beginning and then warmed to a higher temperature (25 °C). A control experiment was performed without $CuSO_4·5H_2O$, which resulted in no reaction at all (Table 1, entry 5). Another oxidant, H_2O_2 was then used in place of $Na_2S_2O_8$. However, in this case, only a trace amount of **2a** was obtained (2.6% assay yield; Table 1, entry 6). In marked contrast, the use of Oxone led to very rapid bromination, although there was considerable formation of the dibromide (**2a**/**3a** = 81:19; Table 1, entry 7).

With the optimized conditions in hand, the substrate scope was examined (Scheme 1). Functional groups such as ester (**2b**, **2l**), halogen (**2c**–**2e**, **2h**, and **2i**), ketone (**2g**), and nitro (**2a** and **2k**) groups are compatible with this transformation. If the substituent is located *ortho* to the amino group, *para*-bromination predominates (**2a**–**2f**). For substrates with *para*-substituents, *ortho*-bromination preferentially took place (**2g**–**2l** and **2e** from 4-bromoaniline (**1j**)), although 2,6-dibrominated products were produced in minor amounts. It should be noted that every reaction was conducted with approximately 1.0 g of substrate to demonstrate the scalability and reproducibility of this process.

To gain further insight on the reaction mechanism, the addition of a radical scavenger (TEMPO) was tested (Table 2). When 1.0 equiv. of TEMPO was added under the standard reaction conditions, the bromination apparently accelerated; that is, 83 and 89% conversion were attained after reaction at 7 °C for 1 and 2 h, respectively (Table 2, entries 1 and 2) versus 54 and 63% for 1 and 2 h, respectively, without TEMPO (Table 1, Entries 2 and 3). This result demonstrates that the reaction does not proceed by intervention of a radical as an intermediate.[9] Furthermore, if such radical species are involved in this reaction, the dimerization product should be produced via formation of a cation radical, similar to those reported for the dimerization of 2,6-dimethylphenol with $CuSO_4/Na_2S_2O_8$.[10] However, no such byproduct was found in the reaction mixture to support the radical reaction mechanism (see below).

Based on the results mentioned above, a possible mechanism has been postulated for the oxidative bromination of **1a** (Scheme 2). As the active reactant, a bromonium ion (Br^+), rather than a bromide radical ($Br^·$), is proposed. It might be formed rapidly from NaBr through two-electron

Table 1 Screening of the Catalytic System for the Bromination of 2-Nitroaniline (**2a**)[a]



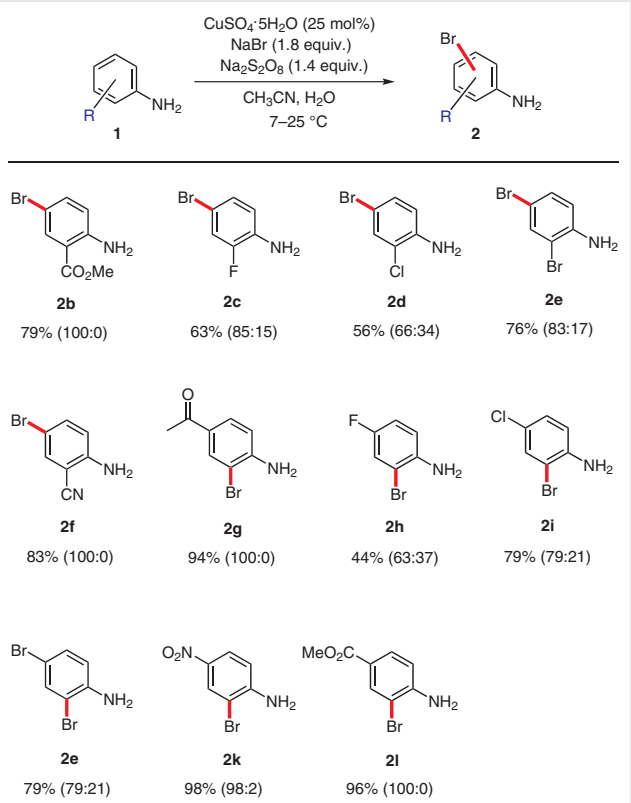
1a **2a** **3a**

Entry	NaBr (x equiv.)	Oxidant (y equiv.)	Temp (°C)	Time (h)	**2a**/**3a**[b]	Conv.[c] (%)	Yield[d] of **2a** (%)
1	1.2	$Na_2S_2O_8$ (1.2)	7 25	4 18	94:6	62	36
2	1.8	$Na_2S_2O_8$ (1.4)	7	1	100:0	54	–[e]
3	1.8	$Na_2S_2O_8$ (1.4)	7	2	100:0	63	–[e]
4	1.8	$Na_2S_2O_8$ (1.4)	7 25	2 22	99.9:0.1	99	95
5[f]	1.8	$Na_2S_2O_8$ (1.4)	7 25	2 22	–[e]	0	0
6	1.8	H_2O_2 (1.4)	7 25	2 13	100:0	2.6	2.6
7	1.8	Oxone (0.7)	7	1	81:19	100	75

[a] Reaction conditions: 2-Nitroaniline (1.0 g, 7.24 mmol), $CuSO_4·5H_2O$ (0.452 g, 1.81 mmol, 25 mol%), NaBr (x equiv.), and oxidant (y equiv.) in a mixture of CH_3CN (20 mL) and H_2O (10 mL).
[b] Ratio based on HPLC area percentage.
[c] Conversion from **1a** into **2a** based on HPLC area percentage.
[d] Determined by HPLC.
[e] Not assayed.
[f] The reaction was conducted without $CuSO_4·5H_2O$.

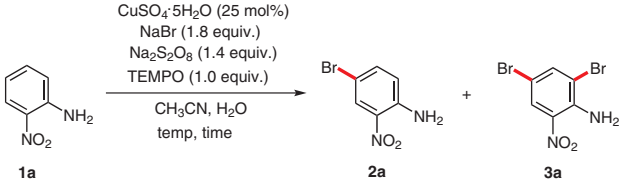
oxidation via steps I and II involving sulfate radicals ($SO_4^{\bullet-}$) generated by thermal decomposition of $Na_2S_2O_8$.[11] The Br^+ ion thus obtained would react *para* to the amino group of **1a** to afford intermediate **A**, which, upon deprotonation, results in the formation of desired brominated aniline **2a**.[12] The acceleration effect of TEMPO mentioned above may be explained by the ability of TEMPO to oxidize Cu^I into Cu^{II} species,[13] which would result in enhanced generation of the active brominating species Br^+.

In conclusion, a novel and practical bromination of free anilines has been developed. The new protocol is applicable to a variety of substrates to give monobrominated anilines preferentially and regioselectively. Only a catalytic amount of copper salt ($CuSO_4·5H_2O$) is required, which causes much less environmental impact than the reported methods that need a stoichiometric amount of $CuBr_2$. The use of readily available reagents and mild reaction conditions, as well as the ease of operation, for this process will permit much easier access to brominated anilines, which are compounds of increasing interest.



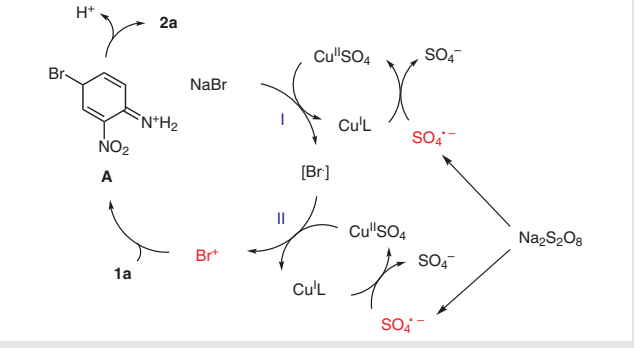
Scheme 1 Substrate scope of the Cu-catalyzed bromination of anilines. *Reagents and conditions*: Substrate **1** (7.24 mmol), $CuSO_4·5H_2O$ (0.452 g, 1.81 mmol, 25 mol%), NaBr (1.34 g, 13.0 mmol, 1.8 equiv.), and $Na_2S_2O_8$ (2.41 g, 10.1 mmol, 1.4 equiv.) in a mixture of CH_3CN (20 mL) and H_2O (10 mL), 7 °C for 2 h then 25 °C for 22 h. The ratios in parentheses are those of the monobrominated/dibrominated products.

Table 2 Effect of a Radical Scavenger on the Cu-Catalyzed Bromination of Anilines[a]



Entry	Temp (°C)	Time (h)	**2a**/**3a**[b]	Conv.[c] (%)	Yield[d] of **2a** (%)
1	7	1	100:0	83	–[e]
2	7	2	100:0	89	–[e]
3	7 25	2 13	99.8:0.2	100	92

[a] Reaction conditions: 2-Nitroaniline (1.0 g, 7.24 mmol), $CuSO_4·5H_2O$ (0.452 g, 1.81 mmol, 25 mol%), NaBr (1.34 g, 13.0 mmol, 1.8 equiv.), and $Na_2S_2O_8$ (2.41 g, 10.1 mmol, 1.4 equiv.) in a mixture of CH_3CN (20 mL) and H_2O (10 mL).
[b] Ratio based on HPLC area percentage.
[c] Conversion from **1a** into **2a** based on HPLC area percentage.
[d] Determined by HPLC.
[e] Not assayed.



Scheme 2 Possible reaction mechanism

^1H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were recorded with tetramethylsilane used as an internal standard. Silica gel column chromatography was performed using Kieselgel 60 (Merck). TLC was carried out on Merck 0.25 mm precoated glass-backed plates (60 F_{254}). Development was accomplished by using 5% phosphomolybdic acid in ethanol followed by heat or was visualized by UV light where feasible. All solvents and reagents were used as received.

4-Bromo-2-nitroaniline (2a); Typical Procedure for Bromination

2-Nitroaniline (1.0 g, 7.24 mmol) was added to a suspension of $CuSO_4·5H_2O$ (0.452 g, 1.81 mmol, 25 mol%) in a mixture of CH_3CN (20 mL) and H_2O (10 mL) at 25 °C, and the mixture was stirred at 25 °C for 15 min. NaBr (1.34 g, 13.0 mmol, 1.8 equiv.) and $Na_2S_2O_8$ (2.41 g, 10.1 mmol, 1.4 equiv.) were then added simultaneously in three portions at 7 °C over 15 min. After addition was complete, the mixture was further stirred at 7 °C for 2 h and at 25 °C for 22 h. $Na_2S_2O_3$ (572 mg, 3.62

mmol) was added to the mixture. The pH value of the mixture was then adjusted to 9.0 by adding 10% aq. NaOH (8 mL). The mixture was diluted with H_2O (100 mL) and extracted with AcOEt (100 mL). The organic phase was separated and subjected to HPLC analysis (X Bridge C18, 5 µm, 4.6 × 150 mm, 30 °C, 1 mL min^{-1}, 50–90% CH_3CN (0–20 min) then 50% (20–40 min), 254 nm) to obtain the assay yield of **2a** (1.49 g, 94.9%) and the ratio of **2a**/**3a** (99.9:0.1). Pure samples of **2a** and **3a** for analysis were obtained by purification of the evaporated mixture with silica gel column chromatography (*n*-hexane/AcOEt = 15:1).

Characterization Data of Products

4-Bromo-2-nitroaniline (2a)[8]

White solid; assay yield: 1.5 g (97%); **2a**/**3a** = 99.9/0.1.

^{1}H NMR ($CDCl_3$): δ = 8.27 (1 H, d, *J* = 2.0 Hz), 7.43 (1 H, dd, *J* = 8.8, 2.4 Hz), 6.72 (1 H, d, *J* = 8.4 Hz), 6.08 (2 H, br s).

^{13}C NMR ($CDCl_3$): δ = 143.6, 138.5, 132.6, 128.4, 120.4, 107.9.

4,6-Dibromo-2-nitroaniline (3a)[4a]

White solid.

^{1}H NMR ($CDCl_3$): δ = 8.30 (1 H, d, *J* = 2.4 Hz), 7.81 (1 H, d, *J* = 2.4 Hz), 6.64 (2 H, br s).

^{13}C NMR ($CDCl_3$): δ = 141.4, 140.9, 128.3, 112.8, 107.0.

Methyl 5-Bromoanthranilate (2b)[4b]

White solid; assay yield: 1.3 g (79%); **2b**/**3b** = 100:0.

^{1}H NMR ($CDCl_3$): δ = 7.96 (1 H, d, *J* = 2.8 Hz), 7.32 (1 H, dd, *J* = 9.0, 2.8 Hz), 6.56 (1 H, d, *J* = 8.8 Hz), 5.75 (2 H, br s), 3.87 (3 H, s).

^{13}C NMR ($CDCl_3$): δ = 167.6, 149.4, 136.8, 133.5, 118.4, 112.1, 107.4, 51.9.

4-Bromo-2-fluoroaniline (2c)[4c]

White solid; assay yield: 867 mg (63%); **2c**/**3c** = 85:15.

^{1}H NMR ($CDCl_3$): δ = 7.13 (1 H, dd, *J* = 10.4, 2.0 Hz), 7.05 (1 H, ddd, *J* = 8.8, 2.0, 1.6 Hz), 6.65 (1 H, dd, *J* = 14.6, 8.0 Hz), 3.72 (2 H, br s).

^{13}C NMR ($CDCl_3$): δ = 152.6, 150.2, 133.9, 133.8, 127.5, 127.4, 118.8, 118.6, 117.9, 117.8, 109.0, 108.9.

4,6-Dibromo-2-fluoroaniline (3c)[4d]

White solid.

^{1}H NMR ($CDCl_3$): δ = 7.34 (1 H, t, *J* = 2.0 Hz), 7.10 (1 H, dd, *J* = 10, 2.4 Hz), 4.12 (2 H, br s).

^{13}C NMR ($CDCl_3$): δ = 152.0, 149.5, 133.2, 133.1, 130.1, 130.0, 118.0, 117.7, 109.8, 109.7, 108.1, 108.0.

4-Bromo-2-chloroaniline (2d)[4e]

White solid; assay yield: 837 mg (56%); **2d**/**3d** = 66:34.

^{1}H NMR ($CDCl_3$): δ = 7.37 (1 H, d, *J* = 2.0 Hz), 7.15 (1 H, dd, *J* = 8.0, 2.4 Hz), 6.63 (1 H, d, *J* = 8.8 Hz), 4.05 (2 H, br s).

^{13}C NMR ($CDCl_3$): δ = 142.2, 131.7, 130.6, 120.0, 116.9, 109.4.

4,6-Dibromo-2-chloroaniline (3d)[4f]

White solid.

^{1}H NMR ($CDCl_3$): δ = 7.45 (1 H, d, *J* = 2.4 Hz), 7.34 (1 H, d, *J* = 2.4 Hz), 4.50 (2 H, br s).

^{13}C NMR ($CDCl_3$): δ = 140.5, 133.2, 131.0, 119.7, 109.3, 108.5.

2,4-Dibromoaniline (2e)[4d]

Yield: 1.38 g (76% from 2-bromoaniline (**1e**)); **2e**/**3e** = 83:17; 1.44 g (79% from 4-bromoaniline (**1j**)); **2e**/**3e** = 79:21.

^{1}H NMR ($CDCl_3$): δ = 7.53 (1 H, d, *J* = 2.0 Hz), 7.19 (1 H, dd, *J* = 8.0, 2.4 Hz), 6.64 (1 H, d, *J* = 8.4 Hz), 4.09 (2 H, br s).

^{13}C NMR ($CDCl_3$): δ = 143.3, 134.6, 131.2, 116.8, 109.7, 109.6.

2,4,6-Tribromoaniline (3e)[4g]

White solid.

^{1}H NMR ($CDCl_3$): δ = 7.50 (2 H, s), 4.57 (2 H, br s).

^{13}C NMR ($CDCl_3$): δ = 141.4, 133.9, 108.9.

4-Bromo-2-cyanoaniline (2f)[4h]

White solid; assay yield: 1.2 g (83%); **2f**/**3f** = 100:0.

^{1}H NMR ($CDCl_3$): δ = 7.48 (1 H, d, *J* = 1.6 Hz), 7.40 (1 H, dd, *J* = 8.6, 2.0 Hz), 6.64 (1 H, d, *J* = 8.8 Hz), 4.44 (2 H, br s).

^{13}C NMR ($CDCl_3$): δ =148.6, 137.0, 134.2, 116.8, 116.2. 108.8.

4-Acetyl-2-bromoaniline (2g)[4i]

White solid; assay yield: 1.5 g (94%); **2g**/**3g** = 100:0.

^{1}H NMR ($CDCl_3$): δ = 8.06 (1 H, d, *J* = 2.4 Hz), 7.33 (1 H, dd, *J* = 8.6, 2.4 Hz), 6.74 (1 H, d, *J* = 8.4 Hz), 4.62 (2 H, br s), 2.50 (3 H, s).

^{13}C NMR ($CDCl_3$): δ = 195.5, 148.5, 133.8, 129.4, 128.8, 114.3, 108.3, 26.1.

2-Bromo-4-fluoroaniline (2h)[4j]

White solid; assay yield: 605 mg (44%); **2h**/**3h** = 63:37.

^{1}H NMR ($CDCl_3$): δ = 7.17 (1 H, dd, *J* = 8.2, 2.8 Hz), 6.86 (1 H, ddd, *J* = 8.6, 7.8, 2.8 Hz), 6.71 (1 H, dd, *J* = 8.6, 5.2 Hz), 3.93 (2 H, br s).

^{13}C NMR ($CDCl_3$): δ = 156.6, 154.2, 140.6, 119.3, 119.1, 115.9, 115.8, 115.4, 115.1, 108.7, 108.6.

2,6-Dibromo-4-fluoroaniline (3h)[4k]

White solid.

^{1}H NMR ($CDCl_3$): δ = 7.19 (2 H, d, *J* = 8.0 Hz), 4.37 (2 H, br s).

^{13}C NMR ($CDCl_3$): δ = 155.4, 152.9, 139.0, 119.1, 118.9, 108.0, 107.9.

2-Bromo-4-chloroaniline (2i)[4l]

White solid; assay yield: 1.2 g (79%); **2i**/**3i** = 79:21.

^{1}H NMR ($CDCl_3$): δ = 7.40 (1 H, d, *J* = 2.4 Hz), 7.06 (1 H, dd, *J* = 8.6, 2.4 Hz), 6.67 (1 H, d, *J* =4.0 Hz), 4.07 (2 H, br s).

^{13}C NMR ($CDCl_3$): δ = 142.8, 131.8, 128.3, 123.0, 116.2, 109.1.

2,6-Dibromo-4-chloroaniline (3i)[4f]

White solid.

^{1}H NMR ($CDCl_3$): δ = 7.38 (2 H, s), 4.54 (2 H, br s).

^{13}C NMR ($CDCl_3$): δ = 141.0, 131.2, 122.6, 108.4.

2-Bromo-4-nitroanigline (2k)[4m]

White solid; assay yield: 1.5 g (98%); **2k**/**3k** = 98:2.

^{1}H NMR ($CDCl_3$): δ = 8.37 (1 H, d, *J* = 2.4 Hz), 8.03 (1 H, dd, *J* = 8.8, 2.0 Hz), 6.75 (1 H, d, *J* = 9.2 Hz), 4.86 (2 H, br s).

^{13}C NMR ($CDCl_3$): δ = 150.0, 139.1, 129.3, 125.0, 113.6, 107.1.

2,6-Dibromo-4-nitroaniline (3k)[4f]

White solid.

^{1}H NMR ($CDCl_3$): δ = 8.35 (2 H, s), 5.29 (2 H, br s).

^{13}C NMR ($CDCl_3$): δ = 147.5, 138.6, 128.0, 106.5.

Methyl 4-Amino-3-bromobenzoate (2l)[4n]

White solid; assay yield: 1.6 g (96%); **2l**/**3l** = 100:0.

^{1}H NMR ($CDCl_3$): δ = 8.12 (1 H, d, *J* = 2.0 Hz), 7.79 (1 H, dd, *J* = 8.2, 2.0 Hz), 6.73 (1 H, d, *J* = 8.8 Hz), 4.52 (2 H, br s), 3.86 (3 H, s).

^{13}C NMR ($CDCl_3$): δ = 166.0, 148.1, 134.5, 130.3, 120.8, 114.3, 107.9, 51.9.

Conflict of Interest

The authors declare no conflict of interest.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1441-3236.

References

(1) Joseph, P. J. A.; Priyadarshini, S. *Org. Process Res. Dev.* **2017**, *21*, 1889.

(2) For examples, see the following references and those cited therein: (a) Seki, M. *ACS Catal.* **2011**, *1*, 607. (b) Seki, M.; Nagahama, M. *J. Org. Chem.* **2011**, *76*, 10198. (c) Seki, M. *Synthesis* **2012**, *44*, 3231. (d) Seki, M. *RSC Adv.* **2014**, *4*, 29131. (e) Seki, M. *Synthesis* **2014**, *46*, 3249. (f) Seki, M. *ACS Catal.* **2014**, *4*, 4047. (g) Seki, M. In *Catalytic Transformations via C–H Activation, Chap. 1.1.4*; Yu, J.-Q., Ed.; Georg Thieme Verlag KG: Stuttgart, **2015**. (h) Seki, M. *Synthesis* **2015**, *47*, 1423. (i) Seki, M. *Synthesis* **2015**, *47*, 2985. (j) Seki, M. *Org. Process Res. Dev.* **2016**, *20*, 867. (k) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (l) Li, B.; Dixneuf, P. H. *Chem. Soc. Rev.* **2013**, *42*, 5744. (m) Wang, C.-S.; Dixneuf, P. H.; Soulé, J.-F. *Chem. Rev.* **2018**, *118*, 7532. (n) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. *Chem. Rev.* **2019**, *119*, 2192. (o) Loup, J.; Dhawa, U.; Pesciaioli, F.; Wencel-Delord, J.; Ackermann, L. *Angew. Chem. Int. Ed.* **2019**, *58*, 12803. (p) Friis, S. D.; Johansson, M. J.; Ackermann, L. *Nat. Chem.* **2020**, *12*, 511.

(3) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (c) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320. (d) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (e) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. (f) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969. (g) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.

(4) (a) Hegde, M.; Sharath Kumar, K. S.; Thomas, E.; Ananda, H.; Raghavan, S. C.; Rangappa, K. S. *RSC Adv.* **2015**, *5*, 93194. (b) Chen, K.; Geraghty, R. J.; Lian, J.; Mao, L.; Pillon, G.; Soto-Acosta, R.; Wu, J.; Zhang, G.; Zhang, J.; Zheng, S. *J. Org. Chem.* **2020**, *85*, 4515. (c) Childress, E. S.; Salamoun, J. M.; Hargett, S. R.; Alexopoulos, S. J.; Chen, S.-Y.; Shah, D. P.; Santiago-Rivera, J.; Garcia, C. J.; Dai, Y.; Tucker, S. P.; Hoehn, K. L.; Santos, W. L. *J. Med. Chem.* **2020**, *63*, 2511. (d) Ni, K.; Meng, L.-G.; Wang, K.; Wang, L. *Org. Lett.* **2018**, *20*, 2245. (e) Hammill, J. T.; Bhasin, D.; Scott, D. C.; Min, J.; Chen, Y.; Lu, Y.; Yang, L.; Kim, H. S.; Connelly, M. C.; Hammill, C.; Holbrook, G.; Jeffries, C.; Singh, B.; Schulman, B. A.; Guy, R. K. *J. Med. Chem.* **2018**, *61*, 2694. (f) Ghorpade, P. V.; Pethsangave, D. A.; Some, S.; Shankarling, G. S. *J. Org. Chem.* **2018**, *83*, 7388. (g) Mishra, N.; Singh, A. S.; Agrahari, A. K.; Singh, S. K.; Singh, M.; Tiwari, V. K. *ACS Comb. Sci.* **2019**, *21*, 389. (h) Li, Q.; Liu, J.; Wei, Y. *Shi M.* **2020**, *85*, 2438. (i) Zhao, Q.-Q.; Li, M.; Xue, X.-S.; Chen, J.-R.; Xiao, W.-J. *Org. Lett.* **2019**, *21*, 3861. (j) Berg, M. E. A.; Naams, J.-B.; Hautala, L. C.; Tolvanen, T. A.; Ahonen, J. P.; Lehtonen, S.; Wähälä, K. *ACS Omega* **2020**, *5*, 1430. (k) Schnitte, M.; Lipinski, S.; Schiebel, E.; Mecking, S. *Organometallics* **2020**, *39*, 13. (l) Dinh, A. N.; Maddox, S. M.; Vaidya, S. D.; Saputra, M. A.; Nalbandian, C. J.; Gustafson, J. L. *J. Org. Chem.* **2020**, *85*, 13895. (m) Liu, F.; Jiang, L.; Qiu, H.; Yi, W. *Org. Lett.* **2018**, *20*, 6270. (n) McAulay, K.; Hoyt, E. A.; Thomas, M.; Schimpl, M.; Bodnarchuk, M. S.; Lewis, H. J.; Barratt, D.; Bhavsar, D.; Robinson, D. M.; Deery, M. J.; Ogg, D. J.; Bernardes, G. J. L.; Ward, R. A.; Waring, M. J.; Kettle, J. G. *J. Am. Chem. Soc.* **2020**, *142*, 10358.

(5) (a) Onaka, M.; Izumi, Y. *Chem. Lett.* **1984**, *13*, 2007. (b) Srivastava, S. K.; Chauhan, P. M. S.; Bhaduri, A. P. *Chem. Commun.* **1996**, 2679. (c) Roche, D.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2000**, *41*, 2083. (d) Le, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis* **2004**, 2809. (e) Ganguly, N. C.; De, P.; Dutta, S. *Synthesis* **2005**, 1103. (f) Das, B.; Venkateswarlu, K.; Krishnaiah, M.; Holla, H. *Tetrahedron Lett.* **2006**, *47*, 8693. (g) Pingali, S. R. K.; Madhav, M.; Jursic, B. S. *Tetrahedron Lett.* **2010**, *51*, 1383. (h) Wang, H.; Wen, K.; Nurahmat, N.; Shao, Y.; Zhang, H.; Wei, C.; Li, Y.; Shen, Y.; Sun, Z. *Beilstein J. Org. Chem.* **2012**, *8*, 744. (i) Huang, Z.; Li, F.; Chen, B.; Lu, T.; Yuan, Y.; Yuan, G. *ChemSusChem* **2013**, *6*, 1337. (j) Tang, R.-J.; Milcent, T.; Crousse, B. *J. Org. Chem.* **2018**, *83*, 930. (k) Gayakwad, E. M.; Patel, K. P.; Shankarling, G. S. *New J. Chem.* **2019**, *43*, 6001. (l) Zhao, H.-Y.; Yang, X.-Y.; Lei, H.; Xin, M.; Zhang, S.-Q. *Syn. Commun.* **2019**, *49*, 1406. (m) Granados, A.; Shafir, A.; Arrieta, A.; Cossío, F. P.; Vallribera, A. *J. Org. Chem.* **2020**, *85*, 2142.

(6) Yang, L.; Lu, Z.; Stahl, S. S. *Chem. Commun.* **2009**, 6460.

(7) Seki, M.; Takahashi, Y. *unpublished results.*

(8) (a) Ramadoss, V.; Alonso-Castro, A. J.; Campos-Xolalpa, N.; Solorio-Alvarado, C. R. *J. Org. Chem.* **2018**, *83*, 10627. (b) Dockendorff, C.; Gandhi, D. M.; Kimball, I. H.; Eum, K. S.; Rusinova, R.; Ingólfsson, H. I.; Kapoor, R.; Peyear, T.; Dodge, M. W.; Martin, S. F. *Biochemistry* **2018**, *57*, 2733. (c) Das, S.; Mallick, S.; Sarkar, S. D.; Aldrich, R. W.; Andersen, O. S.; Sack, J. T. *J. Org. Chem.* **2019**, *84*, 12111. (d) Wang, X.; Liu, H.; Xie, C.; Zhoua, F.; Ma, C. *New J. Chem.* **2020**, *44*, 2465. (e) Nykaza, T. V.; Li, G.; Yang, J.; Luzung, M. R.; Radosevich, A. T. *Angew. Chem. Int. Ed.* **2020**, *59*, 4505.

(9) In contrast, the recently developed azidation process employing $CuSO_4{\cdot}5H_2O/NaN_3/Na_2S_2O_8$ was speculated to proceed via radical intermediates.[7]

(10) Bacon, R. G. R.; Lzzat, A. R. *J. Chem. Soc. C* **1966**, 791.

(11) Liang, C.; Su, H.-W. *Ind. Eng. Chem. Res.* **2009**, *48*, 5558.

(12) Bromination of free anilines with $KBr/4Na_2SO_4{\cdot}2H_2O_2{\cdot}NaCl$[5k] has been shown to proceed by a similar process in which nucleophilic attack of Br^+OAc takes place *para* to the amino group.

(13) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Org. Biomol. Chem.* **2003**, *1*, 3232.

