Leaving Group Ability in Nucleophilic Aromatic Amination by Sodium Hydride-Lithium Iodide Composite

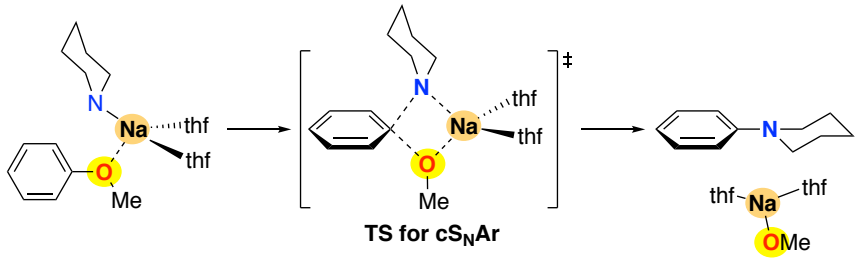
Jia Hao Pang[a]
Derek Yiren Ong[a]
Kohei Watanabe[b]
Ryo Takita*[b]
Shunsuke Chiba*[a]

[a] Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore.

[b] Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

*shunsuke@ntu.edu.sg; takita@mol.f.u-tokyo.ac.jp

Click here to insert a dedication.



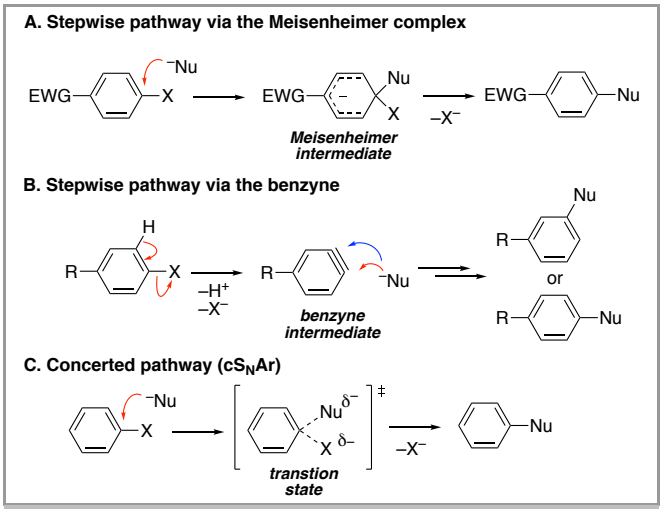
Received:
Accepted:
Published online:
DOI:

Abstract A methoxy group is generally considered as a poor leaving group for nucleophilic substitution reactions. This work verified superior ability of the methoxy group in nucleophilic amination of arenes mediated by the sodium hydride and lithium iodide through experimental and computational approaches.

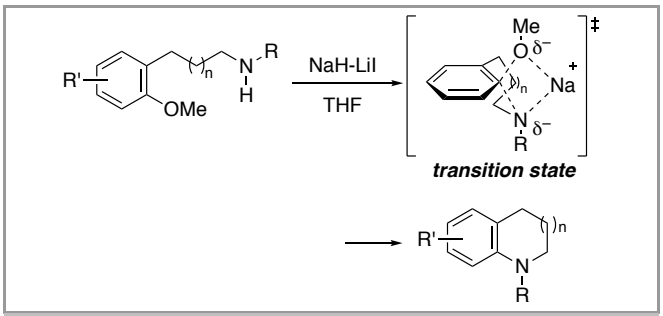
Key words Nucleophilic amination, concerted aromatic substitution, a methoxy group, sodium hydride, DFT calculation

The nucleophilic substitution reaction is a central subject in chemical synthesis, enabling construction of carbon-carbon and carbon-hetero atom bonds from various sets of nucleophiles and electrophiles.[1] The choice of a leaving group on the electrophile is one of the important factors to render the nucleophilic substitution reaction occurring in highly efficient and selective manner with prevention from undesired side reactions such as elimination reactions.

In nucleophilic aromatic substitution (S_NAr) reactions,[2] where an sp^2 hybridized aromatic carbon having a leaving group (X) is substituted by a nucleophile (Nu), several mechanistic scenarios are conceived: two-step pathways through a Meisenheimer complex (Scheme 1A) or a benzyne (Scheme 1B) as the reaction intermediate are commonly accepted reaction mechanisms, whereas a concerted process (cS_NAr) has been considered as a rare case (Scheme 1C).[3-6] Recently, Jacobsen revealed through the experimental and computational studies that the ability of the leaving group greatly affects the reaction course of nucleophilic aromatic substitution reactions, implying that there might be more cases of cS_NAr than expected.[7,8] Our group has also recently developed intra- and intermolecular nucleophilic amination of methoxy(hetero)arenes by NaH in the presence of LiI in THF, where a methoxy group, that is generally considered as a poor leaving group, is substituted with the sodium (lithium) amide nucleophile presumably under the cS_NAr mechanism.[9-11] This work verified a superior ability of the methoxy group to other conventional leaving groups in intermolecular nucleophilic aromatic amination through experimental and computational approaches. Leaving group ability of the aryloxy groups was also investigated.



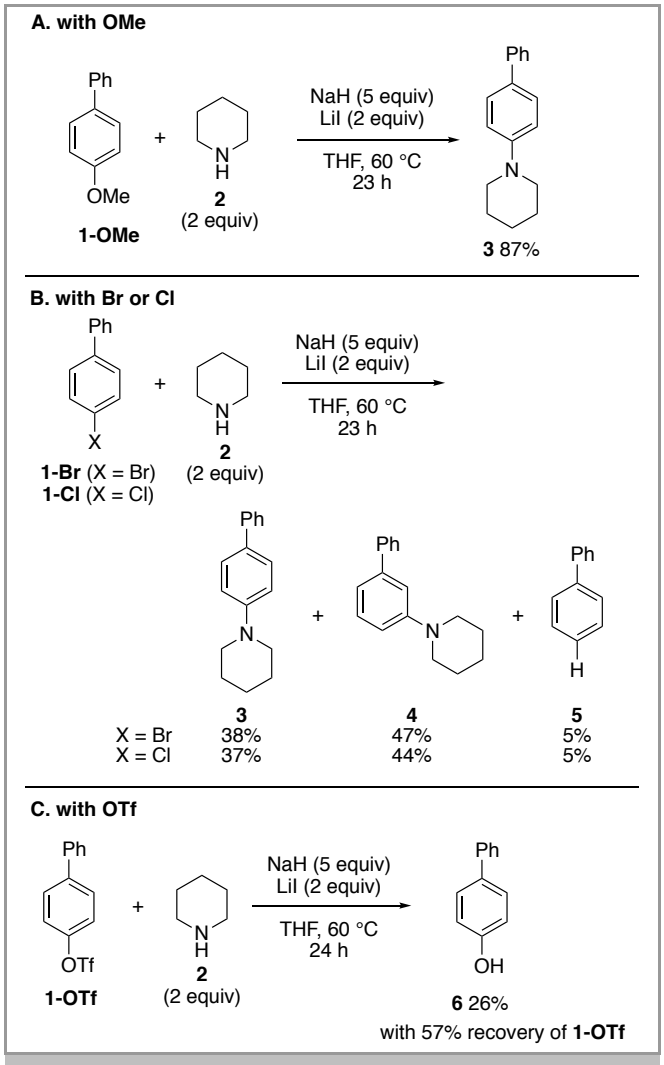
Scheme 1 Nucleophilic aromatic substitution reactions



Scheme 2 Nucleophilic amination of methoxyarenes by NaH-LiI

We commenced our investigation with reactivity comparison between methoxy- and (pseudo)haloarenes (Scheme 3). For this purpose, we utilized substrates **1** based on a biphenyl motif. The reaction of 4-methoxybiphenyl (**1-OMe**) with 2 equiv of

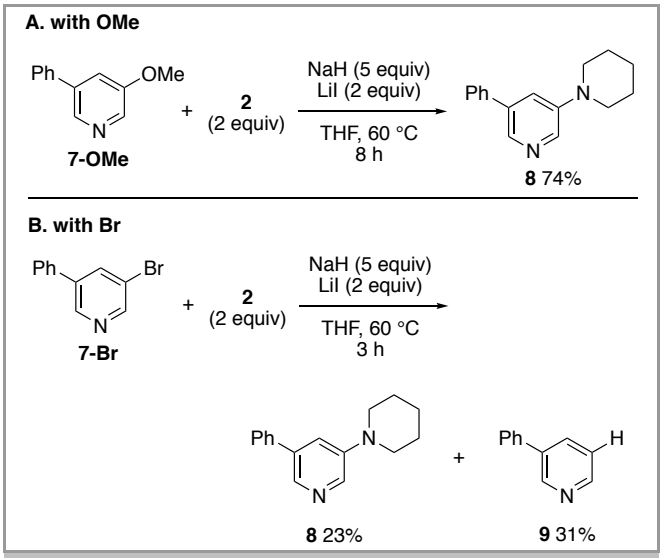
piperidine (**2**) in the presence of NaH (5 equiv) and LiI (2 equiv) in THF at 60 °C gave aminated product **3** in 87% yield as a sole product (Scheme 3A). On the other hand, from bromide (**1-Br**) and chloride (**1-Cl**), a mixture of *para*-aminated **3** and *meta*-aminated **4** was formed through a transient benzyne intermediate (Scheme 3B).[12] We also isolated a small amount of biphenyl (**5**) that should be formed via hydrodehalogenation by the NaH-LiI system.[13] The reaction of triflate **1-OTf** gave only phenol **6** through acyl substitution (Scheme 3C).



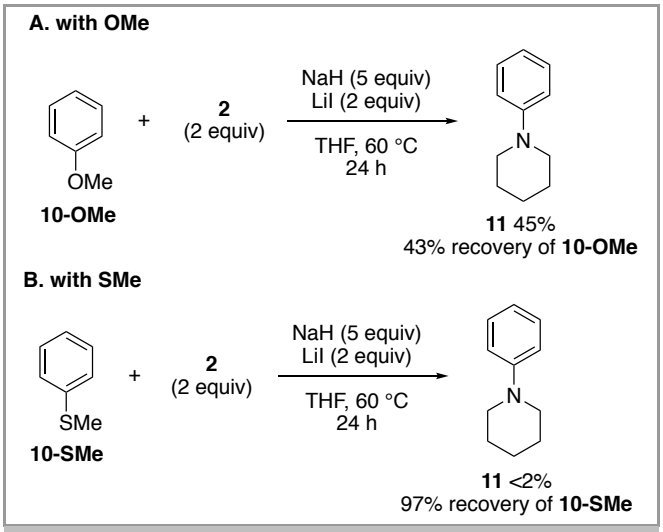
Scheme 3 Methoxyarenes vs (pseudo)haloarenes

Ability of the leaving group in installation of the amine functionality onto the pyridine scaffold was also tested using substrates **7**. Methoxypyridine **7-OMe** could be aminated to afford **8** as a sole product in 74% yield (Scheme 4A). On the other hand, the reaction of 3-bromopyridine **7-Br** afforded amine **8** in only 23% yield along with the formation of hydrodebrominated product **9** in 31% yield (Scheme 4B).

Tobisu recently reported a method for construction of dibenzothiophenes via concerted intramolecular nucleophilic aromatic substitution of thioanisoles by a benzothiolate anion.[14] This stimulated us to investigate reactivity difference between anisole (**10-OMe**) and thioanisole (**10-SMe**) toward the intermolecular nucleophilic amination (Scheme 5). We found obvious reactivity difference: almost no formation of aminated product **11** from the reaction with thioanisole (**10-SMe**) under the present reaction conditions (Scheme 5B).



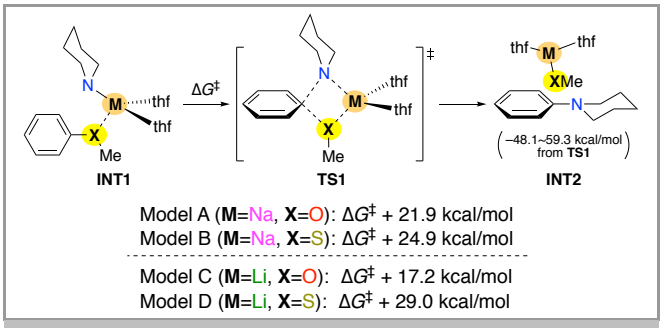
Scheme 4 Methoxypyridine vs bromopyridine



Scheme 5 Anisole vs thioanisole

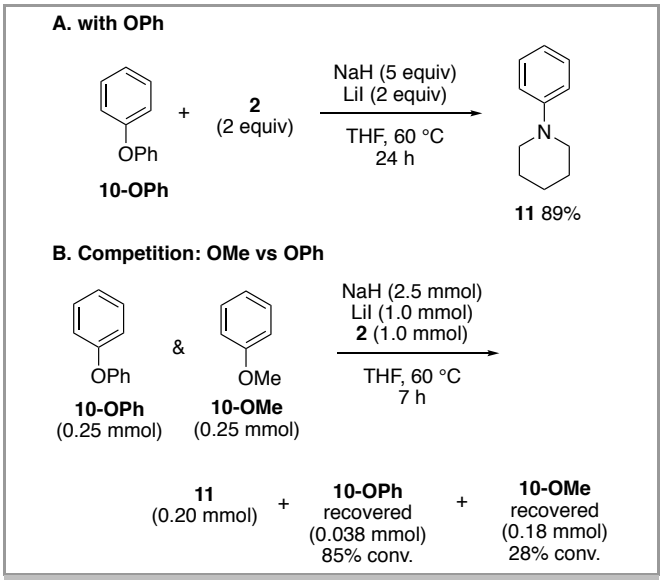
DFT calculations were performed at the B3LYP/6-31+G* (scrf=pcm, THF) level of theory to gain the insight on the observed reactivity difference between anisole (**10-OMe**) and thioanisole (**10-SMe**) (Scheme 6).[15] When Na piperidide that should be generated under the present reaction conditions promoted the reaction, the structurally similar transition state structures were obtained with both **10-OMe** and **10-SMe** (model A and B). However, the activation barrier ($\Delta G^{\ddagger}$) in model A was reasonably lower than that in model B (+21.9 vs +24.9 kcal/mol), which is consistent with the experimental results in Scheme 5. In addition, the reactions promoted by Li piperidide species were also investigated; the low activation energy (+17.2 kcal/mol) was obtained with **10-OMe** in model C, while the very high energy was necessary for the reaction with **10-SMe**. In both of the cases, the counter cation (sodium or lithium) and the sulfur atom in TS1 seems to have a weak interaction (cf. Na–O length: 2.34 Å in model A and Na–S length: 2.95 Å in model B; Li–O length: 1.95 Å in model C and Li–S length: 3.01 Å in model

D. See the Supporting Information.), probably making it difficult to build up the organized 4-membered transition state. Although it is not certain as to which counter cation (either Na or Li) plays a dominant role in the present process, the reaction with **10-OMe** should proceed much faster in both of the cases. It should be also noted that all of model reactions were found to proceed in a concerted fashion.



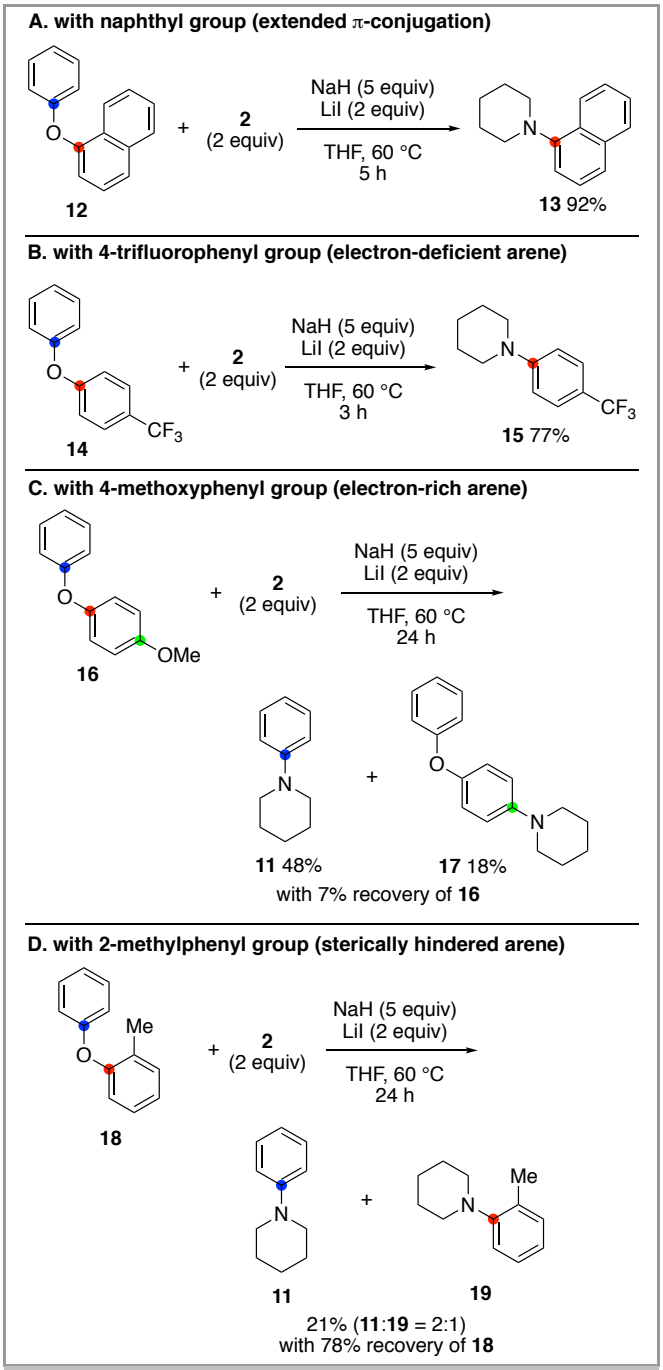
Scheme 6 DFT calculations for the model reactions of **10-OMe** or **10-SMe** with Na or Li piperidide at the B3LYP/6-31+G* (scrf=pcm, THF) level of theory.

The reaction of diphenyl ether (**10-OPh**) proceeded smoothly to give **11** in 89% yield (Scheme 7A). The higher leaving group ability of the phenoxy group could be ascertained by a competitive reaction between **10-OPh** and **10-OMe** (Scheme 7B).



Scheme 7 Nucleophilic aromatic substitution of diphenyl ether (**10-OPh**) and anisole (**10-OMe**)

These findings intrigued us to investigate electronic and steric factors for the nucleophilic amination of unsymmetrical biaryl ethers (Scheme 8). The reaction of 1-phenoxynaphthalene (**12**) gave N-(1-naphthyl)piperidine (**13**) in 92% yield as a single product, suggesting that the naphthyl carbon (marked in red), having lower LUMO due to longer π-conjugation, is preferred for the nucleophilic attack (Scheme 8A). Similarly, in the case of 1-phenoxy-4-trifluoromethylbenzene (**14**), the more electron deficient red carbon was aminated to form N-(4-trifluoromethylphenyl)piperidine (**15**) solely (Scheme 8B). On the other hand, 1-methoxy-4-phenoxybenzene (**16**) possesses three different C(sp²)-O bonds (Scheme 8C). From the reaction of **16**, formation of amines **11** and **17** was observed, suggesting that the process evades the seemingly most electron rich sp² carbon marked in red for the nucleophilic substitution. The nucleophilic amination of biaryl ethers was found very sensitive to the steric factor (Scheme 8D): installation of an *ortho*-methyl group (for substrate **18**) made the reaction progress sluggish, resulting in incomplete conversion to afford a mixure of **11** and **19** in 2:1 ratio in only 21% yield in total even after stirring for 24 h.



Scheme 8 Nucleophilic aromatic substitution of diaryl ethers.

To summarize, this work validated that the methoxy group, which is commonly considered as a poor leaving group, is most superior for nucleophilic aromatic substitution reactions under

the NaH-LiI system from the view points of reaction efficiency and atom economy. Although the aryoxy group generally possesses a better leaving group ability than the methoxy does, regioselectivity of the amination of unsymmetrical biaryl ethers is heavily affected by electronic and steric factors.

Procedures

All experiments were carried out under a N_2 atmosphere with anhydrous solvents. Tetrahydrofuran (THF) was taken from a solvent purification system (PS-400-5, innovative technology Inc.). NaH (60% dispersion in mineral oil), LiI were purchased from Sigma-Aldrich, Inc. LiI was dried over P_2O_5 under reduced pressure at 120 °C. Due to moisture sensitivity of NaH, it was consistently handled under an Ar atmosphere in a glovebox or with Schlenk techniques under a N_2 atmosphere. The arene substrates **1-Br**,[16] **1-Cl**,[17] **1-OTf**,[18] **7-Br**,[19] **12**,[20] **14**,[21] **16**,[22] and **18**[23] were prepared using the reported methods. The substrates **1-OMe**, **7-OMe**, **10-OMe**, **10-SMe**, and **10-OPh** were commercially available and used as received. TLC analyses were performed on silica gel glass plates (Merck silica gel 60), and the spots were visualized with UV light (254 and 365 nm). Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Shimadzu GC-2010 was used for the GC analyses. ^{1}H NMR spectra (400 MHz) were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ [using TMS (for ^{1}H, δ = 0.00) as internal standard]. ^{13}C NMR spectra (100 MHz) were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ (using $CDCl_3$ (for ^{13}C, δ = 77.00) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, brs = broad.

General Procedure

To a mixture of NaH (60% dispersion, 100 mg, 2.50 mmol) and LiI (134 mg, 1.00 mmol) in a 25 mL sealed tube was added a solution of arene substrate (0.50 mmol) in THF (0.5 mL) and piperidine (85.2 mg, 99 µL, 1.00 mmol). The reaction was stirred at 60 °C (the reaction time was indicated in the respective scheme) and was quenched with water at 0 °C. The organic materials were extracted with dichloromethane (20 mL × 3). The combined organic extracts were washed brine and dried over $MgSO_4$. The volatile materials were removed *in vacuo* and the resulting crude residue was purified by flash column chromatography (the eluent system was indicated for the respective substrate) to give the product.

Scheme 3A

1-([1,1'-Biphenyl]-4-yl)piperidine (3)[9a]

The spectroscopic data for **3** are identical to those reported in the literature

Yield: 103 mg (0.434 mmol, 87%); 23 h; 2% ethyl acetate in hexane as the eluent; white solid; mp 124-126 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.39 (dd, *J* = 8.2, 8.2 Hz, 2H), 7.26 (t, *J* = 8.2 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.21 (t, *J* = 5.5 Hz, 4H), 1.75 – 1.69 (m, 4H), 1.62 – 1.55 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 141.1, 131.6, 128.7, 127.7, 126.5, 126.3, 116.4, 50.4, 25.8, 24.4.

Scheme 3B with 1-Br

1-([1,1'-Biphenyl]-4-yl)piperidine (3)[9a] and **1-([1,1'-biphenyl]-3-yl)piperidine (4)**[24] were obtained as an inseparable mixture. The spectroscopic data for **3** and **4** are identical to those reported in the literature.

Yield: 99.9 mg, (0.421 mmol, 85%, **3**: 38%, **4**: 47%); 23 h; 2% ethyl acetate in hexane as the eluent; light brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 – 7.54 (d, *J* = 8.2 Hz, 2 × 0.45 H + 2 × 0.55H), 7.49 (d, *J* = 8.8 Hz, 2 × 0.45 H), 7.43 – 7.37 (dd, *J* = 8.2, 8.1 Hz, 2 × 0.45 H + m, 2 × 0.55H), 7.34 – 7.24 (t, *J* = 8.2 Hz, 1 × 0.45H + m, 2 × 0.55H), 7.14 (t, *J* = 2.0 Hz, 1 × 0.55 H), 7.07 (d, *J* = 7.6 Hz, 1 × 0.55 H), 6.99 (d, *J* = 8.2 Hz, 2 × 0.45 H), 6.93 (dd, *J* = 8.5 Hz, 2.4 Hz, 1 × 0.55 H), 3.22 – 3.19 (t, *J* = 5.5 Hz, 4 × 0.45 H + t, *J* = 5.5 Hz, 4 × 0.55 H), 1.75 – 1.69 (m, 4 × 0.45H + m, 4 × 0.55H), 1.62 – 1.55 (m, 2 × 0.45H + m, 2 × 0.55H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 151.5, 142.2, 142.0, 141.1, 131.6, 129.4, 128.7, 128.6, 127.7, 127.2, 127.1, 126.5, 126.3, 118.3, 116.4, 115.6, 115.5, 50.8, 50.4, 25.9, 25.8, 24.4 (overlapped).

Biphenyl (5)[25] was formed in 5% yield based on ^{1}H NMR of the crude material using dibromoethane as the internal standard. The spectroscopic data are identical to those reported in the literature.

Scheme 3B with 1-Cl

1-([1,1'-Biphenyl]-4-yl)piperidine (3)[9a] and **1-([1,1'-biphenyl]-3-yl)piperidine (4)**[24] were obtained as an inseparable mixture. The spectroscopic data for **3** and **4** are identical to those reported in the literature.

Yield: 97.0 mg, (0.409 mmol, 81%, **3**: 37%, **4**: 44%); 23 h; 2% ethyl acetate in hexane as the eluent; light brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 – 7.54 (d, *J* = 8.2 Hz, 2 × 0.45 H + 2 × 0.55H), 7.49 (d, *J* = 8.8 Hz, 2 × 0.45 H), 7.43 – 7.37 (dd, *J* = 8.2, 8.1 Hz, 2 × 0.45 H + m, 2 × 0.55H), 7.34 – 7.24 (t, *J* = 8.2 Hz, 1 × 0.45H + m, 2 × 0.55H), 7.14 (t, *J* = 2.0 Hz, 1 × 0.55 H), 7.07 (d, *J* = 7.6 Hz, 1 × 0.55 H), 6.99 (d, *J* = 8.2 Hz, 2 × 0.45 H), 6.93 (dd, *J* = 8.5 Hz, 2.4 Hz, 1 × 0.55 H), 3.22 – 3.19 (t, *J* = 5.5 Hz, 4 × 0.45 H + t, *J* = 5.5 Hz, 4 × 0.55 H), 1.75 – 1.69 (m, 4 × 0.45H + m, 4 × 0.55H), 1.62 – 1.55 (m, 2 × 0.45H + m, 2 × 0.55H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 151.5, 142.2, 142.0, 141.1, 131.6, 129.4, 128.7, 128.6, 127.7, 127.2, 127.1, 126.5, 126.3, 118.3, 116.4, 115.6, 115.5, 50.8, 50.4, 25.9, 25.8, 24.4 (overlapped).

Biphenyl (5)[25] was formed in 5% yield based on ^{1}H NMR of the crude material using dibromoethane as the internal standard. The spectroscopic data are identical to those reported in the literature.

Scheme 3C

[1,1'-biphenyl]-4-ol (6)[26]

The spectroscopic data for **6** are identical to those reported in the literature.

Yield: 22.1 mg, (0.130 mmol, 26%); 24 h; 10% ethyl acetate in hexane as the eluent; white solid; mp 164 – 166 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.4 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.41 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.88 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.0, 140.7, 134.0, 128.7, 128.4, 126.7 (overlapped), 115.6.

Scheme 4A

3-phenyl-5-(piperidin-1-yl)pyridine (8)[9b]

The spectroscopic data for **8** are identical to those reported in the literature.

Yield: 88.2 mg, (0.370 mmol, 74%); 8 h; 5% ethyl acetate in CH_2Cl_2 as the eluent; pale orange solid; mp 73 – 75 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 2.6 Hz, 1H), 8.28 (d, *J* = 2.0 Hz, 1H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.46 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.34 (dd, *J* = 2.6, 2.0 Hz, 1H), 3.26 (t, *J* = 5.4 Hz, 4H), 1.77 – 1.70 (m, 4H), 1.65 – 1.59 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 138.6, 138.6, 137.6, 136.7, 128.9, 127.9, 127.3, 121.2, 49.9, 25.6, 24.1.

Scheme 4B

3-phenyl-5-(piperidin-1-yl)pyridine (8)[9b]

Yield: 27.1 mg, (0.114 mmol, 23%); 3 h.

3-phenylpyridine (9)[27]

The spectroscopic data for **9** are identical to those reported in the literature.

Yield: 23.7 mg, (0.153 mmol, 31%); 3 h; 20% ethyl acetate in hexane as the eluent; light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.59 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.86 (ddd, *J* = 7.9, 2.3, 1.7 Hz, 1H), 7.59 – 7.56 (m, 2H), 7.50 – 7.45 (m, 2H), 7.42 – 7.38 (m, 1H), 7.35 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5, 148.3, 137.8, 136.6, 134.4, 129.1, 128.1, 127.2, 123.6.

Scheme 5A

1-phenylpiperidine (11)[9a] was formed in 45% yield (for 24 h) with recovery of **10-OMe** in 43% yield based on ^{1}H NMR of the crude material using 1,1,2,2-tetrachloroethane as the internal standard. The spectroscopic data are identical to those reported in the literature.

Scheme 5B

1-phenylpiperidine (11)[9a] was formed in <2% yield (for 24 h) with recovery of **10-SMe** in 97% yield based on ^{1}H NMR of the crude material using 1,1,2,2-tetrachloroethane as the internal standard. The spectroscopic data are identical to those reported in the literature.

Scheme 7A

1-phenylpiperidine (11)[9a]

The spectroscopic data for **11** are identical to those reported in the literature.

Yield: 70.1 mg, (0.435 mmol, 89%); 24 h; 2% ethyl acetate in hexane as the eluent; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 8.3, 7.3 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 6.82 (t, *J* = 7.3 Hz, 1H), 3.15 (t, *J* = 5.4, 4H), 1.74 – 1.68 (m, 4H), 1.60 – 1.54 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 129.0, 119.2, 116.6, 50.7, 25.9, 24.3.

Scheme 7B

To a mixture of NaH (60% dispersion, 102 mg, 2.54 mmol) and LiI (135 mg, 1.01 mmol) in a 25 mL sealed tube was added a solution oxydibenzene **10-OPh** (42.6 mg, 0.250 mmol) and anisole **10-OMe** (27.2 mg, 0.252 mmol) in THF (0.5 mL). piperidine (85.2 mg, 98.8 µL, 1.00 mmol) and dodecane (84.8 mg, 0.498 mmol). The reaction was stirred at 60 °C for 24 h. A sample of the reaction mixture was taken to perform gas chromatography analyses to determine recovery of **10-OMe** (72% yield). The reaction was quenched with water at 0 °C. The organic materials were extracted with dichloromethane (20 mL × 3). The combined organic extracts were washed with brine and dried over $MgSO_4$ The volatile materials were removed *in vacuo* and the resulting crude residue was purified by flash column chromatography using 2% ethyl acetate in hexane as the eluent to give **11** as a clear oil (yield: 32.6 mg, 0.202 mmol); and **10-OPh** as a clear oil (yield: 6.2 mg, 0.037 mmol, 15% yield). The spectroscopic data for **11** and **10-OPh** are identical to those reported in the literature.

Scheme 8A

1-(naphthalen-1-yl)piperidine (13)[9a]

The spectroscopic data for **13** are identical to those reported in the literature.

Yield: 94.8 mg, (0.449 mmol, 92%); 5 h; 2% ethylacetate in hexane as the eluent; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 – 8.18 (m, 1H), 7.80 – 7.78 (m, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.37 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.03 (dd, *J* = 7.6, 0.9 Hz, 1H), 3.03 (brs, 4H), 1.83 (quint, *J* = 5.5 Hz, 4H), 1.64 (brs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1, 134.8, 129.2, 128.3, 125.9, 125.7, 125.2, 123.9, 123.0, 114.5, 54.7, 26.7, 24.7.

Scheme 8B

1-(4-(trifluoromethyl)phenyl)piperidine (15)[28]

The spectroscopic data for **15** are identical to those reported in the literature.

Yield: 88.5 mg, (0.386 mmol, 77%); 3 h; 4% diethyl ether in pentane as the eluent; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 3.27 – 3.25 (m, 4H), 1.71 – 1.67 (m, 4H), 1.63 – 1.61 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 126.3 (q, *J* = 3.8 Hz), 124.9 (q, *J* = 270.4 Hz), 119.6 (q, *J* = 32.6 Hz), 114.6, 49.3, 25.4, 24.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -61.2.

Scheme 8C

1-phenylpiperidine (11)[9a]

The spectroscopic data for **11** are identical to those reported in the literature.

Yield: 38.4 mg, (0.238 mmol, 48%); 24 h; 2% ethylacetate in hexane as the eluent; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 8.3, 7.3 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 6.82 (t, *J* = 7.3 Hz, 1H), 3.15 (t, *J* = 5.4, 4H), 1.74 – 1.68 (m, 4H), 1.60 – 1.54 (m, 2H).

13C NMR (100 MHz, $CDCl_3$): δ 152.3, 129.0, 119.2, 116.6, 50.7, 25.9, 24.3.

1-(4-phenoxyphenyl)piperidine (17)[29]

The spectroscopic data for **17** are identical to those reported in the literature.

Yield: 23.0 mg, (0.091 mmol, 18%); 24 h; 2% ethylacetate in hexane as the eluent; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (dd, *J* = 7.7 Hz, 2H), 7.02 (t, *J* = 7.7 Hz, 1H), 6.95 – 6.91(m, 6H), 3.10 (t, *J* = 5.4 Hz, 4H), 1.75 – 1.70 (m, 4H), 1.59 – 1.54 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 149.4, 149.0, 129.5, 122.2. 120.4, 118.1, 117.5, 51.5, 26.0, 24.2.

Scheme 8D

1-phenylpiperidine (11)[9a] and **1-(o-tolyl)piperidine (19)**[30] were obtained as an inseparable mixture. The spectroscopic data for **11** and **19** are identical to those reported in the literature.

Yield: 16.1 mg, (0.106 mmol, 21%, **11**: 14%, **19**: 7%); 24 h; 4% diethyl ether in pentane as the eluent; pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 8.3, 7.3 Hz, 2×1H), δ 7.17 – 7.12 (m, 2×0.5H), 6.99 (d, *J* = 7.1 Hz, 1×0.5H), 6.94 (d, *J* = 8.3 Hz, 2×1H + dd, *J* = 7.1, 7.1 Hz, 1×0.5H), 6.82 (t, *J* = 7.3 Hz, 1×1H), 3.16 – 3.14 (m, 4×1H), 2.84 – 2.82 (m, 4×0.5H), 2.30 (s, 3×0.5H), 1.73 – 1.68 (m, 4×1H + m, 4×0.5H), 1.60 – 1.55 (m, 2×1H + m, 2×0.5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 152.3, 132.6, 130.9, 129.0, 126.4, 122.5, 119.2, 118.9, 116.6, 53.3, 50.7, 26.6, 25.9, 24.4, 24.3, 17.8.

Funding Information

This work was supported by funding from Nanyang Technological University (NTU) (for S.C.), the Singapore Ministry of Education (Academic Research Fund Tier 1: RG10/17 for S.C.), and JSPS Grant-in-Aid for Scientific Research (C) (19K0662), Takeda Science Foundation, The FUGAKU Trust for Medicinal Research, and Uehara Memorial Foundation (for R.T.).

Acknowledgment

Computations were performed using Research Center for Computational Science at Okazaki, Japan.

Supporting Information

YES

Primary Data

NO

References

(1) Brückner, R. in: *Organic Mechanisms: Reactions, Stereochemistry and Synthesis*, (Ed.: Harmata, M.), Springer, Berlin, Heidelberg, **2010**, chapter 2 and chapter 5.
(2) Terrier, F. Modern Nucleophilic Aromatic Substitution, Wiley-VCH, Weinheim, **2013**.
(3) For vicarious nucleophilic substitution, see: Błaziak, K.; Danikiewicz, W.; Mąkosza, M. *J. Am. Chem. Soc*. **2016**, *138*, 7276, and references therein.
(4) For radical-nucleophilic aromatic substitution ($S_{RN}1$), see: Rossi, R. A.; Pierini, A. B.; Peñeñory, A. B. *Chem. Rev*. **2003**, *103*, 71.
(5) For base-promoted homolytic aromatic substitution, see: Studer, A.; Curran, D. P. *Nat. Chem*. **2014**, *6*, 765.
(6) For nucleophilic aromatic substitution via S_N1 type mechanism, see: Crespi, S.; Protti, S.; Fagnoni, M. *J. Org. Chem*. **2016**, *81*, 9612.
(7) Kwan, E. E.; Zeng, Y.; Besser, H. A.; Jacobsen, E. N. *Nat. Chem*. **2018**, *10*, 917.
(8) For our review on cS_NAr reactions, see: Rohrbach, S.; Smith, A. J.; Pang, J. H.; Poole, D. L.; Tuttle, T.; Chiba, S.; Murphy, J. A. *Angew. Chem. Int. Ed*. **2019**, in press (DOI: 10.1002/anie.201902216R1).
(9) (a) Kaga, A.; Hayashi, H.; Hakamata, H.; Oi, M.; Uchiyama, M.; Takita, R.; Chiba, S. *Angew. Chem. Int. Ed*. **2017**, *56*, 11807. (b) Pang, J. H.; Kaga, A.; Chiba, S. *Chem. Commun*. **2018**, *54*, 10324.
(10) For Ni-catalyzed amination of methoxyarenes, see: (a) Tobisu, M.; Shimasaki, T.; Chatani, N. *Chem. Lett*. **2009**, *38*, 710. (b) Tobisu, M.; Yasutome, A.; Yamakawa, K.; Shimasaki, T.; Chatani, N. *Tetrahedron* **2012**, *68*, 5157.
(11) For amination of methoxyarenes via their cation radical intermediates generated under organic photoredox catalysis, see: Tay, N. E. S.; Nicewicz, D. A. *J. Am. Chem. Soc*. **2017**, *139*, 16100.
(12) For nucleophilic amination of aryl iodides with magnesium amides via single-electron-transfer mechanism, see: Kiriyama, K.; Okkura, K.; Tamakuni, F.; Shirakawa, E. *Chem. Eur. J*. **2018**, *24*, 4519.
(13) Ong, D. Y.; Tejo, C.; Xu, K.; Hirao, H.; Chiba, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 1840.
(14) Masuya, Y.; Kawashima, Y.; Kodama, T.; Chatani, N.; Tobisu, M. *Synlett* (DOI: 10.1055/s-0037-1611974).
(15) We assumed that counter ion metathesis between NaH and LiI allows for generation of activated form of NaH, that possesses enhanced basisity to promote the present process. Our preliminary work on the materials characterization, see: Hong, Z.; Ong, D. Y.; Muduli, S. K.; Too, P. C.; Chan, G. H.; Tnay, Y. L.; Chiba, S.; Nishiyama, Y.; Hirao, H.; Soo, H. S. *Chem. Eur. J*. **2016**, *22*, 7108.
(16) Pérez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155.
(17) Li, J.-H.; Liu, W.-J. *Org. Lett*. **2004**, *6*, 2809.
(18) Kalvet, I.; Magni, G.; Schoenebeck, F. *Angew. Chem. Int. Ed*. **2017**, *56*, 1581.
(19) Crisenza, G. E. M.; Dauncey, E. M.; Bower, J. F. *Org. Biomol. Chem.* **2016**, *14*, 5820.
(20) Jammi, S.; Sakthivel, S.; Rout, L.; Mukherjee, T.; Mandal, S.; Mitra, R.; Saha, P.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 1971.
(21) Burgos, C.H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 4321.
(22) Liu, X.; Zhang, S. *Synlett* **2011**, *2011*, 268.

(23) Yong, F.-F.; Teo, Y.-C.; Yan, Y.-K.; Chua, G.-L. *Synlett* **2012**, 101.
(24) Girard, S. A.; Hu, X.; Knauber, T.; Zhou, F.; Simon, M.-O.; Deng, G.-J.; Li, C.-J. *Org. Lett.* **2012**, *14*, 5606.
(25) Yasui, K.; Higashino, M.; Chatani, N.; Tobisu, M. *Synlett* **2017**, *28*, 2569.
(26) Gauchot, V.; Lee, A.-L. *Chem. Commun*. **2016**, *52*, 10163.
(27) Cao, Q.; Howard, J. L.; Wheatley, E.; Browne, D. L. *Angew. Chem. Int. Ed.* **2018**, *57*, 11339.
(28) Lim, C.-H.; Kudisch, M.; Liu, B.; Miyake, G. M. *J. Am. Chem. Soc*. **2018**, *140*, 7667.
(29) Zhang, J.; Park, S.; Chang, S. *J. Am. Chem. Soc*. **2018**, *140*, 13209.
(30) Fang, Y.; Zheng, Y.; Wang, Z. *Eur. J. Org. Chem*. **2012**, 1495.