HETEROCYCLES, Vol. 95, No. 2, 2017, pp. 1272-1284. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 1st November, 2016, Accepted, 2nd December, 2016, Published online, 17th February, 2017
DOI: 10.3987/COM-16-S(S)90

SELECTIVE ARYL RADICAL TRANSFERS INTO *N*-HETEROAROMATICS FROM DIARYLIODONOIUM SALTS WITH TRIMETHOXYBENZENE AUXILIARY

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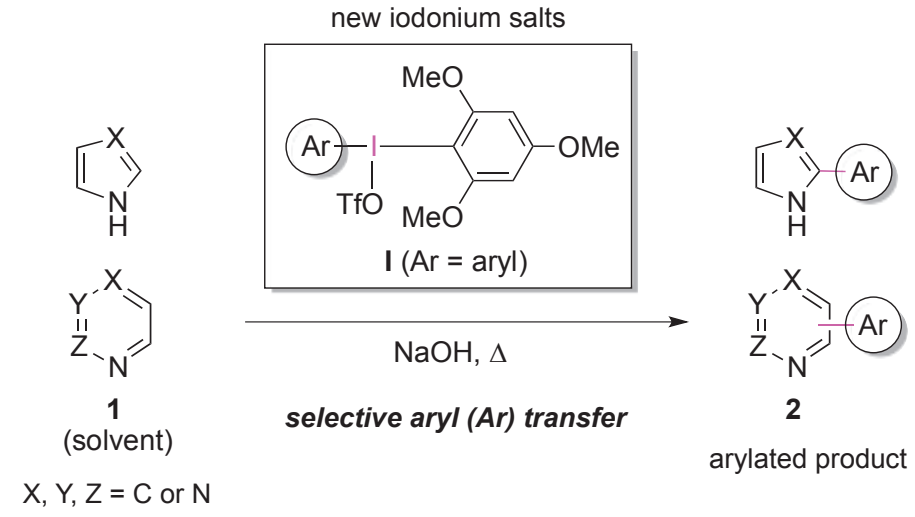
Abstract – We have found that a series of trimethoxybenzene-based diaryliodonium(III) salts **I** ($ArI^+Ar'X^-$, where Ar = various aryl groups, Ar' = 2,4,6-trimethoxyphenyl, X^- = counterion) can exclusively cause Ar-transfers during the base-induced radical couplings with *N*-heteroaromatic compounds **1** by working the trimethoxybenzene ring (Ar') as an inert coupling auxiliary. By the treatment with *N*-heteroaromatics **1** as the solvent, the metal-free arylations utilizing the specific salts **I** initiated by solid NaOH upon heating selectively produced the corresponding biaryls **2** in good yields without the formation of the trimethoxybenzene (Ar') coupling product.

In Celebration of Professor Masakatsu Shibasaki on His 70th Birthday

With respect to the recent green chemistry aspects, the metal-free advances that can avoid the use of transition metal catalysts and organometallic compounds in the conventional methodologies are strongly required in the modern coupling reaction developments.[1] Hypervalent iodine reagents are now widely accepted as a safe alternative to toxic heavy-metal oxidants for developing environmentally benign oxidations and has recently become a significant tool for reproducing the synthetic transformations that are conventionally performed with rare metal catalysts.[2] One of the most significant contributions to this area is our oxidative cross-coupling strategy for aromatic compounds discovered in recent years. In 2008,

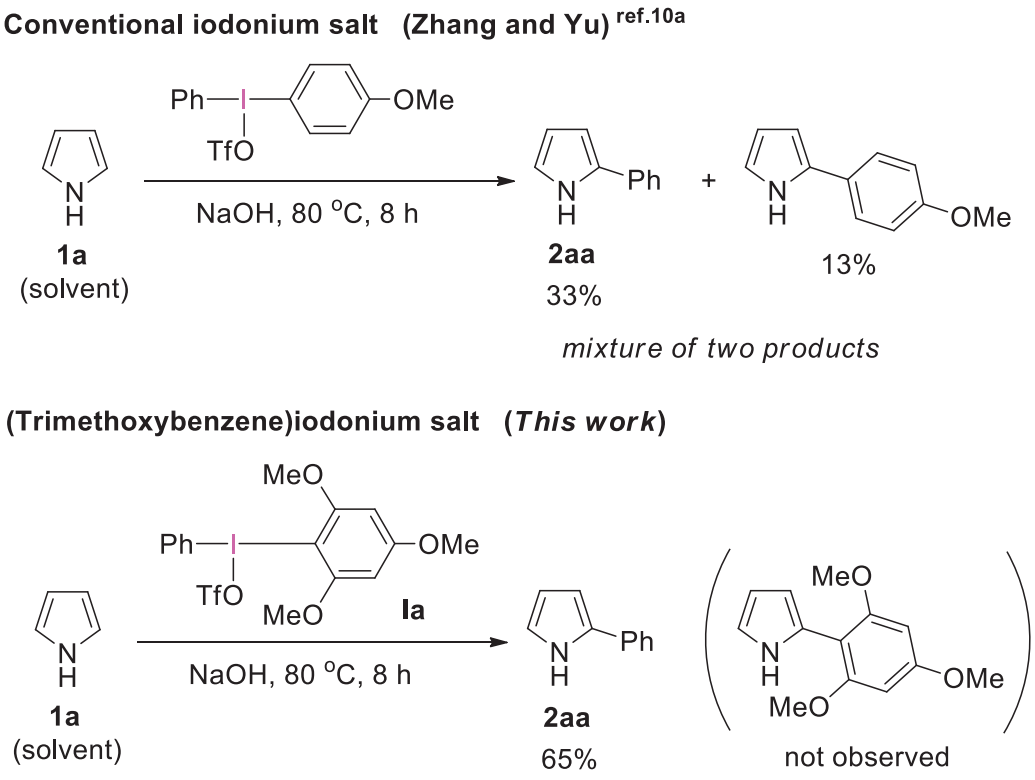
we first effectively realized the metal-free oxidative C-H cross-coupling between unfunctionalized aromatic substrates, naphthalenes and alkylbenzenes, using a hypervalent iodine-induced single electron transfer (SET) oxidation strategy into the naphthalene rings.[3] An exciting new metal-free coupling alternative for the mixed biaryl synthesis of heteroaromatic compounds was then developed in 2009 by pioneering the novel reactivities of the σ-heteroaryliodonium(III) salts generated *in situ* by the treatment of a hypervalent iodine reagent with various heteroaromatic compounds.[4] Due to their advantage for avoiding the use of metal catalysts and metal waste generations, such an oxidative aryl coupling strategy for making a new C-C bond directly from the C-H groups under metal-free conditions is a promising greener alternative to the classical methods.[5,6]

One of the important and well-investigated intermediates for developing new coupling reactions in recent studies is the diaryliodonium(III) salt, which have two aryl groups bound to a hypervalent iodine(III) center, having significant applications as highly reactive arylating agent that even allows the metal-free couplings by the formal S_NAr processes.[7] In order to achieve such effective couplings, pioneering a new aromatic ring activation strategy was essential together with the appropriate design of the iodonium salts for the reactions. In our continuous interest for the metal-free aryl-aryl coupling reactions initiated by Lewis acids,[8] the chemical behaviors and aryl transfer abilities of extensive diaryliodonium salts under acidic conditions have been revealed in recent years.[9] However, controlling the aryl group transfer reactivities of the diaryliodonium salts under basic conditions has rarely been reported to date, though there are presently some interesting reports for the metal-free aryl couplings initiated by the base activators.[10] In this paper, we report the new reactivities of the trimethoxybenzene-based diaryliodonium salts **I** as a highly selective entry for the base-induced radical couplings with *N*-heteroaromatics **1**, such as pyrrole, pyridine, and other related compounds (Scheme 1).



Scheme 1. Metal-free aryl coupling of *N*-heteroaromatics **1** by diaryliodonium(III) salts **I** having non-transferring trimethoxybenzene group

In 2012, Zhang, Yu, and coworkers revealed that upon heating of the diaryliodonium salts, pyrroles and other six-membered *N*-heteroarenes can cause arylations *via* some radical mechanism without the use of any metal catalyst when treating these *N*-heteroaromatics as a solvent.[10a] Unfortunately, when using the diaryliodonium salt having two different aryl groups ($Ar^1I^+Ar^2X^-$, X^- = counterion), the coupling events were uncontrolled regarding transferring of the aryl groups from the iodonium salts, and mixture of the Ar^1 and Ar^2 coupling products were produced in the study. For example, the NaOH-promoted coupling reaction of pyrrole **1a** as a solvent with (4-anisyl)phenyliodonium triflate at 80 °C gave a mixture of the two arylated products, 2-phenylpyrrole **2aa** and 2-(4-anisyl)pyrrole, in 33% and 13% yields, respectively (Scheme 2, above), in which the less electron-rich phenyl ring seems to be favorable for the aryl transfer. In our continuous reactivity studies of the diaryliodonium salts attached to electron-rich aryl groups,[9] we have examined various alternative iodonium salts in our library for this transformation, and the salt **Ia** having the trimethoxybenzene group[11] was found to be optimal for the effective phenylation suppressing the random aryl transfers of conventional diaryliodonium salts. The result is that instead using the specific salt **Ia** as an aryl source for the same treatment of the pyrrole **1a**, 2-phenylpyrrole **2aa** was smoothly obtained as a single arylation product in the somewhat higher yield of 65% (Scheme 2, below). Gratefully, we now report a product as a result of the coupling with the trimethoxybenzene group in the salt **Ia** was not detected during the reaction (<1% formation by ^{1}H NMR analysis of the crude reaction mixture).

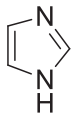
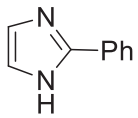
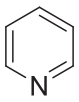
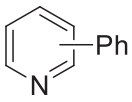
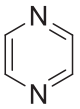
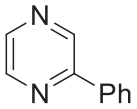
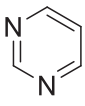
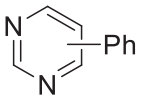
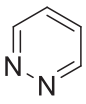
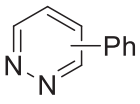


Scheme 2. Arylation of pyrrole **1a**: Aryl transfer selectivities by conventional salt versus new **Ia**

Although the significant utility of this type trimethoxybenzene auxiliary for directing the courses of the aryl transfers have become recognized in recent few transformations,[12] its general applications in the metal-free couplings are rare and this is the first example revealing its non-transferring ability during the aryl radical coupling process to furnish the biaryl product.

Strongly encouraged by the new and unique aryl transfer reactivity of the (trimethoxybenzene)iodonium salt **Ia** in the arylation, we then examined other representative *N*-heteroaromatic substrates. For the imidazole **1b**, pyridine **1c**, and other six-membered *N*-heteroaromatics **1d-f**, comparable results were obtained in regard to the selectivity of the phenyl transfer from the salt **Ia** to the heteroaromatic rings (Table 1). Since *N*-heteroaromatic substrates **1b-f** were employed as the solvent, the yields of the products **2ba-fa** were calculated based on the stoichiometries of the salt **Ia** used for the reactions in these cases. The yield of the products changed in some cases in comparison to the pyrrole **1a**, and the imidazole **1b** reacted to give the phenylation product **2ba** in a slightly decreased yield, that is 44% (entry 1), while the

Table 1. *N*-Heteroaromatics **1b-f** for the selective phenyl-transfer reactions using the salt **Ia**[a]

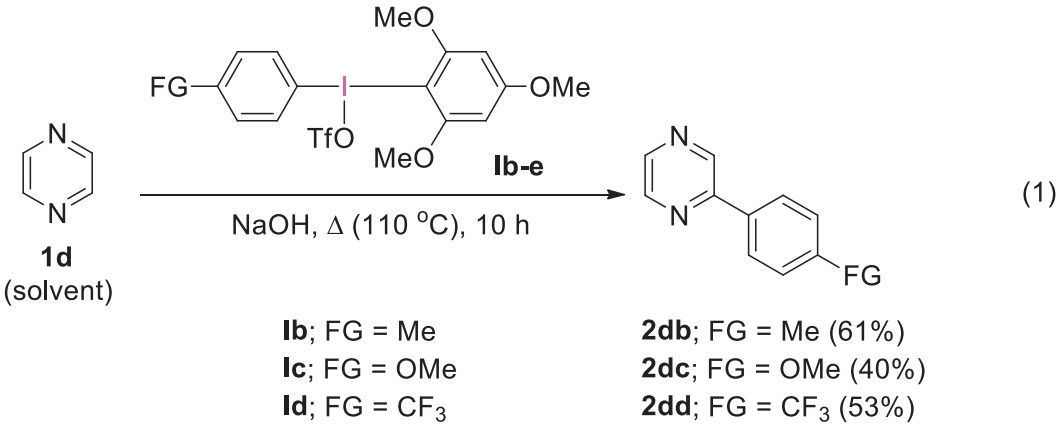
entry	substrate	phenylation product (yield)[b]
1	 **1b**	 **2ba** (44%)
2	 **1c**	 **2ca** (60%, 2-:3-:4- = 32:46:22)
3	 **1d**	 **2da** (86%)
4	 **1e**	 **2ea** (66%, 2-;4-:5- = 24:60:16)
5[c]	 **1f**	 **2fa** (67%, 3-:4- = 9:91)

[a] Reactions were performed using these heteroaromatics 1b-f as a solvent (1 mL) at 110 °C for 10 h in the presence of the iodonium salt Ia (0.2 mmol) and solid sodium hydroxide (1.5 mmol).
[b] Isolated yield after column chromatography. The regioisomeric ratios were then determined by ^{1}H NMR.
[c] Reaction was progressed at 80 °C.

pyrazine **1d** smoothly produced 2-phenylpyrazine **2da** in a good yield (entry 3). The phenylation selectively occurred at the 2-positions of the imidazole **1b** and pyrazine **1d** as those previously reported.[10] Meanwhile, pyridine **1c** and pyridazine **1e** were reacted under the same conditions producing the regiomixture of the phenylated products **2ca** and **2ea** in a ratio of 2-:3-:4- = 32:46:22 for pyridine **1c** (entry 2) and 2-;4-:5- = 24:60:16 for pyridazine **1e** (entry 4). It seems that these results by using the iodonium salt **Ia** basically match with the similar results of the phenyl radical generations[13] and their involvement in the radical substitution processes toward the *N*-heteroaromatic rings. However, this time, the iodonium salt **Ia** showed a somehow different outcome of the regio-preferences at the reacting ring positions for the phenylations when compared to the conventional iodonium salts employed in the early studies.[10] Specifically, the *meta*-phenylation for pyridine **1c** and 4-phenylation for pyrimidine **1e** are favored when using the salt **Ia**, and the major products were the 3-phenylpyridine **2ca** (3-phenyl) and 4-phenylpyrimidine **2ea** (4-phenyl). In addition, pyridazine **1f**, which is known in aryl radical coupling processes to give a mixture of 3- and 4-phenylated regioisomers, caused phenylation almost totally at the 4-position and mostly produced 4-phenylpyridazine **2fa** in 58% yield as the major product (entry 5).

The unique direction of the trimethoxybenzene group in the aryl transfer is generally for the group of iodonium salts **Ib-f**, and no coupling product incorporating the trimethoxybenzene ring was detected in all the examples shown in Scheme 3. For the coupling with pyrazine **1d**, the reaction with the iodonium salt **Ic** even proceeded for the introduction of the benzene ring having an electron-donating methoxy group, and 2-(4-anisyl)pyrazine **2dc** was obtained in 40% yield (Eq. 1). Such an electron-rich aryl group transfer is known to scarcely occur when using the conventional diaryliodonium salts,[10] which would suggest not only the high utility of the iodonium salt **Ic** over others in this metal-free arylation process, but also some positive contribution of the trimethoxybenzene group to the reactivity of the salt **Ic** for more effectively producing the arylation product **2dc**. Also, the benzene ring having an electron-withdrawing substituent, such as the trifluoromethyl group, could react with the pyrazine **1d** to give 2-(4-trifluoromethylphenyl)pyrazine **2dc** as the sole product, albeit in a lower yield compared to the introduction of the phenyl group by the salt **Ia**. In addition, the arylation also proceeded using the iodonium salt **Ie** having a heteroaromatic group, such as the thiophene ring (Eq. 2). It is interesting to note that, however, the sterically-congested 2,4-dimethylphenyl and mesityl groups in the salts **If** and **Ig**, which are known to be highly reactive in other couplings with anionic nucleophiles,[14] were found not to cause effective transfer (Eq. 3). This is in good agreement with the facts of the non-transferring ability of the similarly-substituted trimethoxybenzene ring in the salts **I** during the base-induced arylating strategy and of the apparent involvement of a different mechanism from that of other arylating methods for anionic nucleophiles,[14] which thus might give some positive support for the postulated aryl radical mechanisms in literatures.[10]

Iodonium salts Ib-e having an electron-donating or withdrawing group

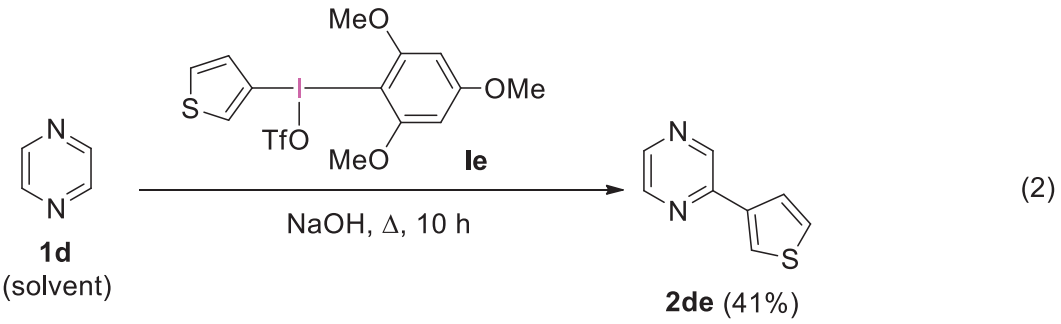


(1)

Ib; FG = Me
Ic; FG = OMe
Id; FG = CF_3

2db; FG = Me (61%)
2dc; FG = OMe (40%)
2dd; FG = CF_3 (53%)

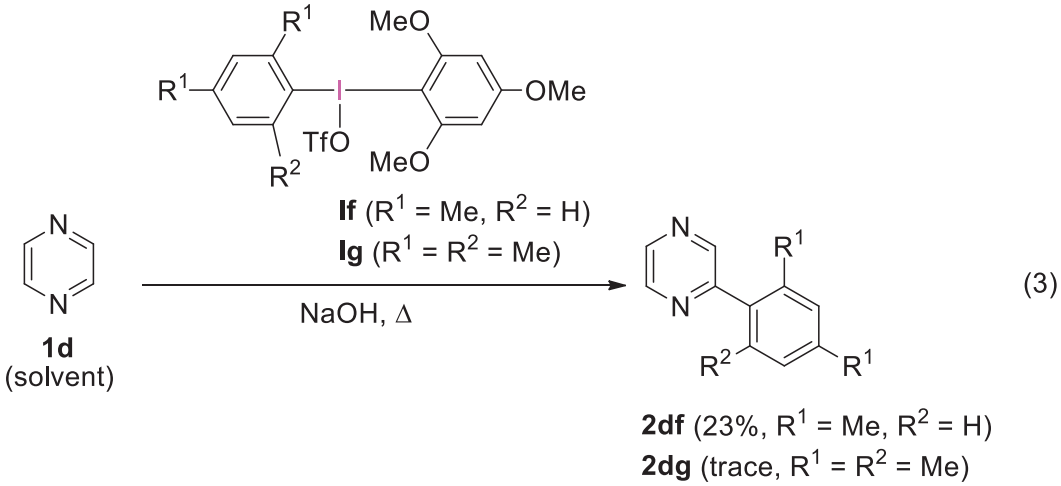
Heteroaromatic iodonium salt Ie



(2)

2de (41%)

Sterically-congested iodonium salts If and Ig



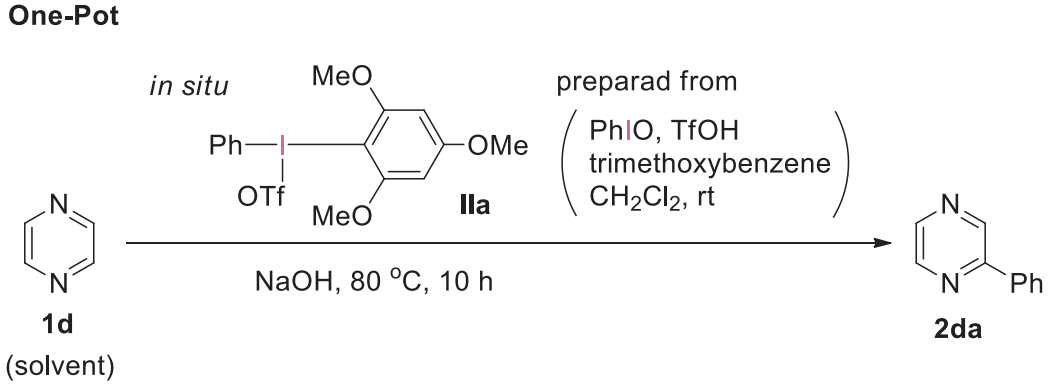
(3)

2df (23%, R^1 = Me, R^2 = H)
2dg (trace, R^1 = R^2 = Me)

Scheme 3. Reactions of pyrazine **1d** with a set of diaryliodonium(III) salts **Ib-g**: The transferring aryl groups

One of the advantages in using the diaryliodonium salts **I** bearing the trimethoxybenzene group lies in their easy preparative operations,[11,12] and the specific aryl group-transfer abilities of the (trimethoxybenzene)iodonium salts **I** can now allow the generation of the salts and their use in the base-induced couplings to occur in a one-pot manner. For example, 2-phenylpyrazine **2da** was also obtained starting

from the iodosobenzene (PhIO) by treatment with equimolar amounts of triflic acid (TfOH) and the trimethoxybenzene in dichloromethane[11] followed by thermal decomposition of the formed iodonium salt **Ia** for the aryl coupling after replacement of the solvent by pyrazine **1d** and then the addition of NaOH (Scheme 4). The smooth formation of the product **2da** corresponds to the high-yield formation of the iodonium salt **Ia** in its preparative step.



Scheme 4. One-Pot diaryliodonium salt formation and aryl coupling

In summary, we have newly found in this study a series of promising diaryliodoum salts **I** having the trimethoxybenzene group ($ArI^+Ar'X^-$, where Ar = various aryl groups, Ar' = 2,4,6-trimethoxyphenyl, X^- = counterion) that are promising for strongly directing the aryl transfer abilities of the salts during the base-induced radical arylations toward the *N*-heteroaromatics **1**. As a result of the exclusive aryl transfer control for the Ar groups over the introduced trimethoxybenzene during the aryl radical processes, the new iodonium salts **I** can expect to give the selective productions of the biaryls **2** and avoid contamination of the undesired arylation products as conventional problems by the competitive aryl transfers from the iodonium salts having two different aryl ligands. With such excellent and unique arylation characteristics now revealed, further applications of the specific iodonium salts **I** in more extensive metal-free coupling processes are currently being investigated in our laboratory, the results of which will be reported in due course.

EXPERIMENTAL

Melting point (mp) is uncorrected. All ^{1}H- and ^{13}C-NMR spectra of the products were measured in $CDCl_3$ by spectrometers operating at 400 MHz (100 MHz for ^{13}C NMR) at 25 °C. Chemical shifts of ^{1}H-NMR were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ = 0.00 ppm) as an internal standard. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, m = multiplet), coupling constant (*J*) in Hz, and integration.

Chemical shifts of ^{13}C-NMR were reported in ppm with the solvent as reference peak ($CDCl_3$: δ = 77.0 ppm). Absorptions of infrared spectra (IR) are reported in reciprocal centimeters (cm^{-1}) for representative peaks. Flash column chromatography was performed with Merck Silica Gel 60 (230-400 mesh) eluting with hexane and ethyl acetate for isolation of the products. Analytical thin-layer chromatography (TLC) was carried out on Merck Silica Gel F_{254} plates (0.25 mm). The spots and bands were detected by UV light of irradiation (254, 365 nm) and/or by staining with 5% phosphomolybdic acid followed by heating.

Materials

The diaryliodonium(III) salts **I** having the trimethoxybenzene group were prepared by using our reported condensation procedure of iodosoarenes,[11] which were obtained by literature oxidation procedures[15] from corresponding commercial iodoarene compounds. The *N*-heteroaromatic compounds **1** used in this study for the coupling reactions are commercially available and used as they stand. All other chemicals for performing the experiments and chromatography were obtained from commercial suppliers and used as received without further purification.

Typical experimental procedure for arylations: The reaction of pyrazine 1d with iodonium salt Ia

The metal-free arylations of *N*-heteroaromatic compounds **1** using (trimethoxybenzene)iodonium salts **I** were performed according to the literature procedure.[10a] In the case of pyrazine **1d**, the iodonium salt **Ia** (104 mg, 0.2 mmol) and sodium hydroxide (ca. 60 mg, 7.5 equiv) were added to pyrazine solution (1 mL) in reflux tube. After stirring at 110 ^{o}C for 10 h, the remaining pyrazine was distilled by rotary evaporator under reduced pressure. The resulting oily residue including the pheylation product **2da** was diluted with EtOAc (20 mL), and washed with brine (15 mL) and water (15 mL), and then the organic layer was dried over anhydrous sodium sulfate. After removal of the solvent, the crude product was subjected to column chromatography on silica-gel (hexane/EtOAc = 5/1) to give a pure 2-phenylpyrazine **2da** (26.8 mg, 0.17 mmol) in 86% yield as a colorless crystals.

Characterization of the arylation products 2

The physical and spectral data of all the products **2** well matched those previously reported.

2-Phenylpyrrole (2aa)[10a]

Colorless solid; IR (KBr): 3083, 3043, 1567, 1480, 1430, 1341, 1262 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): 6.27-6.30 (m, 1H), 6.51 (brs, 1H), 6.83-6.85 (m, 1H), 7.19 (t, J = 7.3 Hz, 1H), 7.34 (t, J = 8.2 Hz, 2H), 7.47 (dd, J = 9.2, 1.0 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): 105.9, 110.1, 118.8, 123.8, 126.2, 128.9, 132.4, 132.8 ppm.

2-Phenylimidazole (2ba)[16a]

Colorless solid; IR (KBr): 3053, 2904, 1564, 1504, 1488, 1415, 1108, 942 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.10 (m, 2H), 7.29-7.36 (m, 3H), 7.80-7.82 (m, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): 123.2, 125.5, 128.5, 128.8, 130.3, 147.2 ppm.

Phenylpyridines (2ca, mixture of regioisomers)[10]

The phenylation products were obtained as a mixture of regioisomers with a ratio of 2-:3-:4- = 32:46:22, determined by ^{1}H NMR analysis after chromatography (hexane: EtOAc). The major product, 3-phenyl-pyridine (**2ca**), was isolated for charactarization (see below).

3-Phenylpyridine (2ca)[10b]

Yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$): 2.18 (t, J = 7.8 Hz, 2H), 2.56 (t, J = 7.8 Hz, 2H), 3.80 (s, 3H), 6.39 (d, J = 10.2 Hz, 2H), 6.84 (d, J = 10.2 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): 123.6, 127.2, 128.1, 129.1, 134.4, 136.6, 137.8, 148.4, 148.5 ppm.

2-Phenylpyrazine (2da)[10]

Colorless solid; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.54-7.45 (m 3H), 8.00-8.03 (m, 2H), 8.50-8.51 (m, 1H), 8.63-8.64 (m, 1H), 9.04 (d, J = 1.96 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): 127.0, 129.1, 129.9, 136.4, 142.3, 142.9, 144.2, 152.9 ppm.

Phenylpyrimidines (2ea, mixture of regioisomers)[10b]

The phenylation products were obtained as a mixture of regioisomers with a ratio of 2-:3-:4- = 24:60:16, determined by ^{1}H NMR analysis after chromatography (hexane: EtOAc). The major product, 4-phenyl-pyrimidine (**2ea**), was isolated for charactarization (see below).

4-Phenylpyrimidine (2ea)[16b]

Colorless solid; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.71 (dd, J = 6.1, 1.5 Hz, 1H), 8.06-8.09 (m, 2H), 8.75 (d, J = 5.36 Hz, 1H), 9.25 (d J = 0.96 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): 117.0, 127.1, 129.1, 131.1, 136.5, 157.5, 159.1, 163.9 ppm.

Phenylpyridazines (2fa, mixture of regioisomers)[13a]

The phenylation products were obtained as a mixture of regioisomers with a ratio of 3-:4- = 9:91, determined by ^{1}H NMR analysis after chromatography (hexane: EtOAc). The major product, 4-phenyl-pyridazine (**2fa**), was isolated for charactarization (see below).

4-Phenylpyridazine (2fa)[16c]

Brown solid; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.50-7.57 (m, 3H), 7.66-7.70 (m, 3H), 9.23 (d, *J* = 5.36 Hz, 1H), 9.47 (d, *J* = 1.00 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): 123.3, 127.1, 129.5, 130.2, 134.5, 138.5, 150.0, 151.4 ppm.

2-(4-Methylphenyl)pyrazine (2db)[16b]

Colorless solid; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.31 (d, *J* = 7.8 Hz, 2H), 7.89-7.91 (m, 2H), 8.46 (d, *J* = 2.4 Hz, 1H), 8.60-8.61 (m, 1H), 8.99 (d, *J* = 1.4 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): 21.4, 126.9, 129.8, 133.6, 140.2, 142.1, 142.6, 144.1, 152.9 ppm.

2-(4-Methoxyphenyl)pyrazine (2dc)[16d]

Colorless solid; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.00-7.04 (m, 2H), 7.95-7.99 (m, 2H), 8.42 (d, *J* = 2.9 Hz, 1H), 8.57-8.58 (m, 1H), 8.96 (d, *J* = 1.4 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): 55.4, 114.5, 128.3, 128.9, 141.6, 142.1, 142.0, 152.5, 161.2 ppm.

2-(4-Trifluoromethylphenyl)pyrazine (2dd)[16e]

Colorless solid; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.77 (d, *J* = 7.8 Hz, 2H), 8.14 (d, *J* = 8.0 Hz, 2H), 8.58 (d, *J* = 1.4 Hz, 1H), 8.68 (m, 1H), 9.08 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): 126.0 (q, *J* = 3.8 Hz), 127.2 , 131.7 (q, *J* = 32.6 Hz), 139.6, 142.3, 143.8, 144.4, 151.2 ppm.

2-(3-Thienyl)pyrazine (2de)[16f]

Colorless solid; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.45 (dd, *J* = 4.9, 2.9 Hz, 2H), 7.67-7.69 (m, 1H), 7.99-8.00 (m, 1H), 8.43 (br, 1H), 8.56 (br, 1H), 8.92 (br, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): 124.8, 125.8, 127.0, 139.0, 141.9, 142.5, 144.2, 149.1 ppm.

2-(2,4-Dimethylphenyl)pyrazine (2df)[16g]

Yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$): 2.31 (s, 6H), 7.06 (d, 1H, *J* = 7.8 Hz), 7.07 (s, 1H), 7.27 (d, 1H, *J* = 8.2 Hz), 8.51 (d, 1H, *J* = 2.4 Hz), 8.67 (dd, 1H, *J* = 2.4, 1.4 Hz), 8.71 (d, 1H, *J* = 1.4 Hz) ppm; ^{13}C-NMR (400 MHz, $CDCl_3$): 20.2, 21.2, 126.9, 129.8, 131.9, 133.8, 136.1, 139.2, 142.0, 143.8, 145.0, 155.7 ppm.

ACKNOWLEDGEMENTS

This work was partially supported by a Grant-in-Aid for Scientific Research (A) and Encouragement of Young Scientists (A) from JSPS. T.D. is thankful to a Grant-in-Aid for Scientific Research (C) from JSPS,

Challenging Exploratory Research (JSPS), and a research fund from the Asahi Glass Foundation.

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