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Graphical Abstract

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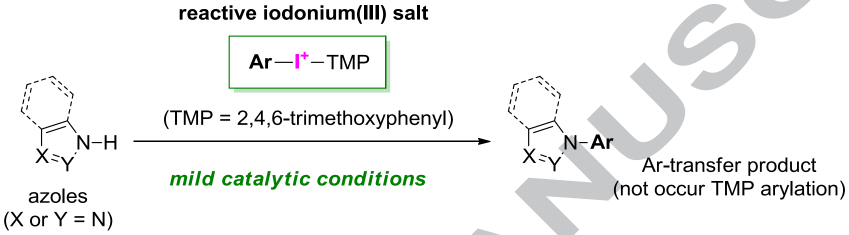

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Efficient *N*-arylation of azole compounds utilizing selective aryl-transfer TMP-iodonium(III) reagents

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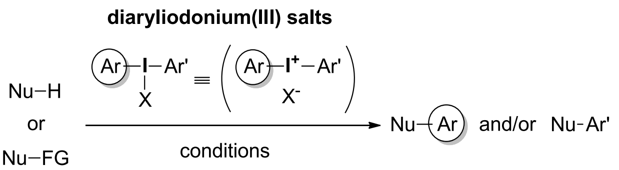
Abstract—It was determined that diaryliodonium(III) triflates bearing a trimethoxybenzene (TMP) auxiliary are more reactive than the reported selective aryl-transfer iodonium salts in the *N*-arylation of benzimidazoles and other types of azole compounds under catalytic conditions. The TMP-iodonium(III) salts can thus effectively facilitate the reaction at 50 °C or below, producing the corresponding *N*-arylated biaryls without the formation of TMP-derived coupling byproducts. Utilization of this TMP reagent under mild conditions would prevent the underlying problem of participation of the auxiliary group in the coupling reactions, which is observed while using the iodonium(III) salts that require elevated temperatures.

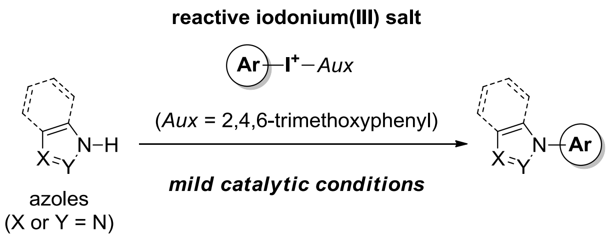
Keywords; arylation; hypervalent compounds; iodine, nitrogen heterocycles

Diaryliodonium (III) salts, $ArI^+Ar'X^-$, (where Ar, Ar' = aryl, X^- = counterion), represent one of the unique classes of hypervalent iodine compounds having two carbon ligands, which show practical applicability in scientific fields.[1] With the liberation of more stable monovalent iodine acting as a driving force, these salts are often utilized as arylating agents and benzyne precursors in organic synthesis.[2] By virtue of the excellent nucleofugality of the aryl iodide moiety,[3] diaryliodonium(III) salts are much more reactive than aryl halides toward nucleophiles, bases, and organometallic reagents in these reactions. Recently, their high reactivity drew a considerable attention from synthetic chemists working on challenges in the practical applicability of the aryl-coupling processes (Scheme 1).[4]

Thus, relying on the high reactivity of the diaryliodonium(III) salts, practical arylations not requiring precious palladium catalyst have become possible in the coupling strategies of many nucleophilic molecules.[5] Due to the compatibility of a broad range of functional groups,[6] development of such improved coupling methods has been actively investigated, especially for the C-N bond formation during the synthesis of *N*-containing bioactive molecules.[7] To this end, optimizing the structure and reactivity of the iodonium(III) salts should obviously be important for further advancement of the aryl amination strategy.[8] Herein, we report an efficient *N*-arylation of azole compounds utilizing the specific diaryliodonium(III) salts containing the 2,4,6-trimethoxyphenyl (TMP)



Scheme 1. Diaryliodonium(III) salts in coupling reactions.
(Nu = nucleophilic group, FG = functional group, such as an organometallic element)



Scheme 2. Efficient *N*-arylation of azole compounds utilizing reactive and selective TMP-iodonium(III) salts.
(Aux = auxiliary to enhance the reactivity for arylation)

auxiliary group[9] to enhance the reactivity in aryl aminations. While retaining the selective aryl-transfer ability of the TMP-iodonium(III) salts,[10] valuable *N*-aryl azole compounds, not only known as the privileged structures in pharmaceutical sciences showing a variety of biological activities, but also employed as building blocks and ligands in synthetic chemistry,[11] are smoothly obtained in good yields under mild reaction conditions (Scheme 2).

In the *N*-arylation strategy of azoles, continuous efforts are being made for realizing mild reaction conditions by modulating the organic ligands in the transition metal-catalyzed coupling of aryl halides and related aryl electrophiles.[12] Alternatively, Chan-Lam-Evans-type reactions, using arylboronic acids, were reported for the *N*-arylation of azoles at ambient temperature, despite the necessity of long reaction time and nearly stoichiometric amount of copper catalyst.[13] Aryllead,[14a] triarylbismuth,[14b–d] arylsiloxanes,[14e] and arenediazonium salts[14f] were also employed as aryl sources to develop efficient coupling reactions under mild conditions. Regarding the diaryliodonium(III) salt, the *N*-arylation of azole compound accelerated by a combined palladium/copper catalytic system for the synthesis of benztriazole was reported in 1998 by Beletskaya and co-workers.[15] Since then, several reports on the *N*-arylation of azoles with diaryliodonium(III) salts have appeared in the literature, but typically, the reaction scope was limited to the salts bearing same aryl groups ($\mathrm{Ar_2I^+X^-}$).[16]

The chemical and physical properties of diaryliodonium(III) salts are highly dependent on the nature of the aryl groups, and for tuning their reactivities in the coupling reactions, several useful auxiliaries have been developed so far.[17] For the diaryliodonium(III) salts having a reactive electron-deficient aryl moiety, to exclude the possibility of transfer of the dummy aryl group, an electron-donating functionality was supportively introduced (see Figure 1).[18] Utilization of the auxiliary and the dummy ligand in diaryliodonium(III) salts for a selective aryl-transfer has become much popular after the discovery of Mes-iodonium(III) salts (Mes = Mesityl),[19] especially for the transition metal-catalyzed couplings.[20] More recent investigations on TMP-iodonium(III) salts have further expanded the scope and utility of the nucleophiles and coupling partners employed in this reaction.[8f–g,9,10]

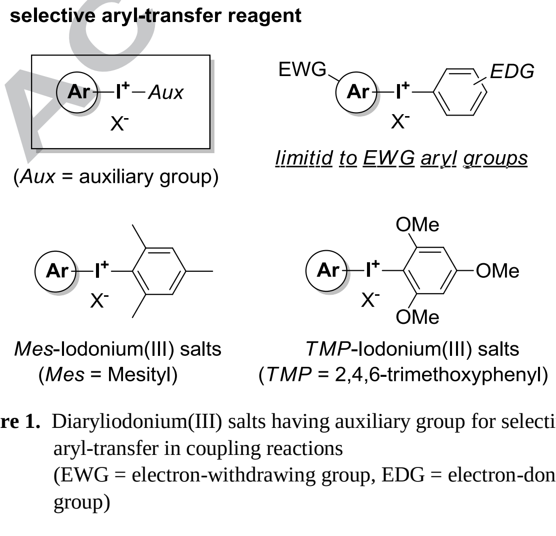
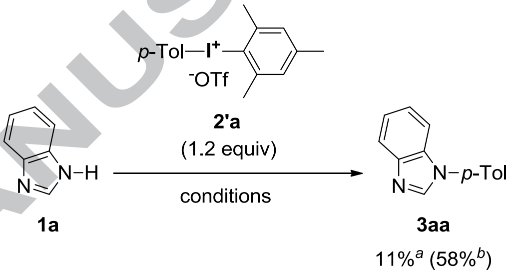


Figure 1. Diaryliodonium(III) salts having auxiliary group for selective aryl-transfer in coupling reactions
(EWG = electron-withdrawing group, EDG = electron-donating group)

Very recently, Pan et al. reported an efficient arylation of 1*H*-indazoles by utilizing the auxiliary diaryliodonium(III) salts, $\mathrm{MesI^+ArX^-}$, as N^2-selective aryl-transfer agents.[21,22] However, the formation of more sterically congested N^1-aryl indazoles and benzimidazoles was rather slow under the catalytic conditions.[23] In fact, *N*-arylation of benzimidazole **1a** using Mes-iodonium(III) salt **2a’** did not proceed efficiently at 50 °C, even in the presence of a stoichiometric amount of the copper catalyst (see Scheme 3).[24]

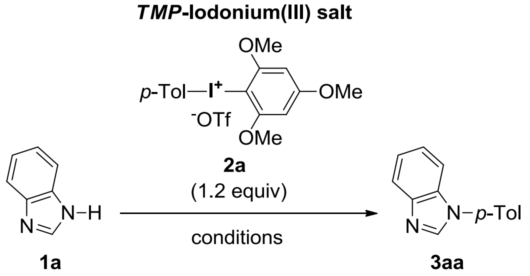


Scheme 3. *N*-arylation of benzimidazole **1a** employing Mes-iodonium(III) salt.
[conditions: cat. copper(I) acetate, triethylamine (2 equiv) in toluene (0.1 M of benzimidazole **1a**) at 50 °C for 12 h under nitrogen atmosphere]
^{a} cat. 10 mol%. ^{b} cat. 100 mol% (stoichiometric).

Thus, for the *N*-arylation of benzimidazoles, we next turned our attention to the reaction of the TMP-iodonium(III) salt. Although the utility of the TMP auxiliary in the iodonium(III) salts for a selective aryl-transfer in other reactions has been reported by Olofsson,[10a,b] Stuart,[8f–g,10c] and our group,[9] to the best of our knowledge, the reactivity of TMP-iodonium(III) salt in copper catalysis has not been investigated in detail in terms of the synthetic scope. In the present study, to our delight, TMP-iodonium(III) salts showed higher reactivities compared to that of Mes salt **2a’** in the desired coupling reactions. *p*-Tolyl benzimidazole **3aa** was thus quantitatively obtained, once the reaction was conducted employing TMP-iodonium(III) salt **2a** under the same conditions as in Scheme 3 (see Eq. 1 in Table 1).

Benzimidazole **1a** could smoothly react with *p*-tolyl (2,4,6-trimethoxyphenyl)iodonium(III) triflate **2a** at 50 °C in toluene in the presence of triethylamine as a base (2 equiv.) and copper(I) catalyst (10 mol%), giving arylated product **3aa** in 99% yield after the reaction time of 6 h (Table 1, entry 1). The reaction conditions with benzimidazole **1a** were further investigated using TMP salt **2a** as the standard substrate. The economical inorganic bases, such as sodium carbonate, sodium hydrogen carbonate, and sodium acetate, were less effective than triethylamine, probably due to their low solubility in toluene (entries 2–4, also see entry 5). As

Table 1. *N*-arylation of benzimidazole employing TMP-iodonium(III) salt: Reaction conditions (Eq. 1)[a]



(1)

Entry	Base	Solvent	Yield of **3aa**[b]
1	triethylamine	toluene	99% (99%)[c]
2	sodium carbonate	toluene	trace
3	sodium hydrogen carbonate	toluene	50%
4	sodium acetate	toluene	32%
5	none	toluene	15%
6	triethylamine	dichloromethane	96%
7	triethylamine	*N*,*N*-dimethyl formamide	63%
8	triethylamine	acetonitrile	trace
9[d]	triethylamine	toluene	3%
10[e]	triethylamine	toluene	49%
11[f]	triethylamine	toluene	57%[c]
12[g]	triethylamine	toluene	49%
13[h]	triethylamine	toluene	76%

[a] The reactions were performed using TMP-iodonium(III) salt **2a** (0.24 mmol) in the presence of copper(I) acetate (10 mol%) and base (2 equiv) in solvent (0.1 M) at 50 ºC under nitrogen atmosphere for benzimidazole **1a** (0.20 mmol), unless otherwise noted.

[b] Yields were determined by ^{1}H NMR based on benzimidazole **1a** used.

[c] Isolated yield based on benzimidazole **1a** used.

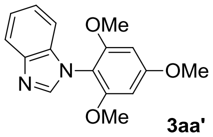
[d] Copper(II) acetate (10 mol%) was instead used.

[e] Copper(I) chloride (10 mol%).

[f] Copper(I) bromide (10 mol%).

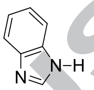
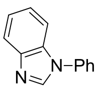
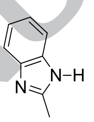
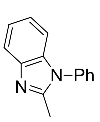
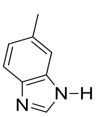
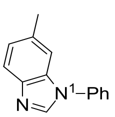
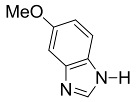
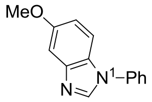
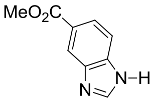
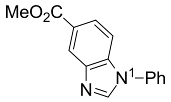
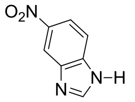
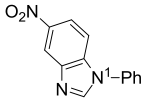
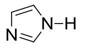
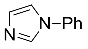
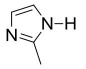
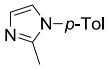
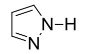
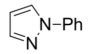
[g] Copper(I) iodide (10 mol%).

[h] Under oxygen atmosphere.



a solvent, the use of non-polar toluene and dichloromethane effectively transferred the aryl group onto benzimidazole **1a** (entries 1 and 6), while the use of polar solvents resulted in low conversions of the substrate[25] (for example, see entries 7 and 8). For this *N*-arylation, only copper(I) salts could work as catalysts (see entry 9), and copper(I) acetate gave the better result than CuX (X = I, Br, Cl) that produce unstable TMP-iodonium(III) halides (entries 1, 10–12). Furthermore, no strict care had to be taken to exclude molecular oxygen from the reaction mixture; the deactivation of the catalyst was relatively slow even under an oxygen atmosphere (entry 13). Nonetheless, in the absence of the copper catalyst, the reaction did not proceed at 50 °C. It should be emphasized that *p*-tolyl benzimidazole **3aa** was selectively produced along with the theoretical formation of TMP iodide, while the formation of byproduct **3aa'**, resulting from the transfer of TMP from iodonium salt **2a** to benzimidazole **1a**, was negligible in the reaction system of entry 1.

Table 2. *N*-phenylation of various azoles **1a–i** using TMP-iodonium(III) salt **1b** and phenyl(2,4,6-trimethoxyphenyl)iodonium(III) triflate[a]

Entry	Azole	Arylation product	Yield[b]
1	 **1a**	 **3ab**	99%
2[c]	 **1b**	 **3bb**	81%
3[c]	 **1c**	 **3cb**	quant (1.16:1)[d]
4[c]	 **1d**	 **3db**	quant (1.06:1)[d]
5[c]	 **1e**	 **3eb**	84% (1.05:1)[d,e]
6[c]	 **1f**	 **3fb**	quant (1.08:1)[d,e]
7	 **1g**	 **3gb**	98%
8[f]	 **1h**	 **3ha**	97%
9	 **1i**	 **3ib**	97%

[a] The reactions were examined under the conditions of Table 1, entry 1 using TMP-iodonium(III) salt **2b** (0.24 mmol).

[b] Isolated yield based on benzimidazole **1a** used.

[c] Dichloromethane was used as a solvent.

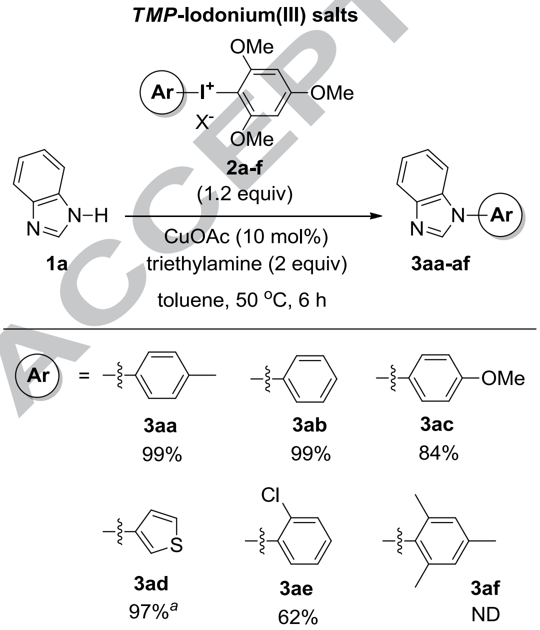
[d] The ratio of regioisomers (N^1 versus N^3-arylated product).

[e] The average of two runs.

[f] TMP-iodonium(III) salt **2a** was used instead of **2b**.

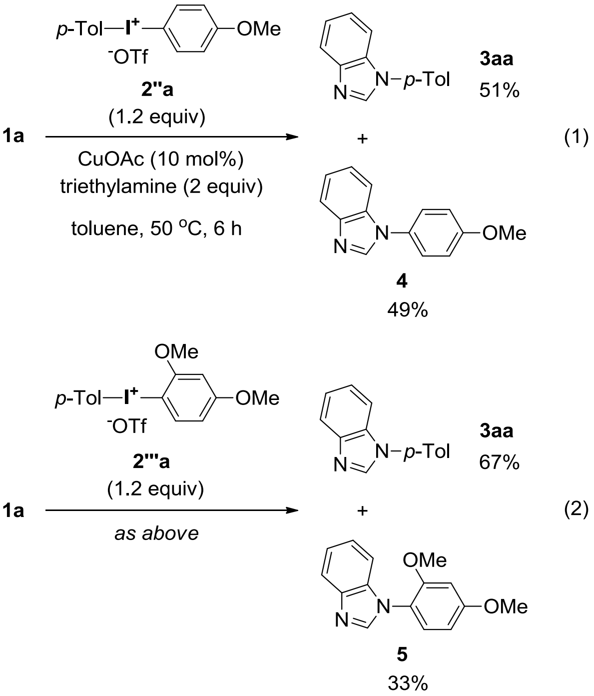
Using phenyliodonium(III) triflate **2b**, we then confirmed the general utility of TMP-iodonium salts for the *N*-arylation of benzimidazoles and related compounds (Table 2).[26] Even in this case, benzimidazole **1a** was efficiently converted into target product **3ab** by the selective phenyl transfer (entry 1). For 2-methylbenzimidazole **1b**, the steric requirement somehow decreased the yield of arylation product **3bb**, and dichloromethane was found to be a better solvent in this case (entry 2). All 5-substituted benzimidazoles **1c–f** could readily react with TMP-iodonium(III) salt **2b** regardless of the electron-rich and deficient groups, but two regioisomers, N^1 and N^3-arylated products **3cb–fb**, were unselectively produced (entries 3–6). Imidazoles **1g** and **1h** could also be used in this reaction, which resulted in *N*-arylated imidazoles **3gb** and **3ha** (for *p*-tolyl salt **2a**) in nearly quantitative yields (entries 7 and 8). Similarly, the reaction with pyrazole **1i** afforded corresponding product **3gb** in excellent yield (entry 9).

Subsequently, the scope of TMP-iodonium(III) salts **2a–f**[27] in the *N*-arylation of benzimidazole **1a** was investigated (Scheme 4). As the transferring aryl group, the electron-rich *p*-anisyl ring of TMP salt **2c** could be selectively introduced, despite a slight decrease in the yield (84%). In addition, thienyl salt **2d** could quantitatively convert substrate **1a** into corresponding *N*-linked heteroaromatic biaryl **3ad**. On the other hand, *ortho*-substituted aryl groups were less reactive in this *N*-arylation process, which is consistent with the observations in the reported copper-catalyzed reactions.[5,6] In fact, mesityl(2,4,6-trimethoxyphenyl)iodonium(III) triflate **2f** did not transfer the Mes group onto benzimidazole **1a** under the reaction conditions due to steric influence of the bulky Mes ring.



Scheme 4. Transferring aryl groups.
[a] Dichloromethane was used as a solvent.
ND = not determined

These results conclude that TMP-iodonium(III) salts **2** are generally more reactive than the Mes-iodonium(III) salt in the *N*-arylation of benzimidazoles and related compounds. Note that using this TMP auxiliary is indispensable not only for the reactivity, but also for the aryl-transfer selectivity.[9,10] During the coupling of iodonium(III) salts **2a–f**, the TMP group was not introduced onto substrate **1**. To clarify the specificity of the TMP auxiliary, we thus conducted the following control experiments using related iodonium(III) salts **2’’a** and **2’’’a** (Scheme 5). First, anisyl(*p*-tolyl)iodonium(III) triflate **2’’a** was reacted with benzimidazole **1a** by the standard *N*-arylation procedure, which furnished two arylation products, **3aa** (for tolyl transfer) and **4** (for anisyl transfer), without any selectivity (Eq. 1). Also, 2,4-dimethoxyphenyl(*p*-tolyl)iodonium(III) triflate **2’’’a** induced a competitive aryl-transfer to some extent (Eq. 2). Therefore, in terms of selectivity, simple anisyl and 2,4-dimethoxyphenyl groups were found to be poor auxiliaries, although the distribution of the products slightly improved in the latter case. Regarding the structural features of TMP-iodonium(III) salt, X-ray crystallographic analysis of a representative compound suggested that in this hypervalent molecule, there exist unique secondary bonding interactions between the iodine(III) center and the two *ortho*-methoxy groups in TMP.[28] Although further investigation is required to make some conclusion, the reason behind high reactivities of TMP-iodonium(III) salts **2a–f** compared to that of Mes salt **2a’** (see Scheme 3) in our *N*-arylation might thus lie in the facile reductive elimination step of the TMP salts, which alleviates the conformational rigidity in their hypervalent iodine state.



Scheme 5. Selectivity of aryl-transfer for iodonium(III) salts, **2’’a** and **2’’’b**, related to the TMP in *N*-arylation of benzimidazole **1a**.

In summary, we have revealed in this study that TMP auxiliary diaryliodonium(III) salts **2** are the promising entries among the selective aryl-transfer agents in the *N*-arylation of benzimidazoles and related compounds. Exploiting the reactivity of the TMP auxiliary is critical for achieving an efficient *N*-arylation process using diaryliodonium(III) salts **2**. Thus, the reactions can be performed at around 50 °C or lower, which definitively expels the problem of participation of the auxiliary groups in the coupling reactions observed at elevated temperatures.

Acknowledgments

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Highlights:

Efficient aryl amination of azole compounds
Coupling reaction employing reactive *pseudo*-halide
TMP-iodonium(III) for reactive/selective aryl-transfer

References and notes

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24. When *p*-iodotoluene was used instead of salt **2a’**, arylation product **3aa** was not formed at all under the same reaction conditions.
25. The reactivity of diaryliodonium(III) salt sometimes decreases in polar solvents due to the solvation of the ionized form. See: (a) Beringer, F. M.; Mausner, M. *J. Am. Chem. Soc.* **1958**, *80*, 4535; (b) Sato, T.; Shimizu, K.; Moriya, H. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1537; (c) Hacker, N. P.; Leff, D. V.; Dektar, J. L. *J. Org. Chem.* **1991**, *56*, 2280; (d) Lee, Y.-S.; Hodošček, M.; Chun, J.-H.; Pike, V. W. *Chem.-Eur. J.* **2010**, *16*, 10418. See also our cases in ref. 9.
26. Typical experimental procedure for the reactions in Table 2: To a stirred solution of copper(I) acetate (2.4 mg, 0.020 mmol, 0.10 equiv.), benzimidazole **1a** (23.6 mg, 0.20 mmol), and TMP iodonium(III) salt **2a** (124.8 mg, 0.24 mmol, 1.2 equiv) in toluene (2 mL), triethylamine (56 L, 0.4 mmol, 2 equiv) was added under a nitrogen atmosphere. The mixture was stirred for 5 min at room temperature, and the resulting solution was then heated to 50 °C for 6 h (the reaction progress was monitored by TLC). After cooling to room temperature, the reaction was quenched by adding 5% aqueous ammonia solution (4 mL). The aqueous layer was extracted thrice with 20 mL of dichloromethane and the

combined organic extracts were dried with anhydrous sodium sulfate. The organic solvents were then evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/ethyl acetate = 1/1) to obtain pure *N*-phenyl benzimidazole **3aa** (38.5 mg, 0.198 mmol) in 99% yield.

27. The reactive diaryliodonium(III) salts having electron-deficient aryl moiety are known to smoothly react with many types of nucleophiles under the catalyst-free conditions without any problem in the aryl-transfer selectivity (see Fig. 1 and ref. 18). Thus, this study would focus on the TMP-iodonium(III) salts **2a–f** that do not bear an electron-withdrawing aryl group.
28. A pure sample compatible for the X-ray crystallographic analysis was obtained by recrystallization from a dichloromethane-hexane solution of phenyl(2,4,6-trimethoxyphenyl)iodonium(III) acetate. For the crystallographic data in CIF, please see CCDC: 1555121.

Highlights:

- Efficient aryl amination of azole compounds
- Coupling reaction employing reactive *pseudo*-halide
- TMP-iodonium(III) for reactive/selective aryl-transfer