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Sustainable and scalable one-pot synthesis of diaryliodonium salts†

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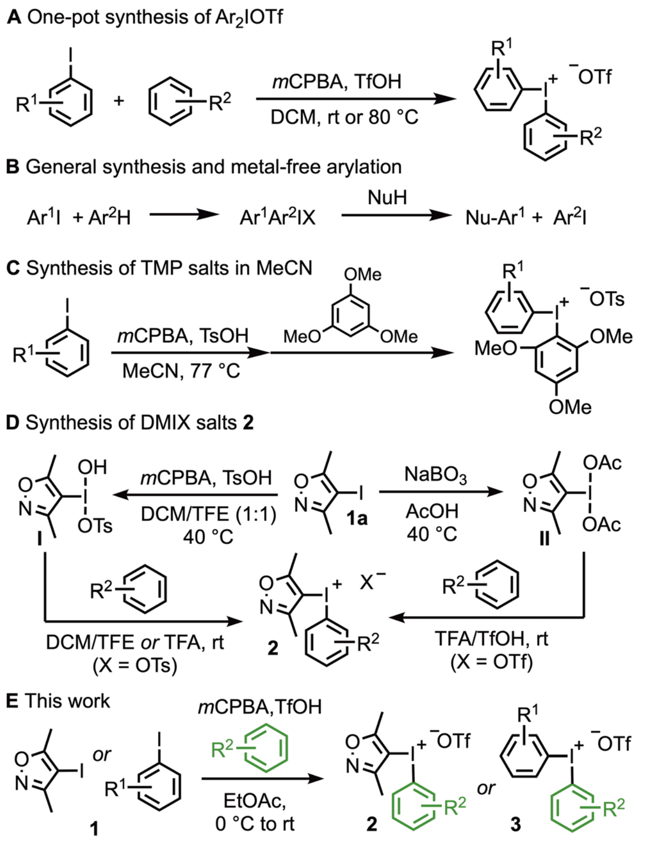
Two one-pot routes from iodoarenes to diaryliodonium triflates have been developed in the sustainable solvent ethyl acetate. The first method yields the recently reported aryl(dimethylisoxazolyl)iodonium triflates, circumventing the need for stepwise synthesis of this chemoselective arylating reagent. The second method gives other types of diaryliodonium salts, and the scalability of the protocols was exhibited with two >45 mmol scale-ups with impressively low *E*-factors.

Due to the high stability and reactivity of diaryliodonium salts (Ar_2IX), they are often employed as electrophilic sources of arenes.[1] A plethora of nucleophiles can be arylated under mild and transition metal-free conditions, including amines, alcohols and carbon-based nucleophiles.[1] This progress was enabled by the development of several efficient one-pot methods to make Ar_2IX, which rendered these reagents inexpensive and easily available.[2] Generally, iodoarenes and arenes are treated with *m*CPBA and triflic acid (TfOH) or tosic acid (TsOH) to give diaryliodonium triflates or tosylates in high yields (Scheme 1A).[2a–c]

From a sustainability perspective, there are two main drawbacks with diaryliodonium chemistry; the over-reliance on halogenated solvents in the synthesis of Ar_2IX, and the formation of stoichiometric iodoarene waste in arylations (Scheme 1B). Several research groups have addressed the first issue by developing methods in acetonitrile,[3] with Stuart's sequential one-pot synthesis of aryl(trimethoxyphenyl)iodonium tosylates having the largest scope (Scheme 1C).[3b] With regard to the second issue, stoichiometric ArI waste can sometimes be circumvented through the one-pot diarylations recently reported by our group.[4] A more general strategy to minimize waste would utilize unsymmetric Ar_2IX where the iodoarene byproduct can be recovered and reused in the synthesis of the Ar_2IX. However, this is challenging as the inherent chemoselectivity trends in arylations with unsymmetric Ar_2IX usually do not match the demands in the synthesis of Ar_2IX.[5] This results in the formation of an iodoarene that cannot be reused in the synthesis of Ar_2IX (Scheme 1B).

To this end, Kita and Dohi reported a synthesis of aryl-(mesityl)-iodonium salts from mesityl iodide, and demonstrated the recyclability of the Mes-I in a range of arylations.[6] The mesityl group is, however, mainly useful as a non-transferable "dummy group"



Scheme 1 (A–D) Established methods for synthesis and arylations with Ar_2IX. (E) This work.

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under metal-catalyzed conditions,[1] and electron-rich aryl groups such as anisyl and trimethoxyphenyl (TMP) groups are often more efficient dummy groups under metal-free conditions.[7]

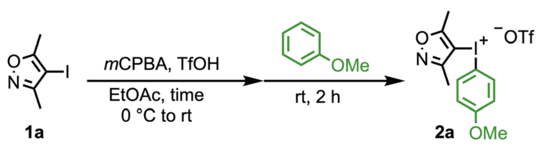
Zhao and coworkers recently reported a new strategy for unsymmetric Ar_2IX, where 2,4-dimethyliodoisoxazole (DMIX-I, **1a**) was converted to DMIX iodonium salts **2** (Scheme 1D).[8] Reagents **2** displayed good reactivity and excellent chemoselectivity in metal-free arylations of a variety of nucleophiles, forming **1a** as a byproduct.[9] However, the two-step synthesis of DMIX salts **2** requires the isolation of DMIX-iodine(III) reagent **I** or **II**, and the use of halogenated solvents or neat, fluorinated acids (trifluoroacetic acid or TfOH).[8,10] Karchava and coworkers later discovered that the synthesis of DMIX(indolyl)iodonium salts from DMIX-iodine(III) reagent **I** could be performed in EtOAc.[11]

We envisioned that a one-pot synthesis of DMIX salts in a sustainable solvent[12] would enable straightforward access to this new type of chemoselective and promising arylating agent, and also decrease the waste production. Herein we present a general one-pot synthesis of both DMIX salts **2** and diaryliodonium salts **3** in ethyl acetate (Scheme 1E).

Iodonium triflates often perform better in arylations than salts with other anions,[1] and we hence opted to use TfOH in the optimization, thus forming **2a** from **1a** (Table 1). Initially, the reaction was carried out under an inert atmosphere using anhydrous EtOAc, and water was added prior to the addition of anisole to quench the excess TfOH, thus preventing overoxidation of anisole.[13] **2a** was obtained in 66% yield with 2 equivalents TfOH (entry 1). Surprisingly, reducing the amount of TfOH to one equivalent resulted in an improved yield (entry 2). The yield was not affected by increased oxidation time, but it proved beneficial to not add water (entries 3 and 4).

We next looked into using the arene as a limiting reagent, which would be beneficial especially when employing more valuable and exotic arenes with minimal waste. To our satisfaction, the same outcome was achieved with a 1 : 1 ratio of **1a** and anisole (entry 5). Furthermore, the reaction performed equally well without inert conditions and in decreased oxidation time (entries 6 and 7). While reduced amount of *m*CPBA significantly lowered the yield (entries 8 and 9), combination with a slight excess of **1a** produced **2a** in an excellent yield of 93% (entry 10).

Table 1 Optimization of the synthesis of DMIX triflate **2a**[a]



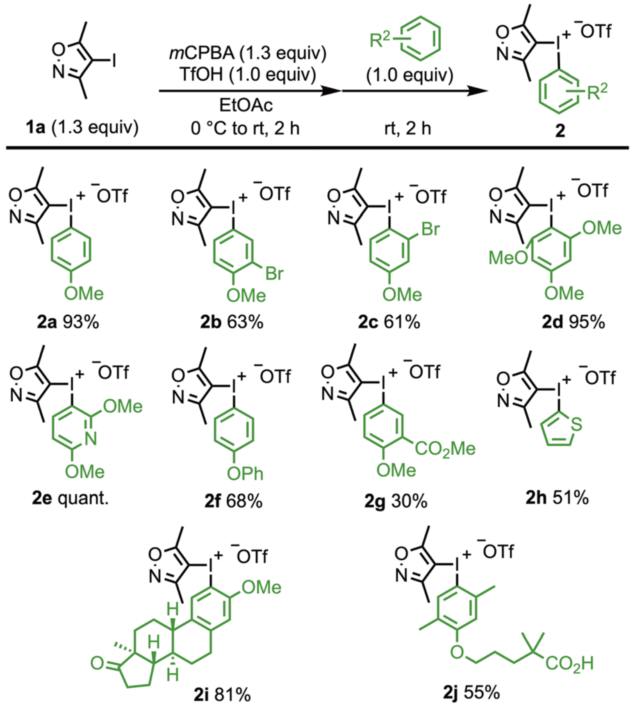
Entry	TfOH (equiv.)	Water (equiv.)	*m*CPBA (equiv.)	Time (h)	Anisole (equiv.)	Yield of **2a**[b] (%)
1	2	3	2	2	1.3	66
2	1	2	2	2	1.3	75
3	1	2	2	3	1.3	74
4	1	—	2	2	1.3	82
5	1	—	2	2	1	84
6[c]	1	—	2	2	1	89
7[c]	1	—	2	1	1	90
8[c]	1	—	1.3	1	1	83
9[c]	1	—	1.1	1	1	77
10[cd]	1	—	1.3	1	1	93

[a] Standard conditions: reactions carried out under inert atmosphere with anhydrous EtOAc. [b] Isolated yields. [c] Reaction open to air, non-dried EtOAc. [d] With 1.3 equiv. of **1a**.

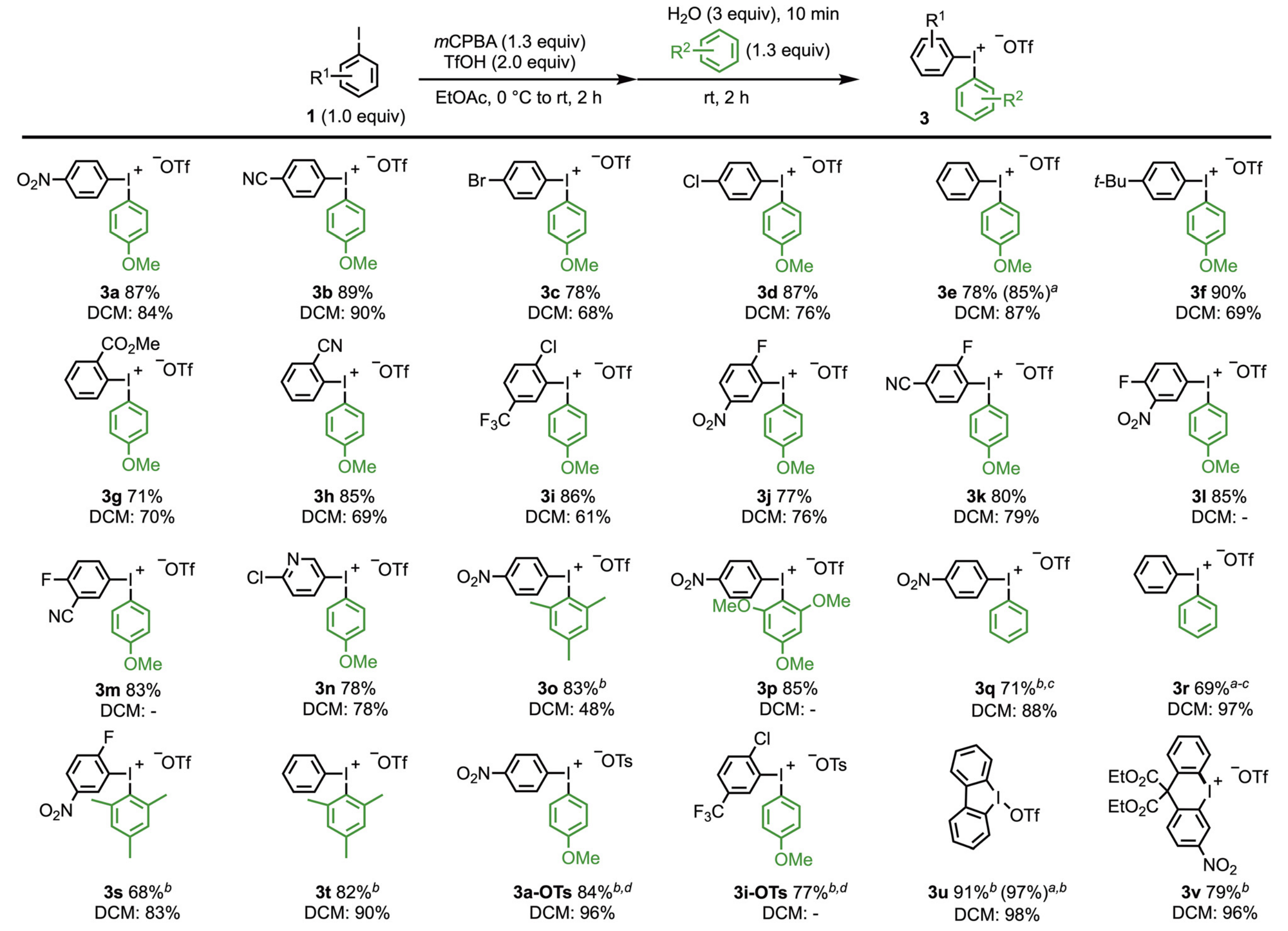
The substrate scope was then evaluated with various arenes (Scheme 2). A bromo-substituent could be introduced in the *meta* or *ortho*-position to give **2b** and **2c**, respectively. The tolerance for steric hindrance was further demonstrated through the synthesis of *ortho*-substituted TMP salt **2d** and dimethoxypyridyl salt **2e** in excellent yields.

In line with Zhao's method,[8] electron rich arenes were the most suitable nucleophiles in this reaction, and product **2g** was formed in modest yield. Thienyliodonium salts are often challenging to synthesize, and it was hence pleasing that a reaction with thiophene provided **2h**. Bioactive substrates can also be utilized in this method, as exemplified by reactions with estrone methyl ether and gemfibrozil to produce products **2i** and **2j** in 81% and 55% yields, respectively.

As the synthesis of DMIX triflates **2** was limited to electron-rich arenes, diaryliodonium salts with another dummy group are needed in arylations where an electron-deficient ring should be transferred. Hence, we set out to develop a general synthetic methodology to diaryliodonium salts **3** in the sustainable solvent ethyl acetate. The anisyl dummy group was selected for the scope studies, as this dummy group is very common in arylations.[1] Two equivalents of triflic acid were used to enable efficient oxidation of electron-deficient iodoarenes **1** (Scheme 3). Furthermore, a water addition step was introduced to avoid side reactions of the arene.[13] To our satisfaction, nitro salt **3a** could be isolated in 87% yield, which is slightly higher than the best



Scheme 2 Scope of aryl(DMIX)iodonium triflates **2** (0.5 mmol scale).



Scheme 3 Scope of diaryliodonium salts **3** (0.5 mmol scale). [a] Anhydrous conditions; [b] no H_2O added; [c] 3 equiv. TfOH, 45 °C. [d] With $TsOH \cdot H_2O$, 60 °C. Yields in DCM are the best found in the literature: (**3a–3d**, **3f**, **3i**, **3k**, **3n–3o**, **3q**),[14] (**3e**),[2b] (**3g**),[15] (**3h**),[16] (**3j**, **3s**),[4a] (**3t**),[17] (**3r**),[18] (**3a-OTs**)[19] (**3u**),[20] (**3v**).[4d]

literature yield in DCM.[14] The tolerance of electronics was explored, and good to excellent yields were obtained with a range of electron-withdrawing and electron-donating iodoarenes (**3a–3f**). Steric hindrance was well tolerated, as demonstrated by the synthesis of salts **3g–3i** with ester, cyano or chloro-moieties in the *ortho*-position.

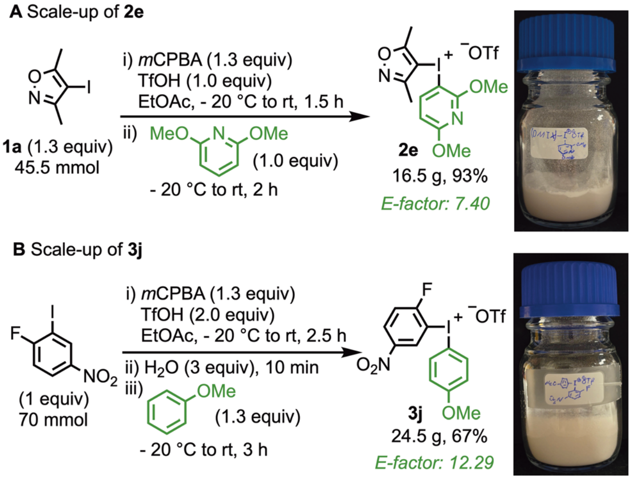
ortho-Fluoro-substituted diaryliodonium salts with an electron-withdrawing group are imperative in our recently published diarylation methodology, which gives atom-efficient access to a range of product classes.[4] Importantly, *ortho*-fluoro salts **3j** and **3k** could be synthesized equally well as with the DCM method, and *para*-fluoro-substituted salts **3l** and **3m** were also obtained in satisfactory yields. Finally, the compatibility with heteroaromatic substrates was investigated, and the synthesis of pyridyl salt **3n** proved equally efficient as in DCM.

Next, we investigated the use of mesityl, TMP and phenyl dummy groups in the synthesis of nitro salts **3o–3q**, and reactions with mesitylene or 1,3,5-trimethoxybenzene resulted in similar yields as **3a**. While phenyl salt **3q** was only produced in moderate yield, satisfactory results were obtained with 3 equivalents TfOH at 45 °C. This modification also enabled the synthesis of diphenyliodonium triflate (**3r**) in a similar yield.

The reactivity with mesitylene was further explored with other iodoarenes, providing mesityl salts **3s** and **3t**. The synthesis of diaryliodonium tosylates was briefly screened, and salts **3a-OTs** and **3b-OTs** could indeed be obtained in good yields at 60 °C. However, the synthesis of TMP salt **3p-OTs** was low-yielding and gave impure product, indicating that our method is complementary to Stuart's synthesis of TMP tosylates.[3b] The method also proved efficient for the synthesis of cyclic salts **3u** and **3v**, which were obtained in 79–91% yields.

In general, our developed one-pot method in EtOAc either outperformed or worked equally well to the state-of-the-art-methods in DCM, which are based upon our original one-pot protocol utilizing *m*CPBA and TfOH/TsOH,[2a–c] thus making it a more sustainable option in the synthesis of diaryliodonium salts.

Finally, **2e** and **3j** were synthesized using 45 and 70 mmol iodoarene, respectively, to demonstrate the scalability of the methods (Scheme 4). The reaction conditions were adjusted to ensure the safe handling of reaction exotherms on a higher scale, and hence the acid and arene were added at −20 °C. Importantly, the reactions proceeded in good to excellent yields without the need for purifications of reagents or solvents, with only minor decreases compared to the small-scale reactions (7% for **2e** and 10% for **3j**). Additionally, the product precipitation could be performed in the sustainable solvent cyclopentyl methyl ether instead of the typically used diethyl ether. The calculated



Scheme 4 Large scale synthesis of DMIX triflate **2e** (A) and anisyl triflate **3j** (B).

E-factors for **2e** and **3j** (7.40 and 12.29, respectively) are comparable to the fine chemical industry,[21] highlighting the minimal waste produced under our conditions.

In conclusion, we have developed the first one-pot synthesis of aryl(DMIX)iodonium triflates **2**, and demonstrated the synthesis of diaryliodonium triflates **3** in the sustainable solvent ethyl acetate. The scalability of the protocol was established with **2e** and **3j**, which were synthesized in high yields and with impressively low *E*-factors, without the need for purification of reagents or solvents.

Conceptualization – SD, LK, PV, BO; investigation and methodology – SD, LK, PV, MA; supervision – SD, PV, BO; writing – original draft – SD, LK; writing – review & editing – SD, LK, PV, BO; funding acquisition, validation, project administration, resources – BO.

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Data availability

The data supporting this article have been included as part of the ESI.† Raw data can be found at: https://doi.org/10.5281/zenodo.14834462.

Conflicts of interest

There are no conflicts to declare.

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