One-Pot C−H Functionalization of Arenes by Diaryliodonium Salts

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Abstract: *A transition-metal-free, mild, and highly regioselective synthesis of nitroarenes from arenes has been developed. The products are obtained in a sequential one-pot reaction by nitration of iodine(III) reagents with two carbon ligands, which are formed in situ from iodine(I). This novel concept has been extended to formation of aryl azides, and constitutes an important step towards catalytic reactions with these hypervalent iodine reagents. An efficient nitration of isolated diaryliodonium salts has also been developed, and the mechanism is proposed to proceed by a [2,2] ligand coupling pathway.*

Hypervalent iodine compounds have become important reagents for a wide variety of transformations, as they have a valuable combination of properties including high reactivity, high functional-group tolerance, and low toxicity.[1] The main drawback with hypervalent iodine reagents is the stoichiometric formation of either an iodine(I) or iodine(III) compound as waste, depending on the oxidation state (III or V) of the starting reagent. This aspect lowers the atom efficiency and may lead to product purification problems. The groups of Ochiai and Kita reported the first catalytic uses of hypervalent iodine reagents in 2005 (Scheme 1a).[2] Since

Scheme 1. In situ formation of iodine(III) reagents. EDG = electron-donating group, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol, *m*CPBA = *m*-chloroperbenzoic acid, Ts = 4-toluenesulfonyl.

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then many other systems have appeared, where a catalytic amount of iodoarene is combined with a stoichiometric amount of an oxidant.[3]
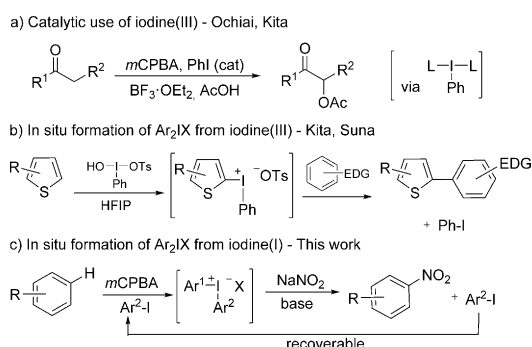
Iodonium salts and their cyclic counterparts benziodoxol-(on)es (e.g. EBX and Togni's reagent) are important iodine(III) reagents for the transfer of carbon ligands (aryl, alkynyl, vinyl, CF$_3$, or CN groups) to a wide range of nucleophiles.[4] These reagents are generally synthesized in one or more steps, isolated, and subsequently reacted with a nucleophile. Kita and co-workers have demonstrated the efficient in situ formation of diaryliodonium salts from other iodine(III) reagents in metal-free arylations (Scheme 1b),[5] and the group of Suna has utilized the same strategy in metal-catalyzed arylations.[6] However, to the best of our knowledge, catalytic reactions with iodonium salts or benziodoxol(on)es remain unknown.[4,7]

In our long-term quest for catalytic arylation conditions, we reasoned that in situ formation of diaryliodonium salts from arenes and iodoarenes in the presence of an oxidant, followed by arylation of a suitable nucleophile under metal-free conditions, would constitute an important step towards this difficult goal. Herein we present our results of an efficient arylation of sodium nitrite with diaryliodonium salts, which can be formed in situ from arenes and iodoarenes under oxidative conditions (Scheme 1c). The methodology compares well to previous routes to nitroarenes, concerning regioselectivity, functional-group tolerance, and ease of handling.[8]

Synthetic routes to aromatic nitro compounds are important, as nitroarenes are key intermediates in the preparation of many dyes, plastics, and explosives.[9] They can be synthesized from arenes under harsh acidic conditions,[9a] by treatment with [bis(trifluoroacetoxy)iodo]benzene (PIFA),[10] and by rhodium-catalyzed oxidative C−H activation,[11] all of which give regioisomeric mixtures. Regiospecific transformations include palladium-catalyzed nitration of aryl chlorides,[12] and either metal-mediated or metal-free conversion of arylboronic acids.[13] Nitroarenes have also been obtained from diaryliodonium salts,[14] thus making this transformation suitable for our envisioned one-pot reaction.

The nitration reaction was first investigated using isolated diaryliodonium salts, as a stepwise and general methodology to nitroarenes could be preferable with advanced diaryliodonium salts carrying sensitive functional groups. Various nitrite sources, solvents, and temperatures were screened, and high yields of nitroarenes were obtained with NaNO$_2$ in either DME or EtOAc at 70 °C,[8] the latter solvent being preferable from an environmental perspective. The nitration proved insensitive to moisture and air, and can be conveniently carried out without special precautions.

Interestingly, the diaryliodonium counterion had a major impact on the reaction, as shown in Table 1. Diphenyliodo-

Table 1: Counterion effect under optimized reaction conditions.[a]

NaOTf	Yield [%][b]			
(equiv)	X = OTf	X = PF$_6$	X = BF$_4$	X = OTs
0	94	91	18	18
0.5		68		
1.0	86		94	87

[a] Reaction conditions: NaNO$_2$ (0.16 mmol) was added to
1 (0.14 mmol) and NaOTf (0–1 equiv) in EtOAc (1 mL). The suspension
was stirred at 70 °C for 16 hours. [b] Yield determined by ^{1}H NMR
analysis using 1,3,5-trimethoxybenzene as internal standard. Tf = tri-
fluoromethanesulfonyl.

nium triflate (X = OTf) and hexafluorophosphate (X = PF$_6$)
gave nitrobenzene (**2a**) in excellent yields, whereas the
corresponding tetrafluoroborate (X = BF$_4$) and tosylate
(X = OTs) resulted in poor conversion into **2a**. This result
was surprising as tetrafluoroborate salts are usually efficient
in both metal-free and metal-catalyzed reactions.[4e,f] We
hypothesized that addition of sodium triflate might improve
the outcome, and discovered that 1 equivalent of NaOTf was
indeed sufficient to provide **2a** in 94% yield. The tosylate salt
could also be efficiently utilized upon addition of NaOTf, and
the trend was verified with other tetrafluoroborate salts.[8]
This finding is important, as anion exchange of diaryliodo-
nium salts can be tedious and waste producing. While the
exact role of NaOTf remains unknown, the additive effect
could be useful in other arylations where the counterion
influences the reaction.

The scope of the arene nitration was subsequently
investigated with diaryliodonium salts **1** (Scheme 2).[15] Tri-
flate, tetrafluoroborate, and tosylate salts could all be
employed, using NaOTf as an additive with the two latter
anions. Nitrobenzene (**2a**) and the halide-substituted prod-
ucts **2b**–**e** were all isolated in high to excellent yields. The
reaction showed great tolerance for steric hindrance in the
ortho-position, as exemplified with the halide products **2d** and
2e, and with the high-yielding synthesis of the di-*ortho*-alkyl-
substituted nitroarenes **2f** and **2g**. While the electron-rich
products **2h** and **2i** were obtained in moderate yields despite
addition of 3 equivalents of NaNO$_2$, the synthesis of **2h** was
improved to 79% yield by changing the solvent. Moderately
electron-donating substituents were well tolerated, and alkyl-
substituted salts were efficiently transformed into **2f**, **2g**, **2j**,
and **2k**. The synthesis of **2k** was easily scaled up to 7 mmol,
thus displaying the robustness of the reaction. Likewise,
products with electron-withdrawing substituents were
obtained in high yields (**2l**–**o**). More elaborate diaryliodo-
nium salts could also be utilized, as demonstrated in the
synthesis of the carbonyl-substituted products **2p**–**q**, and in
the reactions with pyridyl iodonium salts to provide the
heterocycles **2r** and **2s** in 78 and 88% yield, respectively.

Unsymmetric diaryliodonium salts were utilized in several
reactions,[16] and the phenyl group was an efficient "dummy"
group in the nitration of electron-deficient aryl moieties (**2l**,
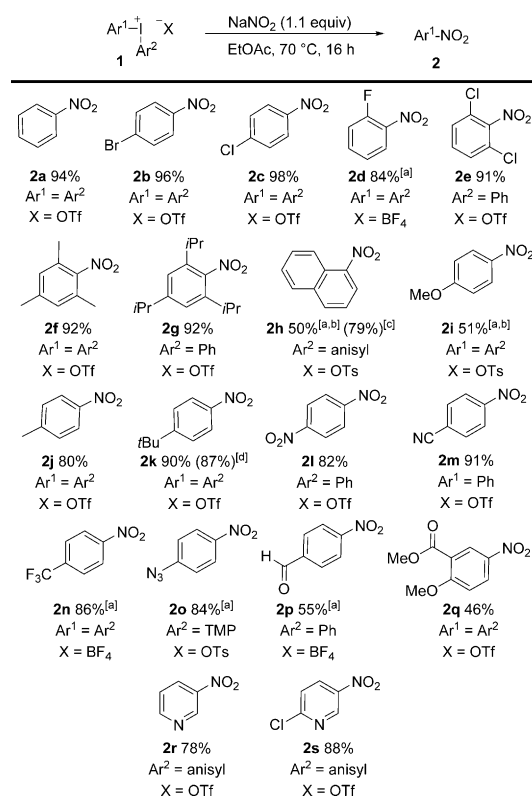
Scheme 2. Scope for the nitration with isolated salts **1**. Reaction
conditions as in Table 1 with **1** (0.5 mmol). Yields are those of isolated
products. [a] NaOTf (1 equiv) was added. [b] NaNO$_2$ (3 equiv) was
used. [c] In CH$_2$Cl$_2$/H$_2$O 1:1. [d] 7 mmol scale.

2m, **2p**). A strong *ortho*-effect[4e–h,17] was observed in
reactions with *ortho*-substituted iodonium salts, which pro-
ceeded with excellent chemoselectivities (**2e**, **2g**, **2h**) despite
competing electronic preferences (**2g**). *p*-Methoxyphenyl
(anisyl) or 2,4,6-trimethoxyphenyl (TMP)[17a,18] dummy
groups were efficiently utilized in reactions yielding **2h**, **2o**,
2r, and **2s**.

The envisioned one-pot sequence was next investigated.
Unfortunately, synthesis of the diaryliodonium salts in either
EtOAc or DME was low yielding, hence the one-pot
sequence was further studied in dichloromethane using our
established methodology.[15] Bromobenzene (**3b**) and 4-bro-
moiodobenzene (**4b**) were treated with *m*CPBA and TfOH to
yield the symmetric 4-bromophenyl iodonium salt **1b** in situ
(Scheme 3a). Sodium nitrite and NaHCO$_3$[19] were then
added, thus providing nitroarene **2b** and unreacted diaryl-
iodonium salt as the major components. Addition of water[14d]
and adjustment of the pH value improved the outcome, and
delivered **2b** in 58% yield with 3 equivalents of NaNO$_2$
within 3 hours.[8] Only the *p*-substituted product **2b** was
observed, and the complete regioselectivity can be attributed
to the known, highly *p*-selective formation of diaryliodonium
salts.[4e,f,h]

Considering the three steps involved in this sequential
one-pot reaction (oxidation, formation of **1b**, and nitration to
2b), this metal-free C–H nitration of bromobenzene is quite
efficient (Scheme 3a). The resulting iodoarene **4b** was
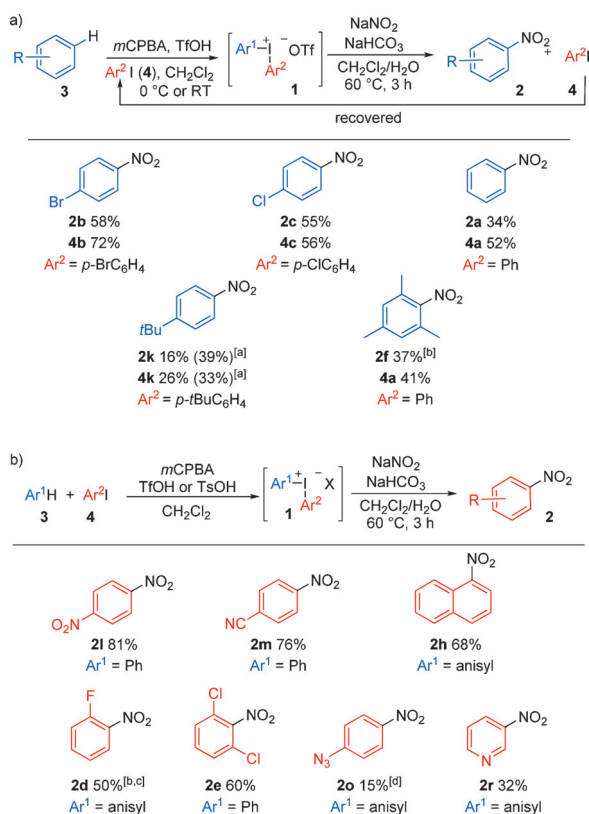
Scheme 3. One-pot nitrations using **4** (0.5 mmol), **3** (1.1 equiv), *m*CPBA (1.1 equiv), TfOH (2–3 equiv). and NaNO$_2$ (3 equiv). Yields are those of isolated products. [a] Nitration at 80°C, with <5% impurity. [b] TsOH·H$_2$O (1 equiv) used instead of TfOH. [c] **2d**/**2i** >20:1. [d] Anisole (5 equiv) used.

isolated in 72%, thus showing the recyclability of this component. In the same fashion, chlorobenzene was converted into **2c** in 55% with recovery of the iodoarene **4c** in similar yield, and benzene was transformed into nitrobenzene (**2a**). One-pot C–H nitration of alkyl benzenes proved more difficult, and the three-step reaction provided **2k** in poor yield, which gratefully was considerably improved at higher temperature.[20]

The synthesis of unsymmetric diaryliodonium salts (Ar^1 ≠ Ar^2) is often high yielding,[15] hence we investigated the nitration of mesitylene by in situ formation of a mesityl-(phenyl)iodonium salt (Scheme 3a). To our delight, the sterically hindered product **2f** was obtained with excellent chemoselectivity (**2a** not observed). In all cases the iodoarenes **4** could be recovered in at least equivalent amounts from the one-pot reactions, thus allowing reuse in subsequent reactions.[21]

The scope investigation was continued with a range of unsymmetric diaryliodonium salts, thus delivering functionalized nitroarenes in good yields with complete regioselectivity (Scheme 3b).[22] Nitroarenes with electron-withdrawing substituents were formed in excellent yields over the three steps (**2l**, **2m**). 1-Nitronaphthalene (**2h**), and the *ortho*-halogenated products **2d** and **2e** were also obtained with high efficiency, thus illustrating that electron-donating substituents

as well as *ortho*-substituents are well tolerated. The *p*-azido product **2o** was obtained in an unsatisfactory yield, which is likely due to the moderate-yielding salt synthesis.[8] Heterocyclic products could also be obtained in a one-pot manner, as exemplified by the synthesis of 3-nitropyridine (**2r**).

The application of this novel one-pot concept to other nucleophiles is currently underway in our laboratory, and preliminary results with sodium azide[23] are promising (Scheme 4).
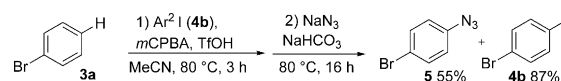
Scheme 4. Preliminary investigation with azide as a nucleophile (^{1}H NMR yield).

A radical mechanism is unlikely, as addition of the radical scavengers, 1,1-diphenylethylene and TEMPO, to the nitration in EtOAc did not hamper the reaction significantly.[8] Hence, we suggest that the reaction proceeds by formation of a T-shaped intermediate containing a Nu–I bond (Scheme 5). The nitrite nucleophile could either form an N–I or O–I intermediate (**A** and **B**), followed by ligand coupling to provide the N-arylated product **2a** or O-arylated product **6** (not observed). While ligand coupling by the [1,2] pathway is the only possibility with some nucleophiles, recent computational studies have found that four- or five-membered transition states can be favored.[17a,b, 24]
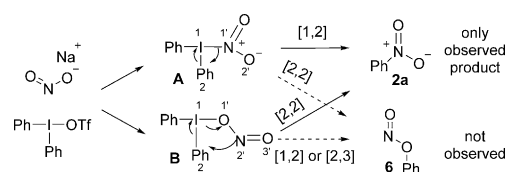
Scheme 5. Mechanistic possibilities.

The suggested pathways were studied by DFT computations (Figure 1).[8] Ligand exchange by a dissociative pathway leads to a large increase in energy, whereas the associative pathway via four-coordinated complexes, to give the intermediates **B1** and **B2**, is energetically favorable by 13 and 25 kJ mol^{-1}, respectively. Ligand coupling via the three-membered **TS1** would give N-arylation, whereas coupling via the three-membered **TS2** or five-membered **TS3** would result in O-arylation. These pathways are, however, all too high in energy to be plausible. The reaction is suggested to give the N-arylated product **2a** via the four-membered **TS5** ($\Delta G^{\ddagger} = 73$ kJ mol^{-1}), which has a lower energy barrier than **TS4** ($\Delta G^{\ddagger} = 87$ kJ mol^{-1}). The energy difference corresponds to a 135:1 ratio in favor of **2a** at 70°C, thus explaining why **6** is not observed.[8]

To conclude, nitroarenes have been efficiently synthesized by a transition-metal-free arylation of sodium nitrite with diaryliodonium salts. An interesting counterion effect was observed, and the unprecedented use of NaOTf as an additive enabled efficient arylations with such salts. The mechanism is
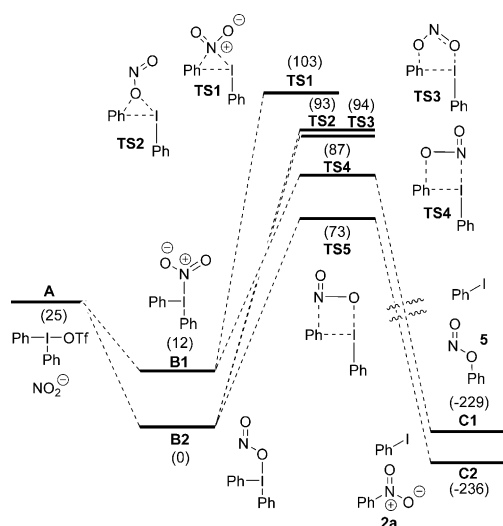
Figure 1. DFT calculated potential energy surfaces for the reaction between **1a**(OTf) and nitrite. Energies are measured in kJ mol^{-1}. $^{-}$OTf omitted for clarity in **B1** and **B2**, **TS1–TS5**, and **C1** and **C2**.

suggested to proceed via an O–I intermediate followed by an unusual [2,2] ligand coupling. The reaction has been extended to a sequential one-pot transformation, where diaryliodonium intermediates are generated from arenes and iodoarenes in a highly regioselective fashion, and subsequently nitrated with recovery of the iodoarene. Azidation also proved possible using the same novel concept, where iodine(III) reagents with two carbon ligands are formed in situ from iodine(I) and subsequently intermolecularly reacted with nucleophiles. This feature constitutes an important step towards catalytic reactions with such hypervalent iodine reagents.

Acknowledgements

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