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# Halonium metathesis reactions

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**Dedicated to Professor Sam Zard**

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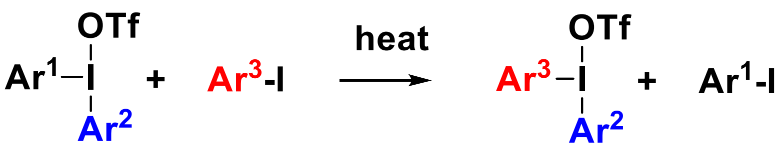
## Abstract

We provide a summary of the discovery of the aryl exchange between a diaryliodonium triflate and an aryl iodide (iodonium metathesis reaction) and relevant mechanistic aspects thereof. Some initial applications are illustrated, together with more recent developments in the field of diarylhalonium metathesis; in particular, the noteworthy extension of the process to diaryl chloranes by Uchiyama and collaborators.



**Keywords:** Hypervalent halogen, iodanes, iodonium metathesis, mechanism, organoiodine compounds.

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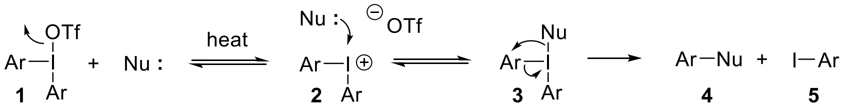
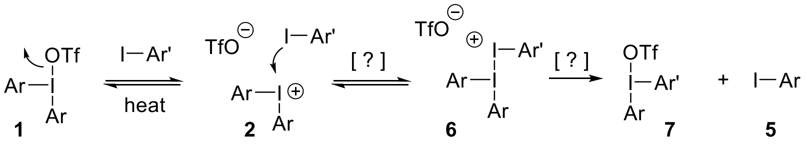
## 1. Introduction

A synthetic problem induced us to consider the use of diaryliodonium salts,[1] $(Ar^1)(Ar^2)I\text{-}X$ (X = halide, sulfonate, etc.), more accurately described as $\lambda^3$ iodanes (IUPAC nomenclature),[2] as aryl transfer agents. Early preparative routes to these hypervalent iodine species, which have been known since the 1890's,[3] have been improved considerably in recent times.[4] While newer techniques seemed to be entirely adequate for the synthesis of the structurally complex iodanes we required, a detailed review of the technical literature brought to light a number of facts that captured our attention. To wit, the thermal dissociation of, e.g., a diaryliodonium triflate, **1** (Scheme 1), reversibly produces a "superelectrophilic" diaryliodonium ion, **2**, which can transfer an aryl group even to exceedingly poor nucleophiles.[5] A plausible mechanism for such aryl transfer events is believed to involve association of the nucleophile with **2** and fragmentation of the resulting iodane **3** to a molecule of product, **4**, and one of aryl iodide, **5**.[6] The latter – the formal leaving group in the arylation reaction – is estimated to be $10^6$ times more nucleofugal than triflate ion.[7] Notice that an aryl iodide undergoes a formal reductive elimination from complex **3**. On the other hand, the iodine atom in an aryl iodide is sufficiently nucleophilic to function as an effective silyl transfer agent in Yamamoto's iterative Mukaiyama aldol reactions,[8,9] to undergo oxidation to the iodoso state upon reaction with a peroxyacid,[10,11] to be converted into a $\lambda^3$ dichloro iodane by the action of $Cl_2$,[12] and establish halogen bonds.[13]



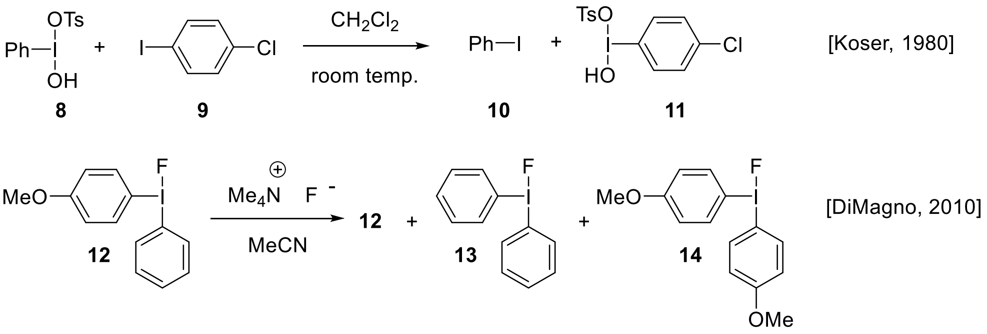
**Scheme 1**

The foregoing led to the provocative hypothesis that the iodine atom of an aryl iodide may be sufficiently nucleophilic to undergo arylation with a diaryliodonium salt, through the *iodonium metathesis reaction* depicted in Scheme 2. This then-unknown process seemed to offer a new, practical, and concise entry to the structurally complex iodanes we required, as well as nicely complement the latest preparative methods.



**Scheme 2**

A number of tantalizing observations augured well for the feasibility of the reaction. In 1980, Koser described the redox metathesis of aryl iodides with [hydroxy(tosyloxy)iodo]benzene (Koser's reagent, **8**; cf. **8** → **11**, Scheme 3).[14] Some years later, Moriarty employed the technology to prepare hypervalent derivatives of iodocubane and proposed a mechanism for it.[15,16] More recently, Legault found that Lewis acids are effective catalysts for this transformation.[17] Finally, DiMagno reported that fluoride ion promotes aryl group exchange between iodonium salts:[18] a remarkable observation that – curiously – stimulated no further study of scope and mechanism.



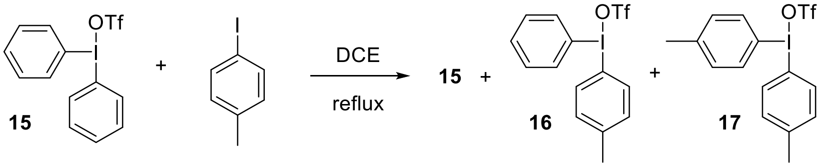
**Scheme 3**

On the down side, Olofsson detected no aryl exchange upon heating a DMF solution of an aryl iodide and a diaryliodonium salt.[19] This cast uncertainty on the feasibility of iodonium metathesis. A mitigating factor was that the reaction had been attempted in a strongly coordinating solvent that might have outcompeted the aryl iodide for the electrophilic diaryliodonium cation, thus suppressing metathesis. Perhaps, conduct of the reaction in a weakly coordinating solvent was key to success.

Beyond the sheer interest of exploring new territory, iodonium metathesis was appealing as a new avenue to iodane substrates for radiofluorination. Fluorine-18 radiopharmaceuticals find application as imaging agents in Positron Emission Tomography (PET).[20] Many $^{18}$F PET imaging agents are aryl fluorides,[21,22] which may be prepared by reaction of an aryliodane with radiolabeled fluoride ion.[23] All the above induced us to launch an effort to achieve iodonium metathesis.

## 2. Discovery of the Iodonium Metathesis Reaction

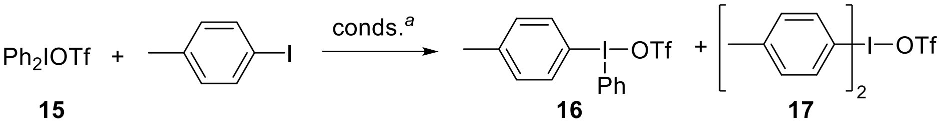
Our very first experiment (Scheme 4) entailed refluxing a 1,2-dichloroethane (DCE) solution of commercial diphenyliodonium triflate, **15**, and excess 4-iodotoluene for several hours, whereupon products **16** and **17** of iodonium metathesis were indeed detected by NMR and mass spectrometry. The reaction was thus possible.[24]



## Scheme 4

A number of problems were rapidly uncovered. First, metathesis seemed to proceed only with diphenyliodonium triflate, while no aryl exchange was observed with the tosylate, tetrafluoroborate, or hexafluorophosphate salt. Second, no reaction occurred in lower boiling, or relatively nonpolar, or strong donor solvent (the latter in accord with Olofsson),[19] such as THF, acetone, $CHCl_3$, $CH_2Cl_2$, acetonitrile, chlorobenzene, 1,2-dichlorobenzene, DMF, or DMSO. Third, product formation (NMR, MS) occurred only after an induction period of 3-4 hours. Fourth, product distribution varied significantly among experiments carried out under seemingly identical conditions. Finally, significant conversion required prolonged heating at reflux (12-24 h), but then only about 10-20% of the theoretical mass of iodanes (starting **15** and metathesis products) were recovered (Table 1). Suspecting that some of the foregoing difficulties arose as a consequence of thermal degradation of the iodanes, the reaction was attempted at temperatures below the boiling point of DCE (84 °C), but this resulted in virtually no reaction. Fortunately, more consistent results and satisfactory mass recoveries were achieved by the use of $Ph_2IOTf$ freshly recrystallized from MeCN/ether.

**Table 1**. Results of initial iodonium metathesis experiments



| entry | method | mass recovery[b] | prod. distrib. **15** : **16** : **17**[c] |
|---|---|---|---|
| a | DCE, refl., 3 h | >80% | no reaction |
| b | DCE, refl., 15 h | 15% | not determined |
| c | DCE, 60-70 °C, 15 h | 50-60% | no reaction |
| d | neat, press. tube, 120 °C, 24h | 60% | 31% : 21% : 48% |
| e | DCE, press. tube, 120 °C, 24 h | 48% | 3% : 3% : 94% |

[a] 0.1 mmol (1 equiv) of Ph2IOTf, 0.5 mmol (5 equiv) of 4-iodotoluene, 0.5 mL of DCE (0.2 M) or neat.

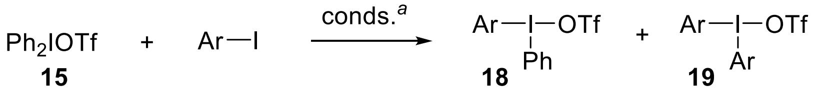
[b] Combined recovery of iodanes after chromatography.

[c] Calculated by $^1H$ and quantitative $^{13}C$ NMR analysis of reaction mixtures before purification.

A reaction mixture that had accidentally gone dry upon refluxing overnight left a residue that contained a high proportion of **16** and **17**, plus iodotoluene (used in excess). The low melting point of the latter (35 °C) led to the surmise that metathesis might be achievable simply by heating a mixture of the reactants without added solvent. This was indeed the case, but conversion was low. Much better results were obtained by heating a DCE solution of the reactants in a pressure tube sealed with a Teflon cap and immersed in an oil bath maintained at 120 °C. As shown in Table 1, entry e, very high, clean conversion of **15** into **17** was thus achieved.

Electronic effects with respect to the aryl iodide were investigated through the reaction of various such halides with $Ph_2IOTf$ (Table 2). High conversions were observed with 1-iodonaphthalene and 4-iodoanisole (entries a and b), although in the former case mass recovery was a disappointing 14%. This may be due to the sterically hindered nature (*peri*-effect)[25] of naphthyl iodanes, which tends to promote decomposition.[26] In any event, the above iodides, together with 4-iodotoluene were clearly good I-nucleophiles in iodonium metathesis. This was not the case for aryl iodides based on an excessively electron-rich nucleus, such as 4-iodoveratrole and 4-iodo-*N*,*N*-dimethylaniline (entries c and d). A DCE solution of these substrates and **15** rapidly developed a deep green or blue color and produced an intractable mixture containing little or no metathesis products. This suggests the fast occurrence of single electron transfer (SET) processes, and consequent suppression of iodonium metathesis. Aryl iodides carrying electron-withdrawing groups reacted slowly (cf. 4-bromo-iodobenzene, entry e) or not at all (cf. methyl 4-iodobenzoate, entry f).

**Table 2**. Electronic effects in iodonium metathesis reactions



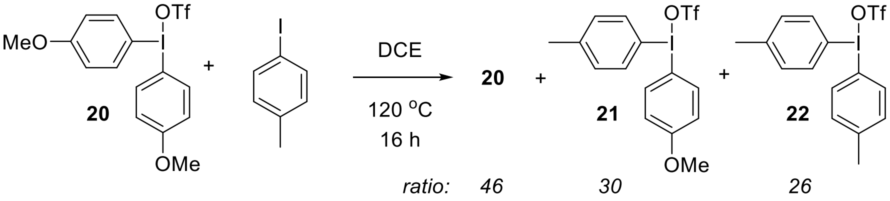
| entry | Ar | time (h) | mass recovery[b] | prod. distrib. **15** : **18** : **19**[c] |
|---|---|---|---|---|
| a | 1-naphthyl | 26 | 14% | 0% : 66% : 33% |
| b | 4-$MeOC_6H_4$ | 25 | 78% | 2% : 53% : 45% |
| c | 3,4-$(MeO)_2C_6H_3$ | 12 | 0% | decomp. |
| d | 4-$(Me_2N)C_6H_4$ | 12 | 0% | decomp. |
| e | 4-$BrC_6H_4$ | 12 | 64% | 21% : 32% : 47% |
| f | 4-$MeOOCC_6H_4$ | 12 | > 80% | no reaction |

[a] 0.1 mmol (1 equiv) of Ph2IOTf, 0.5 mmol (5 equiv) of 4-iodotoluene, 0.5 mL of DCE (0.2 M); heavy-walled glass vial sealed with a Teflon cap, 120 °C oil bath temperature.

[b] Combined recovery of iodanes after chromatography.

[c] Calculated by $^1H$ and quantitative $^{13}C$ NMR analysis of reaction mixtures before purification.

More interesting results were obtained by varying the electronic properties of the iodane. Iodonium salts with electron-rich aryls, e.g., di(4-anisyl)triflate, **20**, underwent metathesis at a very slow rate, progressing to ca. 54% conversion after 16 hours ($^1H$ NMR) to give comparable amounts of **21** and **22** (Scheme 5).[27]

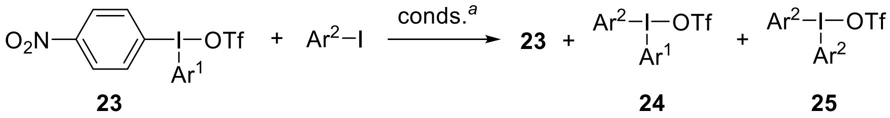


**Scheme 5**

Unsymmetrical iodanes incorporating both an electron-poor and an electron-rich aryl reacted efficiently with nucleophilic iodides, and nearly complete conversion was observed in every case. Representative results obtained with 4-nitrophenyl(aryl)iodonium triflates appear in Table 3. Surprisingly, virtually exclusive transfer of the more electron-rich aryl group to the incoming aryl iodide took place. This is in sharp contrast to Beringer's observation that the arylation of ordinary nucleophiles occurs with very selective transfer of the more electron-deficient aryl;[28] a fact that induced Ochiai to propose a mechanism that possesses character of nucleophilic aromatic substitution.[29] Such a mechanism clearly cannot be operative in iodonium metathesis (*vide infra*). Notice, however, the formation of some (1-naphthyl)(4-nitrophenyl)iodonium triflate in experiment h. Selectivity for the transfer of the more electron-rich aryl ligand was retained even in the case of (mesityl)(4-nitrophenyl)iodonium triflate (entries i-k). Again, this is contrary to the reactivity of (mesityl)aryliodonium triflates, which tend to transfer the aryl, not the mesityl, group to incoming nucleophiles.[30,31] On a final note, the formation of di-(4-anisyl)iodonium triflate in experiments e and h is attributable to liberation of some 4-iodoanisole, perhaps by decomposition of the starting **23**, and subsequent metathesis with other iodanes present in the medium. Its extent of formation, even in the presence of a large excess iodobenzene or 1-iodonaphthalene, may reflect its thermodynamic stability relative to other diarylidonium triflates, as evidenced also by its poor reactivity.

More surprising still was the behavior of (aryl)(2-thienyliodonium) triflates. The 2-thienyl group is regarded as electron-rich. According to the foregoing, an (aryl)(2-thienyliodonium) triflate should then transfer the thienyl group selectively, especially if the aryl ligand were electron-deficient. However, the exact opposite was observed. Representative examples with (4-carbomethoxyphenyl)(2-thienyl)iodonium triflate are provided in Table 4. While (aryl)(2-thienyliodonium) salts are known to transfer the aryl group selectively to external nucleophiles,[32] attributing this to electronic factors creates a logical conflict with the data in Table 3, unless thienyl iodanes undergo metathesis by a different mechanism. This seemed extremely unlikely. Clearly, the notion that iodonium metathesis reactions proceed with selective transfer of the "more electron-rich aryl ligand" is overly simplistic. This called for a more detailed mechanistic investigation.

**Table 3**. Metathesis reaction of 4-nitrophenyl iodanes



| entry | Ar$^1$ | Ar$^2$ | mass recovery[b] | prod. distrib. **23** : **24** : **25**[c] | others[d] |
|---|---|---|---|---|---|
| a | Ph | Ph | 65% | 7% : - : 93%[e] | - |
| b | " | 4-MeC$_6$H$_4$ | 73% | 0% : 43% : 57% | - |
| c | " | 4-MeOC$_6$H$_4$ | 76% | 1% : 63% : 36% | - |
| d | " | 1-naphthyl | 59% | 3% : 83% : 15% | - |
| e | 4-MeOC$_6$H$_4$ | Ph | 60% | 4% : 54% : 37% | 5%[f] |
| f | " | 4-MeC$_6$H$_4$ | 79% | 0% : 56% : 44% | - |
| g | " | 4-MeOC$_6$H$_4$ | 89% | 13% : - : 87%[e] | - |
| h | " | 1-naphthyl | 64% | 10% : 68% : 10% | 8%[f], 5%[g] |
| i | Mesityl | 4-MeC$_6$H$_4$ | 26% | 0% : 12% : 88% | - |
| j | " | 4-MeOC$_6$H$_4$ | 37% | 0% : 7% : 93% | - |
| k | " | 1-naphthyl | 27% | 47% : 6% : 47% | - |

[a] 0.1 mmol (1 equiv) of Ph$_2$IOTf, 0.5 mmol (5 equiv) of 4-iodotoluene, 0.5 mL of DCE (0.2 M); heavy-walled glass vial sealed with a Teflon cap, 120 °C oil bath temperature, 12 h.

[b] Combined recovery of iodanes after chromatography.

[c] Calculated by $^1$H and quantitative $^{13}$C NMR analysis of reaction mixtures before purification.

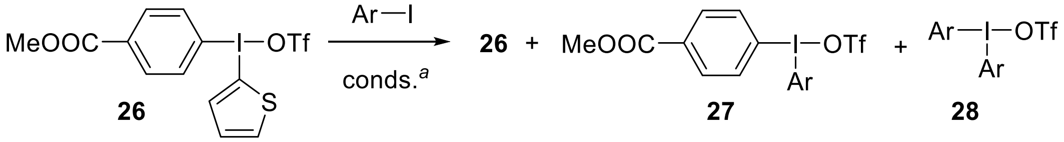
[d] Based on MS and $^1$H NMR analysis of crude reaction mixtures.

[e] **24** and **25** are identical.

[f] di(4-Anisyl)IOTf.

[g] (1-naphthyl)(4-nitro-phenyl)IOTf.

**Table 4**. Metathesis reactions of (4-carbomethoxyphenyl)(2-thienyl)iodonium triflate



| entry | Ar | mass recovery[b] | prod. distrib. **26** : **27** : **28**[c,d] |
|---|---|---|---|
| a | Ph | 40% | 0% : 6% : 94% |
| b | 4-$MeC_6H_4$ | 66% | 0% : 13% : 87% |
| c | 4-$MeOC_6H_4$ | 91% | <1% : 57% : 43% |
| d | 1-naphthyl | 38% | <1% : 20% : 80% |

[a] 0.1 mmol (1 equiv) of $Ph_2IOTf$, 0.5 mmol (5 equiv) of 4-iodotoluene, 0.5 mL of DCE (0.2 M); heavy-walled glass vial sealed with a Teflon cap, 120 °C oil bath temperature, 12 h.

[b] Combined recovery of iodanes after chromatography.

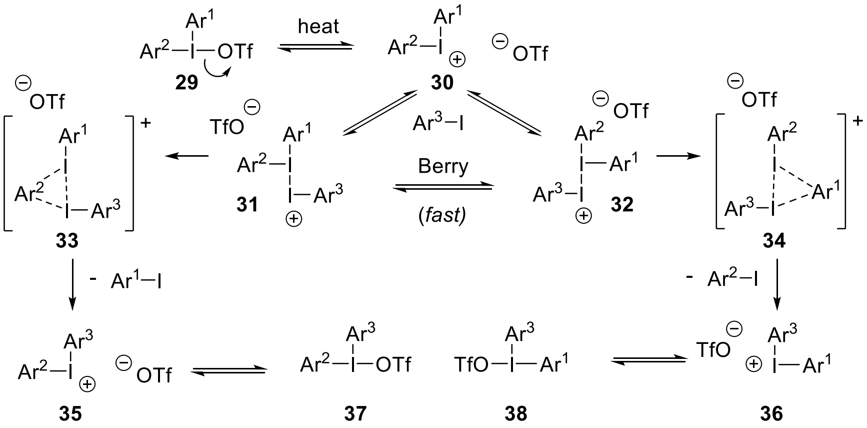
[c] Calculated by $^1H$ and quantitative $^{13}C$ NMR analysis of reaction mixtures before purification.

[d] Traces of (2-thienyl)(aryl)iodonium triflates were detected by MS and $^1H$ NMR in all cases.

## 3. Mechanistic Aspects of the Iodonium Metathesis Reaction

The Moriarty mechanism for redox metathesis, which is supported by theoretical studies,[33] seemed translatable to the iodonium metathesis case as per Scheme 6. The requirement for temperatures above 80 °C and for a polar solvent (the dielectric permittivity $\varepsilon$ of DCE is 10.36)[34] is consistent with the obligatory initial dissociation of **29** to **30**.[35] In lower-boiling and less polar solvents like $CH_2Cl_2$ ($\varepsilon = 8.93$) or $CHCl_3$ ($\varepsilon = 4.81$), the extent of dissociation of **29** may be insufficient to establish a steady-state concentration of **30** conducive to an adequate reaction rate. Higher boiling donor solvents would probably solvate iodonium ion **30** quite strongly, and possibly bind to it, hampering its nucleophilic capture by the aryl iodide. The reduced rate of formation of **31**-**32** would retard or suppress iodonium metathesis, consistent with Olofsson's observations. Finally, the formation of reactive intermediates **31**-**32** embodies a special case of halogen bonding.[13] The general lines of this mechanism found support in subsequent work by Uchiyama and collaborators,[36] who apparently observed iodonium metathesis independently and at about the same time as us.[37]

The question of why some aryl iodides undergo metathesis easily and others do not was addressed by estimating the partial electrostatic charge on the iodine atom of various aryl iodides. The assumption was that the smaller the positive character of the I atom,[38] the greater its nucleophilicity. The fractional (+)-charge (in



**Scheme 6**

units of electron charge, *e*) on the I-atom of various iodides was thus estimated as the geometric mean[39] of the values calculated by MNDO, MNDO/d, AM1 and PM3[40] for structures energy-minimized by each method. Such estimates are undoubtedly crude, but they were assumed to reflect trends that may shed light on the above issue and various other mechanistic questions. Representative results appear in Table 5. It is apparent that MNDO/d values are in excellent agreement with the geometric mean. Subsequent work thus relied on I-(+)-charges estimated only by MNDO/d.

**Table 5**. Estimated fractional positive charge on the I atom of various aryl iodides (*e*)

| structure | MNDO | MNDO/d | AM1 | PM3 | Geom mean |
|---|---|---|---|---|---|
| iodomesitylene | 0.114 | 0.060 | 0.131 | 0.021 | 0.066 |
| 4-iodotoluene | 0.123 | 0.077 | 0.139 | 0.016 | 0.068 |
| Iodobenzene | 0.122 | 0.075 | 0.140 | 0.017 | 0.068 |
| 1-iodonaphthalene | 0.117 | 0.067 | 0.138 | 0.022 | 0.070 |
| 4-iodoanisole | 0.122 | 0.076 | 0.141 | 0.019 | 0.071 |
| 4-chloro-iodobenzene | 0.134 | 0.089 | 0.150 | 0.030 | 0.086 |
| 4-bromo-iodobenzene | 0.132 | 0.091 | 0.152 | 0.033 | 0.088 |
| 4-fluoro-iodobenzene | 0.132 | 0.091 | 0.151 | 0.036 | 0.090 |
| Me 4-iodobenzoate | 0.135 | 0.095 | 0.155 | 0.038 | 0.093 |
| 4-$CF_3$-iodobenzene | 0.145 | 0.108 | 0.162 | 0.051 | 0.107 |
| 3,5-di(COOMe)iodobenzene | 0.145 | 0.107 | 0.171 | 0.060 | 0.112 |
| 2-chloro-5-iodopyridine | 0.152 | 0.115 | 0.173 | 0.068 | 0.120 |
| 4-nitro iodobenzene | 0.152 | 0.118 | 0.173 | 0.067 | 0.120 |
| 5-iodo-*N*,*N′*-di-Me-uracyl | 0.174 | 0.148 | 0.209 | 0.127 | 0.162 |
| 2-Iodobenzothiophene | 0.179 | 0.154 | 0.205 | 0.134 | 0.166 |
| 2-iodothiophene | 0.181 | 0.154 | 0.202 | 0.136 | 0.166 |
| 2-iodofuran | 0.203 | 0.185 | 0.233 | 0.156 | 0.192 |
| 2-iodo benzofuran | 0.201 | 0.186 | 0.235 | 0.157 | 0.193 |

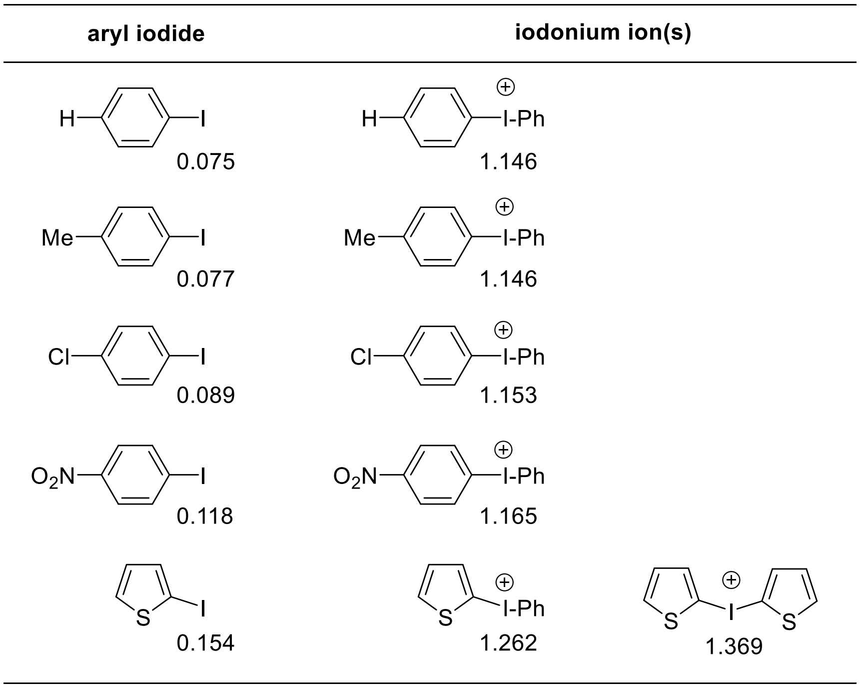
It became instantly apparent that compounds that undergo iodonium metathesis readily, such as 4-iodotoluene, 4-iodoanisole, 1-iodonaphthalene, and iodobenzene, exhibit a small (< +0.080 *e*) partial charge on the iodine atom. These molecules would thus be anticipated to be better I-nucleophiles than aryl iodides with larger I-(+) charges, and for that reason, we describe them as good I-nucleophiles or, equivalently, reactive aryl iodides. Compounds sustaining an I-(+) charge between +0.080 and +0.100 *e* undergo metathesis with difficulty, while those with I-(+) charges greater than about +0.100 *e* generally fail to undergo metathesis. Such compounds may thus be labeled as unreactive aryl iodides.

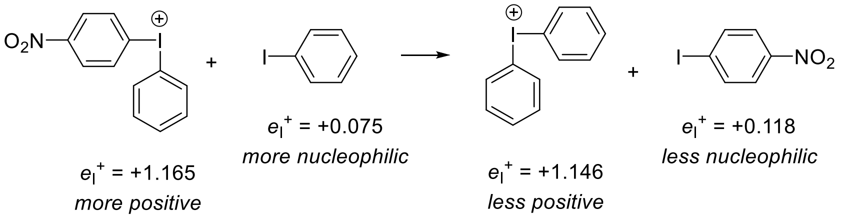
The issue of aryl transfer selectivity also seemed to be related to the extent of (+)-charge on the iodine atom. Indeed, the various effects that have been invoked to account for selective aryl transfer from diaryliodonium salts to ordinary nucleophiles (e.g., azide ion)[41] do not provide a satisfactory rationale for the outcome of iodonium metathesis reactions. On the other hand, it seemed that **31** and **32** are likely to be in fast equilibrium, either through reversible dissociation to **30**, or via the Berry pseudorotation mechanism,[42] or both. That being the case, product distribution – i.e., aryl group transfer selectivity – would be determined by the relative rate of reductive elimination of $Ar^1$-I and $Ar^2$-I, with the proviso that any argument for a faster departure of one aryl iodide over the other must be independent of the electron-rich or electron-deficient nature of the aromatic nucleus (see discussion above). One plausible driver of selectivity was the degree of positive charge on the iodine atom of either departing aryl iodide, $Ar^1$-I or $Ar^2$-I. Given the electronegative nature of iodine, the more I-positive aryl iodide would be more readily inclined to depart and take with it a pair of electrons.

In a like vein, the electronegative I-atom acquires additional positive character as it goes from the univalent to the polyvalent state. Consequently, a more I-positive hypervalent iodine species would be more energetic than a less I-positive one, and it will tend to undergo changes leading to less I-positive products. In the case of complexes such as **31** or **32**, a greater extent of I-(+)-charge on the I-atom should accelerate the rate of reductive elimination of the more I-positive Ar-I. We further surmised that I-positive aryl iodides would give rise to more I-positive hypervalent species. The issue was modeled by estimating the increase in I-(+) character as an aryl iodide advances to an (aryl)phenyiodonium ion (Table 6). Of course, semiempirical methods yield notoriously inaccurate data for hypervalent halogen species,[43] but the rough estimates of Table 6 (MNDO/d) support our hypothesis. Notice the unusually large (+)-charge on di(2-thienyl)iodonium ion, which will be relevant to the discussion of part 4.

The data in Table 6, however crude, strongly suggest that driving force for iodonium metathesis reactions is indeed a decrease in the extent of (+)-charge on the hypervalent I-atom, and that aryl group transfer selectivity is determined by the preferential departure of the aryl halide with the larger I-positive charge. Equivalently, a less I-positive, more I-nucleophilic aryl halide displaces a more I-positive, more nucleofugal one. For example, the reaction of 4-nitrophenyl(phenyl)-iodonium triflate with Ph-I described in Table 3 occurs so that (i) a more I-positive diaryliodonium ion is converted into a less I-positive one, and (ii) a less I-positive aryl halide displaces a more I-positive one (Scheme 7).

**Table 6**. Estimated positive charge (MNDO/d, *e*) on the I atom of some aryl iodides and corresponding iodonium ions





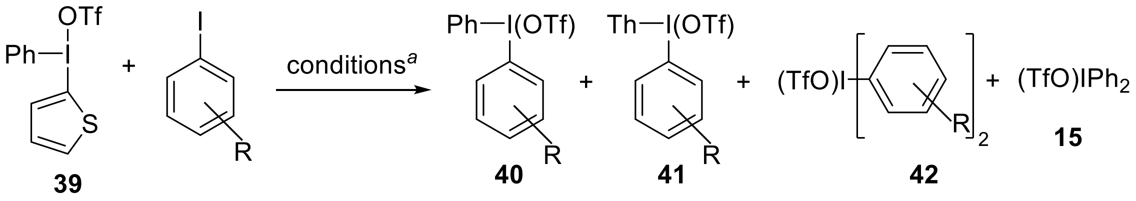
**Scheme 7**

The above data and experimental results further suggest that aryl iodides that are unreactive toward, e.g., $Ph_2IOTf$, should undergo metathesis with an iodane carrying an iodoaryl moiety with a particularly large I-(+) charge; for example, a 2-iodothiophene moiety. The unusually large *I*-(+)-charge of +0.154 *e* (MNDO/d) on the I-atom should impart pronounced nucleofugal character to 2-iodothiophene, or, equivalently, should promote its selective reductive elimination from complexes such as **31**-**32**. A hint that this may well be the case is already obvious from the aryl transfer selectivities of Table 4. Results of more pertinent experiments are summarized in the next section.

## 4. Iodonium Metathesis of Unreactive Aryl Iodides

Initial attempts to promote iodonium metathesis of "unreactive" aryl iodides centered on their reaction with phenyl(2-thienyl)iodonium triflate, **39**. It should be noted that 2-thienyl-based diaryiodonium *tetrafluoroborates* reportedly suffer from poor shelf life.[29] However, we determined that recrystallized **39** and related iodonium triflates are stable for at least one month when stored at room temperature (or below) with careful shielding from light.[44] The large I-positive character of 2-iodothiophene (0.154 *e*, MNDO/d, Table 5) was anticipated to favor phenyl group transfer to unreactive aryl iodides, even to 4-nitro-iodobenzene (0.118 *e*, MNDO/d). Indeed, ligand exchange in the anticipated sense did occur upon heating a DCE solution of an unreactive aryl iodide and **39** for 12 h in a pressure tube immersed in an oil bath maintained at 110 °C, with careful protection from light (*vide infra*).[45] Reaction rates, however, were significantly slower than before. This is attributable both to the diminished I-nucleophilic character of the aryl iodides and to a more difficult dissociation of the iodonium triflate, on account of the larger positive charge on the iodine atom of phenyl(2-thienyl)iodonium ion (1.262 *e*, MNDO/d, Table 6) relative to, e.g., diphenyiodonium ion (1.146 *e*, MNDO/d). Finally, the mixture of iodanes retrieved from such reaction mixtures amounted to a mass recovery of about 50-60%. This appeared to be a consequence of an appreciable degree of thermal degradation of **39**. Interestingly, **39** degraded faster when heated alone rather than with a nucleophilic aryl iodide. Thus, **39** decomposed to a mixture of 2-iodothiophene, Ph-OTf, and some Ph-I with a half-life of ca. 8 h upon heating to 110 °C in a sealed tube in the absence of an aryl iodide and with careful protection from light.[46] In contrast, diphenyliodonium triflate was recovered nearly unchanged after heating in DCE solution under identical conditions. This is presumably because in the latter case fast metathesis occurs to less I-positive, more stable $\lambda^3$-iodanes, which decompose more slowly.

**Table 7**. Thermal iodonium metathesis reactions of unreactive aryl iodides



| entry | R | yield$^b$ | prod. distrib.$^c$ 39 | 40 | 41 | 42 | 15 |
|---|---|---|---|---|---|---|---|
| a | 4-Cl | 79% | 11% | 56% | 9% | 19% | 5% |
| b | 4-Br | 79% | 18% | 58% | 0% | 19% | 5% |
| c | 4-F | 96% | 88% | 12% | 0% | 0% | 0% |
| d | 4-COOMe | 81% | 57% | 39% | ~0%$^d$ | 3% | 1% |
| e$^e$ | 3,5-di-COOMe | 63% | 2% | 37% | 0% | 5% | 6% |
| f$^e$ | 4-$CF_3$ | 92% | 2% | 37% | ~%0$^d$ | ~0%$^d$ | ~0%$^d$ |
| g$^e$ | 4-$NO_2$ | 89% | 75% | 23% | 0% | 0% | 2% |

[a]Conditions: 0.1 M solution of aryl iodide (1.0 mmol, 5 equiv) and **39** (0.2 mmol, 1 equiv) in $(CH_2Cl)_2$, thick-walled glass tube sealed with a Teflon screwcap and immersed in an oil bath maintained at 80 °C, 24 h.

[b]Percent yield of the mixture of diaryliodonium salts after silica gel chromatography.

[c]Molar fraction of each compound in the mixture of diaryiodonium salts ($^1$H and quantitative $^{13}$C NMR) recovered after chromatography.

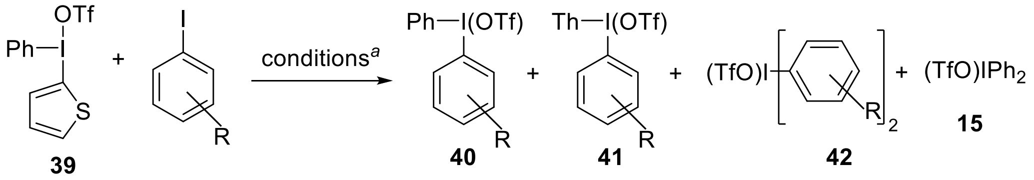
[d]Detected by ESI-MS, but not by $^1$H NMR.

[e]Reaction time shortened to 12h.

Much better results were obtained by operating at 80 °C (Table 7), albeit at the cost of a further reduced rate of metathesis. These reactions were allowed to proceed for only 24 h, at which time only partial conversion was apparent.[47] Mass recoveries were typically around 80% or higher, and product ratios were determined by $^1$H and quantitative $^{13}$C NMR. We presume that $Ph_2IOTf$, **7**, detected in product mixtures arose from metathesis of **39** and/or product iodane(s) with Ph-I released upon partial degradation of those same iodanes.

A significant rate acceleration was observed upon heating reaction mixtures by microwave irradiation (nominal temperature: 100 °C, Table 8).[48] Under such conditions, conversions of more than 70% were achieved in about 4 h, while product formation in the purely thermal regime was apparent only after ca. 12 h. On the other hand, mass recoveries were lower, presumably because of a greater extent of decomposition of the various $\lambda^3$-iodanes.

**Table 8**. Microwave-promoted iodonium metathesis of unreactive aryl iodides



| entry | R | yield[b] | prod. distrib.[c] | 39 | 40 | 41 | 42 | 15 |
|---|---|---|---|---|---|---|---|---|
| a | 4-Cl | 33% | | ~0%[d] | 41% | ~0%[d] | 51% | 8% |
| b | 4-Br | 40% | | 11% | 40% | 0% | 42% | 7% |
| c | 4-F | 77% | | 28% | 65% | 0% | 7% | 0% |
| d | 4-COOMe | 30% | | 14% | 46% | 10% | 19% | 11% |
| e[e] | 3,5-di-COOMe | 21% | | 28% | 31% | 13% | 7% | 21% |
| f[e] | 4-$CF_3$ | 40% | | 33% | 36% | 11% | 9% | 11% |
| g[e] | 4-$NO_2$ | 29% | | 69% | 18% | ~0%[d] | 0% | 13% |

[a] Conditions: 0.1 M solution of aryl iodide (1.0 mmol, 5 equiv) and **39** (0.2 mmol, 1 equiv) in $(CH_2Cl)_2$, sealed (crimp-cap) microwave glass vial, MW irradiation (Biotage® Initiator, 100 °C, high absorption mode), 4 h.

[b] Percent yield of the mixture of diaryliodonium salts after silica gel chromatography to remove nonpolar byproducts.

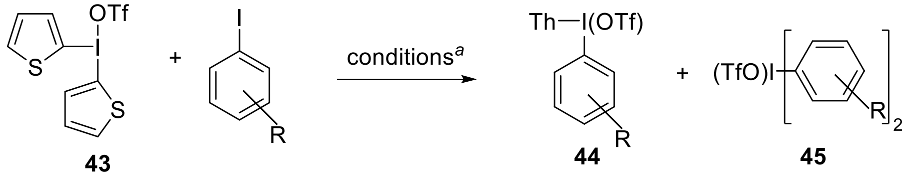
[c] Molar fraction of each compound in the mixture of diaryiodonium salts recovered after chromatography ($^1$H and quantitative $^{13}$C NMR).

[d] Detected by MS, but not by $^1$H NMR.

[e] Reaction time: 2h.

As many as 4 new iodanes, plus unreacted **39**, are present in the reaction mixtures from the experiments described above, complicating NMR analysis. Efforts to limit the number of products focused on metathesis reactions of di(2-thienyl)-iodonium triflate **43**, the use of which soon proved to be problematic. This iodane is rather insoluble in DCE, even at elevated temperatures; consequently, its instant concentration remained low during the various experiments. Also, the great extent of I-(+) charge on free dithienyliodonium ion (1.369 *e*, MNDO/d, Table 6) is likely to oppose heterolysis. Finally, the compound was significantly more thermally labile that other thienyliodanes, completely decomposing to an insoluble, lustrous black solid after ca. 5 h of heating in DCE at 110 °C. Reactions involving **43** had thus to be run at 80 °C. The combined effect of these factors translated into an unusually slow reaction rate, despite the high nucleofugality of 2-iodothiophene. Microwave heating again enhanced reaction rates. Table 9 summarizes the results of experiments carried out at a nominal temperature of 100 °C. Predictably, shorter reaction times translated into higher mass recoveries, especially in the case of more I-positive iodanes. Reaction times were thus reduced to 3 h for entry d and 2 h for entries e-g.

**Table 9**. Microwave-promoted metathesis of unreactive aryl iodides with di(2-thienyl)iodonium triflate



| entry | R | yield[b] | prod. distrib.[c] **43** | **44** | **45** |
|---|---|---|---|---|---|
| a | 4-Cl | 92% | 62% | 33% | 5% |
| b | 4-Br | 56% | 28% | 36% | 36% |
| c | 4-F | 55% | 0% | 23% | 77% |
| d[d] | 4-COOMe | 36% | 41% | 27% | 32% |
| e[e] | 3,5-di-COOMe | 54% | 46% | 35% | 19% |
| f[e] | 4-$CF_3$ | 68% | 59% | 32% | 9% |
| g[e] | 4-$NO_2$ | 71% | 72% | 28% | 0% |

[a] Conditions: 0.1 M solution of aryl iodide (1.5 mmol, 5 equiv) and **43** (0.3 mmol, 1 equiv) in $(CH_2Cl)_2$, sealed (crimp-cap) microwave glass vial, MW irradiation (Biotage® Initiator, 100 °C, high absorption mode), 4 h.

[b] Percent yield of the mixture of diaryliodonium salts after silica gel chromatography to remove nonpolar byproducts.

[c] Molar fraction of each compound in the mixture of diaryiodonium salts recovered after chromatography ($^1H$ and quantitative $^{13}C$ NMR).

[d] Reaction time: 3 h.

[e] Reaction time: 2 h.

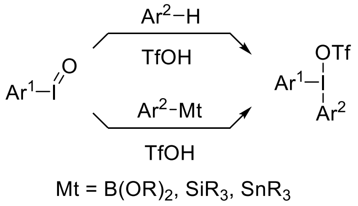
One comment is in order at this juncture. The estimated positive charge on the I atom of 4-halo-iodobenzenes is virtually identical and close to 0.090 *e* (Table 5). The same is true of 1,4-diiodobenzene (0.091 *e*, MNDO/d), which would then be expected to undergo metathesis just like its congeners. This, however is not the case: all attempts in that sense resulted in no reaction by MS and NMR for reasons that still escape us.

On a final note, steric effects have been harnessed to control aryl transfer selectivity from diaryliodonium salts to common nucleophiles. Relief of steric congestion around the hypervalent iodine atom favors displacement of a more sterically encumbered aryl group by a less hindered one. We thus wondered whether such effects could promote iodonium metathesis of unreactive iodides. The question was addressed by attempting metathesis of mesityl(phenyl)iodonium triflate[49] with 4-$NO_2$-, 4-$CF_3$-, 4-COOMe-, and 4-halo-iodobenzenes. The first three iodides failed completely to react (MS, NMR), either under thermal (110 °C, 24 h) or microwave (6h, 100 °C) conditions. The more reactive 4-halobenzenes (except 1,4-diiodobenzene, *vide supra*) did react with preferential (but not exclusive) phenyl transfer, but considerably more slowly than they did with $Ph_2IOTf$. Microwave irradiation had no significant effect on the outcome of these reactions. Evidently, the small I-positive charge on iodomesitylene ($e_I$ = + 0.060, MNDO/d) renders it the poorest nucleofuge among the iodides of Table 1. Additionally, a free (mesityl)phenyl iodonium ion would be expected to exhibit an I-(+) charge slightly smaller than that of diphenyiodonium ion, retarding nucleophilic capture by an unreactive, more I-positive aryl halide leading to complexes **31**-**32**. The sterically encumbered mesityl group is likely to further hamper the process. All this leads to an unacceptably slow reaction rate.

## 5. Further Developments

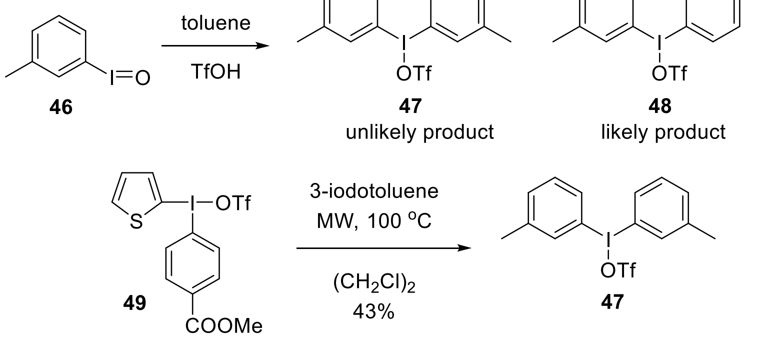
The present review focuses on the discovery of the iodonium metathesis reaction and on investigations aiming to elucidate mechanistic aspects thereof. Significant applications of the new process will probably require additional developmental work. That said, an illustration of the practical dimension of the chemistry is provided below.

Diaryliodonium salts may be conveniently prepared by electrophilic aromatic substitution (EAS), through protonation of an iodosoaryl compound in the presence of a reactive arene (Scheme 8).[50] The directing effect of substituents present on the latter determines the regiochemical outcome of the reaction. If EAS should lead to an undesired regiochemical result, the correct product can still be obtained by employing an organometallic derivative of the arene; for example, a boronic acid, a trialkylsilane, or a trialkylstannane.



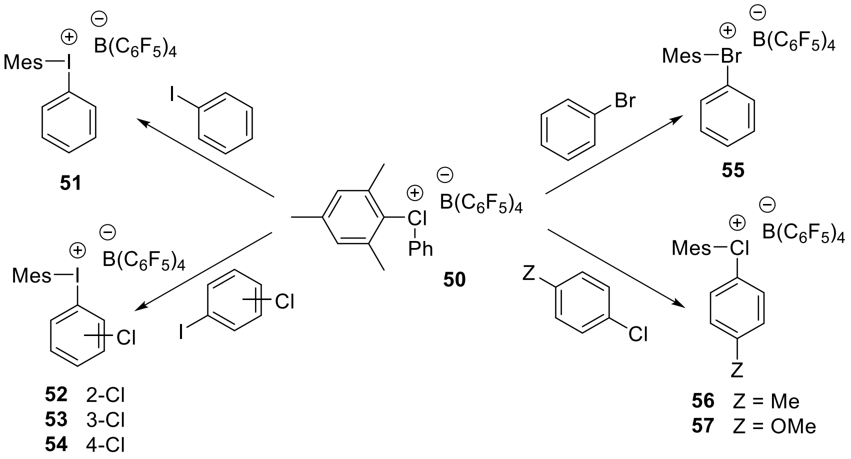
**Scheme 8**

The preparation of, e.g., di(3-tolyl)iodonium triflate, **47**, from 3-iodosotoluene, **46**, would be possible only through the organometallic method, because the *ortho-para* directing effect of the methyl group is likely to result in formation of unwanted **48**. Iodonium metathesis provides a more economical and direct alternative: microwave irradiation of a solution of (4-carbomethoxyphenyl)thienyl-iodonium triflate, **49**, and 3-iodotoluene produces the desired iodane in 43% yield after chromatography (Scheme 9).



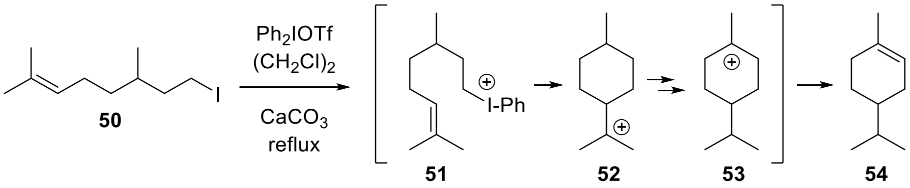
**Scheme 9**

The most recent development in the field expands the scope of the reaction considerably. In 2019, Uchiyama and collaborators described a remarkable route to diarylchloronium tetra(pentafluorophenyl)borate salts such as **50** (Scheme 10).[51] These exceptionally reactive chloranes undergo several noteworthy transformations. In particular, they participate in halonium metathesis not only with aryl iodides, but also with aryl bromides and chlorides, leading respectively, to diarylidonium (cf. **51**-**54**), bromonium (cf. **55**), and chloronium (cf. **56**-**57**) species. This is in sharp contrast to the corresponding iodanes, which are inert toward aryl bromides and chlorides. Interestingly, selective transfer of the mesityl group is observed. Assuming that the mechanistic framework developed for iodonium metathesis is transposable to halonium metathesis in general, the observed group transfer selectivity would be in accord with the principle that the aryl halide with the highest positive charge on the halogen atom is the one that departs preferentially from complexes of the type **31**-**32**.



**Scheme 10**

All the metathesis reactions described so far occur with aryl iodides. Alkyl iodides should undergo I-arylation even more readily, given that the calculated charge on their I atom is negative. For example, MNDO/d suggests that the I atom of 1-iodopropane sustains a charge of –0.058 *e*. On the other hand, it may be anticipated that an (aryl)alkyliodonium salt will not survive the conditions of its formation, given the large positive charge on its (formally) $sp^3$ carbon. This led to the surmise that iodonium metathesis could be harnessed to induce biomimetic cyclization reactions. At this time, only one preliminary result has been recorded: when citronellyl iodide, **50**, is heated with $Ph_2IOTf$ in 1,2-dichloroethane in the presence of powdered $CaCO_3$, it is converted into dihydrolimonene **54** in about 50% yield, arguably by the mechanism outlined in Scheme 10. No reaction occurs in the absence $Ph_2IOTf$.[52]



**Scheme 10**

## Conclusions

The fact that iodonium metathesis occurs at all constitutes a novel aspect of iodane chemistry. The hypothesis that such reactions are electronically driven seems by now firmly established: aryl transfer occurs so that a more I-nucleophilic, less I-positive aryl iodide displaces a less I-nucleophilic, more I-positive one. An aryl iodide that fails to react with a given diaryliodonium triflate may still undergo metathesis with an iodane that incorporates a particularly I-positive aryl iodide. The chemistry of Uchiyama chloranes greatly expands the scope of halonium metathesis. While the chemistry requires additional technical refinements, interesting ramification of the process can be envisioned.

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