Graphical Abstract

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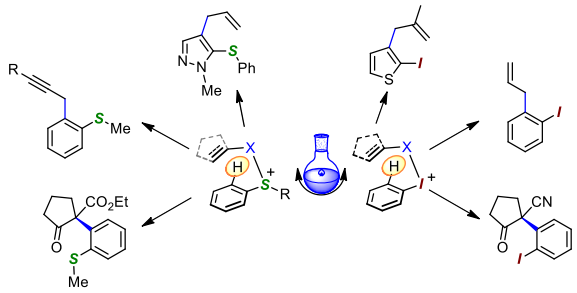
Alexandr Shafir



The emergence of sulfoxide and iodonio- based redox arylation as a synthetic tool

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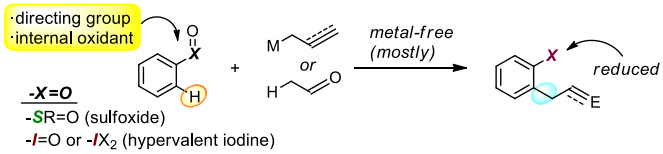
ABSTRACT

This digest highlights the emergence of the directed metal-free arylation approach employing simple sulfoxide and hypervalent aryliodane. These new processes are characterized by an unusual, and synthetically attractive, retention of the reduced -SR and iodine fragment ortho to the newly formed C-C bond. Although the development of the sulfur- and iodane-based methods have occurred independently, it is becoming increasingly obvious that the two processes are highly analogous in terms of the mechanism and the substrate scope. Indeed, both types of reaction are proposed to occur via a [3,3]-sigmatropic Claisen-type rearrangement, and have been carried out on closely related families of substrates. The digest covers the progress made in 2011-2015 both in the sulfoxide-based methods and in the iodane-based reaction. The ultimate goal is to a) highlight the synthetic potential of the approach; b) offer, for the first time, a unified vision of the two processes.

Given that a large percentage of molecules studied to date contain at least one aromatic ring, the introduction and derivatization of aryl building blocks constitutes a major synthetic endeavor. Arylation *via* metal-catalyzed cross-coupling has been one of the most widely used, and relies, in its canonical form, on an *ipso* substitution in ArX (X = halide or equivalent) or Ar-M species (M =electropositive element). More recently, the focus has widened to include metal-catalyzed transformations of aromatic C-H bonds, including the dehydrogenative C-C bond formation.[1] Nevertheless, oxidative conversion of C-H bonds to C-C bond has also been accomplished under metal-free conditions, with a fair number of such methods relying on the use of hypervalent (λ^3) iodine reagents.[2,3]

While a dehydrogenative coupling of two C-H would produce an equivalent of H_2, such reactions are almost universally accomplished with an oxidant to be driven largely by the release of water (or other forms of H^+). A new class of C-H functionalization has emerged in recent years in which a formal dehydrohenative C-C bond formation takes place *ortho* to a hypervalent sulphur or iodine substituents (Scheme 1). These processes are considered redox-neutral, which simply means that the substrate already "packs" an oxidant equivalent in the form of the hypervalent fragment. Mechanistically, this fragment constitutes a directing group, and the new bond is thought to form through a [3,3]-sigmatropic rearrangement. In the last 5 years this unique approach has proven to be a powerful synthetic tool, not the least due to the versatility afforded by the retention of a thio or iodo substutuents *ortho* to the new C-C bond.



Scheme 1. Redox arylation employing a hypervalent sulfur or iodine-based *ortho* directing group.

Although analogous redox arylation processes include other "directing" groups (*e. g.* aryl nitrones[4]), this digest is focused on the chemistries of iodine and sulfur, as these have had a most prolific growth, have led to highly synthetically versatile products and are mechanistically similar. Indeed, the exclusive *ortho* selectivity in both cases has been attributed to a to Claisen-type rearrangement mechanism, and have been carried out on closely related families of substrates. After a brief introduction, the digest covers the progress made in 2011-2016 both in the sulfoxide-based methods (largely by the groups of Maulide and Procter) and in the iodane-based reaction (Zhu *et al*, our own work). The ultimate goals are to a) highlight the synthetic potential of the approach; b) offer a unified vision of the two processes.

Some of the early reports on the functionalization of the *ortho*-position in (hetero)aromatic sulfoxides came from the laboratories of Kita[5] and Padwa[6] in a wider context of interrupted Pummerer processes. Thus, in 2004 Kita *et al.* reported that a reaction between the thienyl or furyl 2-sulfoxide with acetylacetone under Pummerer conditions (2 equiv of trifluoroacetic anhydride, TFAA, in CH_3CN) led to the formation of a C-C bond between the intercarbonylic carbon of the β-

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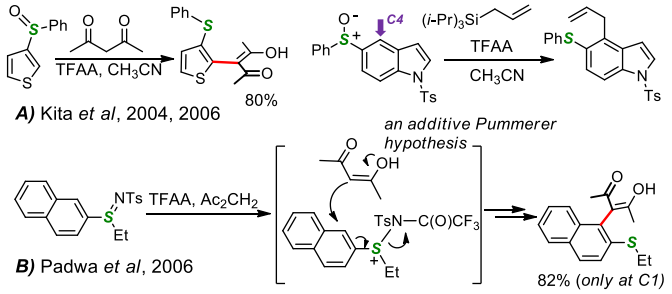
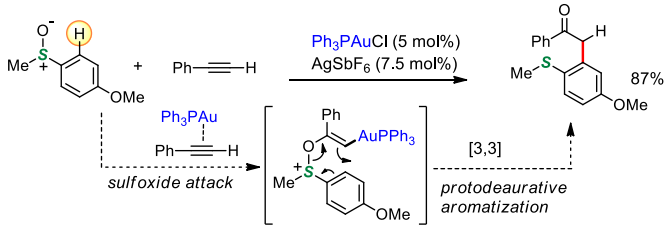
diketone and carbon *ortho* to sulfur (Scheme 2A).[5] The process was accompanied by a reduction of the sulfoxide to sulfide, and so constitutes a formal redox α-arylation of a β-diketone.[5a] The exclusive *ortho* activation was maintained even when the 5-sulfinyl indole was used as substrate, ushering a C-C bond formation exclusively at the indole C4 position, *i.e.* away from the heterocyclic ring.[5b] In the same report *ortho* allylation was also shown to be possible by switching to an allyl silane (or allyl tin) reagent. Around this time an analogous chemistry was reported by Padwa *et al.* using sulfilimines, including one of the first examples of a non-heterocyclic sulfoxide substrate (Scheme 2B).[6] At the time, the *ortho* selectivity was rationalized through an *additive Pummerer* mechanism in which the nucleophile adds to the anhydride-activated sulfoxide or sulfilimines. Though reasonable, in hindsight the mechanism fell short in explaining the lack of regioisomers expected (at least as minor components) in such S_NAr-type reaction.



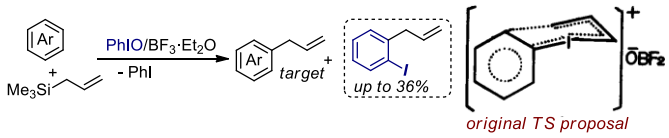
Scheme 2. The *ortho* functionalization of (hetero)aryl sulfoxides by the groups of Kita and Padwa.

Incidentally, an alternative [3,3] thio-Claisen rearrangement mechanism (currently favored for this class of reactions) had already been proposed in 1970 by Bycroft and Landon[7] in the synthesis of allylated indoles from cationic sulfonium species;[7a] this mechanism was later invoked by Yorimitsu and coworkers in the allylation of vinyl sulfoxides.[7b] Interestingly, convincing evidence for a favorable thio-Claisen manifold came from the field of gold catalysis. Thus, while investigating an intermolecular Au(I)-catalyzed addition of aryl sulfoxides to alkynes (the intramolecular version had previously been reported independently by the groups of Toste and Zhang[8]), Cuenca Ujaque, Asensio *et al.* described an oxyarylative coupling taking place through C-C bond formation, once again exclusively *ortho* to the sulfur atom (Scheme 3).[9] In contrast to the previous mechanistic proposal involving the formation of an electrophilic gold carbene,[8] DFT calculations in this case revealed an alternative low-barrier (4-5 kcal/mol) [3,3]-sigmatropic rearrangement of a sulfonium enolate, in turn generated through the sulfoxide attack upon the Au(I)-activated alkyne; in fact a 2013 revision of the earlier *intramolecular* reaction by Zhang and coworkers also indicated a [3,3]-sigmatropic rearrangement mechanism.[9b]



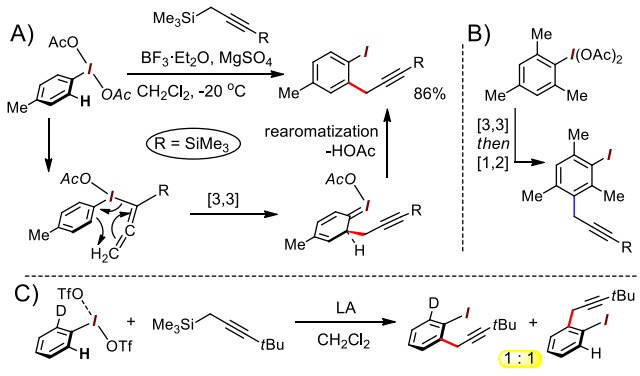
Scheme 3. An example of a Au(I)-catalyzed oxyarylation of alkynes and a [3,3] mechanism established by DFT calculations.

In the meantime, a seemingly parallel chemistry was being uncovered by groups working with hypervalent λ^3 iodane reagents.[10] In a 1988 study, Oh and coworkers reported isolating *o*-allyl iodobenzene as a side products (up to 36%) during attempted electrophilic allylation of anisole by a combination allyltrimethylsilane/PhIO·BF_3.[10a] This observation was rationalized by a "stable six-membered transition state" in a chair-like conformation (original TS drawing in Scheme 4).



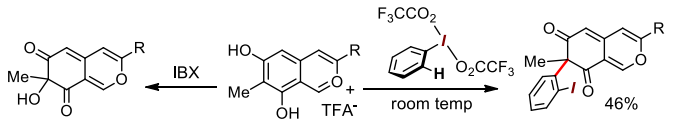
Scheme 4. Evidence for *ortho*-allylation in λ^3 iodanes. The drawing of the transition state by Oh *et al.*, is reprinted from ref. 10a with permission from Elsevier.

Shortly after, Ochiai *et al.* reported that treating $ArI(OAc)_2$ with propargyl silanes (as well as germanes, or stannanes) in the presence of BF_3·Et_2O led to the formation of the corresponding *ortho*-propargyliodoarenes, in what the author refer to as reductive propargylation (Scheme 5).[10b] In line with the earlier proposal, the key hypervalent iodonio allenyl intermediate, obtained *via* the silicon-to-iodine transmetallation, was postulated to undergo a [3,3] shift. Evidence for an intramolecular nature of the process was obtained through a series of cross-over experiments between a hypervalent reagent and a differentiated non-hypervalent ArI, confirming exclusive reactivity of the former. The intermediacy of the allenyl-(aryl)iodinanes was also invoked to explain the reactivity of the aryliodanes blocked at both *ortho* positions. In this case the [3,3] rearrangement product is unable to rearomatize, and instead undergoes a [1,2] shift leading to *meta* propargylation (Scheme 5B).[10d] Despite using the term "iodonio-Claisen", important differences with the classical aromatic Claisen rearrangement process were already observed, including the much lower activation barriers and the formation of the *meta* products for the di-*ortho*-substituted substrates even with an available *para* position. Shortly after, Norton *et al.* proposed the initial formation of the allenyl intermediate to be the overall rate-limiting step for the process, and established the lack of an intramolecular kinetic isotope effect (k_H/k_D 0.99±0.01) for the [3,3]-sigmatropic rearrangement (Scheme 5C), taken as an indication that, of the two last steps, the rearomatization is fast in comparison with the [3,3] sigmatropic rearrangement.[11]



Scheme 5. The *ortho*-propargylation of hypervalent iodine reagents using propargyl silanes.

In a different context, Reddy, and later the groups of Porco and Pettus observed that the dearomatizative treatment of certain phenolic substrate with hypervalent iodine may lead to quinone side products incorporating a 2-iodophenyl group.[12] These observations were rationalized by a [3,3]-sigmatropic rearrangement of a putative aryliodonium phenolate (Scheme 6).



Scheme 6. Examples of a successful (left) and "unsuccessful" (right) hydroxylative dearomatization by Porco *et al.*

When put together, the chemistry presented in this introduction illustrates that the two aromatic hypervalent fragments discussed here, ArS(O)R and $ArIX_2$ can promote a formal dehydrogenative C-C bond formation, and that this coupling will take place exclusively *ortho* to the S or I substituent, except for substrates with substituent at both *ortho* sites (as seen in Scheme 5B). In both cases, experimental evidence supports a Claisen-type [3,3] rearrangement to explain the exclusive *ortho* selectivity (even in the presence of sites more activated towards an S_EAr reaction). Furthermore, in both cases the driving force is provided by the concomitant reduction of the hypervalent director to Ar-SR or Ar-I. This latter feature is relevant to the lowering of the [3,3]-sigmatropic activation barrier well below those for a classical aromatic Claisen rearrangement.

The recent developments in this field have come in the context of an ever increasing interest in the direct functionalization of the aromatic C-H bond, with important discoveries made particularly in the metal-catalyzed CH activation of substrates bearing *ortho*-directing donor groups. In that respect, while the sulfoxide and iodonio-based reactivity also represents a direct oxidative *ortho* functionalization, it *does not* require a metal catalyst (an attractive feature in late stage process development), nor an extra oxidant, given that it is already a part of the directing group.

Most interestingly, the coupling produces species with synthetically valuable thio or iodo substituent preserved *ortho* to the new C-C bond, and the more recent work in this field (2011-present) has dealt with efforts to exploit this *ortho*-functionalization manifold. Interestingly, the two classes of nucleophiles identified earlier, allyl/propargyl metallates and *C*-enolates have remained the coupling partners of choice for both classes of the hypervalent partners (Figure 1).

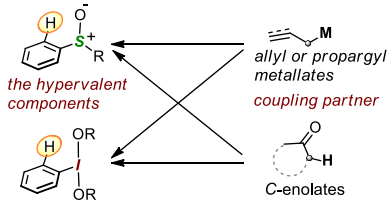
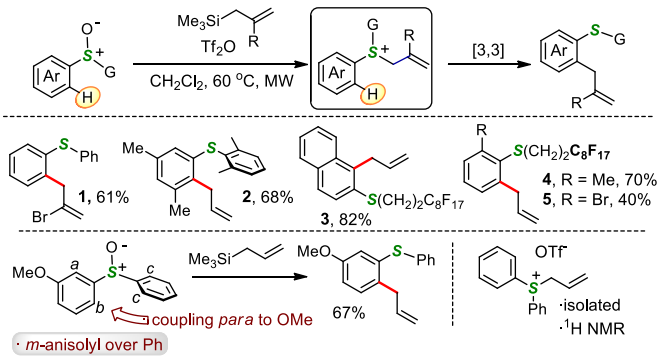


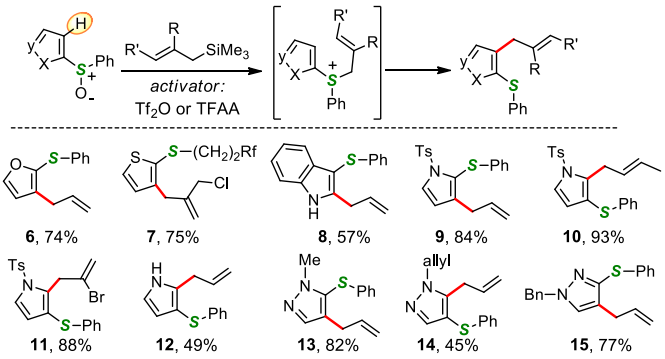
Figure 1. A swath of possibilities in S- or I-based redox arylation.

Hence, focusing on the use of allyl silanes in the context of an interrupted Pummerer processes, the Procter group reported in 2011 a general study on the redox-neutral *ortho*-allylation of aryl sulfoxides.[13] As a result, a series of *o*-allyl aryl sulfides were obtained by treating the sulfoxides with allyl silane in the presence of Tf_2O in CH_2Cl_2 under microwave heating at 60 °C (Scheme 7). As in the earlier works, the process is likely to take place with a double allyl inversion, such that the new C-C bond is formed to the previously silylated allylic position. A variety of aromatic aryl sulfoxides were successfully engaged, including a selective allylation of 2-sulfinyl naphthalenes at the α-naphthyl position.[13a] The method's versatility was further illustrated by the coupling of halogen-substituted allyl fragments, and by the use of aryl sulfoxide bearing fluorinated chains (Scheme 7, products **1**-**3**). The process, however, was less efficient for substrates with electron-poor aryl groups, as seen in a yield from from 70% to just 40% upon replacing an *o*-Me with an *o*-Br group (compare **4** and **5**). Informative from a mechanistic point of view was the coupling of the (*m*-anisolyl)phenylsulfoxide, in which the coupling took place selectively at the anisole ring at the C-H position *para* to the methoxy group. This indicates that while the *ortho* selectivity may be governed by a 6-membered transition state, the process appears to require stabilization of the positive charge in the transition state, a feature shared with electrophilic aromatic substitution reaction (S_EAr).



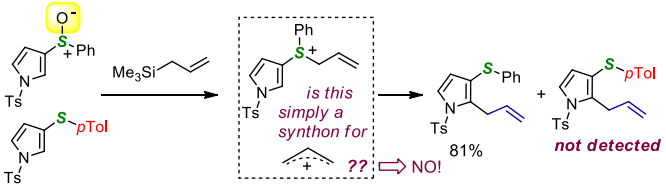
Scheme 7. The *ortho*-allylation of aryl sulfoxides with allyl silanes.

In this and a later (2013) report the method was applied to the coupling of 5-membered (π-excessive) heterocycles. After the initial advances in the allylation of thiophene, furan and indole moieties (Scheme 8, prod. **6**-**8**),[13a] the scope was expanded to *N*-protected pyrroles and pyrazoles (Scheme 8, prod. **9**-**15**).[13b] The coupling of these substrates appeared to be more facile than that of the non-heterocyclic aryl sulfoxide (as in Scheme 7), proceeding in generally at low temperature and with the best overall yields (up to 93%) achieved for the more π-excessive pyrrolyl 2- and 3-sulfoxides (coupling at C2, *e.g.* **10**). Interestingly, the allylation of the unprotected 3-phenylsulfinyl pyrroles was also possible (at C2, **12**) albeit in a moderate 49% yield.



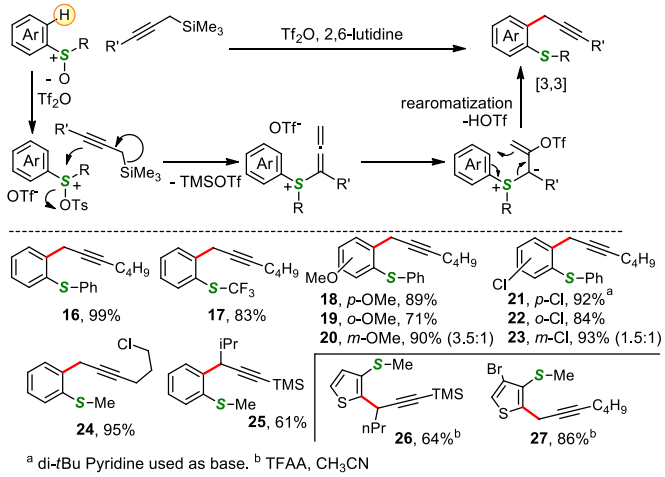
Scheme 8. The *ortho*-allylation of heteroaryl π-excessive sulfoxides.

Once again, the author addressed the lingering possibility of the intermediate allyl sulfonium cation simply acting as an electrophilic allyl cation synthon This, however, was ruled out as no cross-over Friedel-Crafts product were detected when the 3-(p-tolylthio)-1-tosyl-pyrrole was added to a reaction with the corresponding S-Ph sulfoxide (Scheme 9).



Scheme 9. Evidence for an intramolecular allyl transfer.

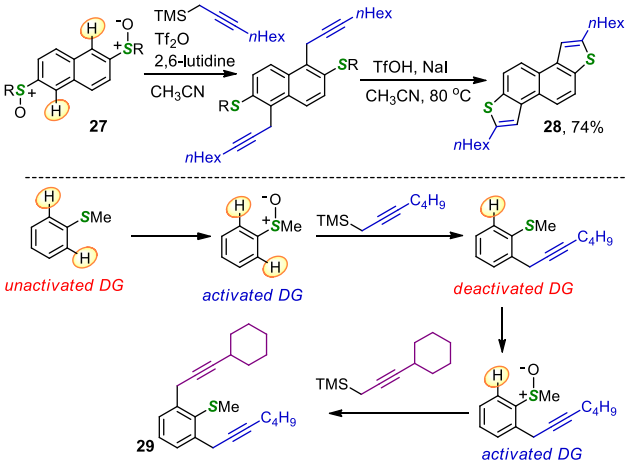
Having mastered the allylation, the same group went on to report on the closely related propargylation (Scheme 10).[14] In an early optimization study, a reaction between diphenylsulfoxide and propargyl trimethylsilanes was explored in CH_3CN in the presence of Tf_2O for sulfoxide activation. While a 73% yield was reached under these conditions, the addition of a hindered pyridine base, such as 2,6-lutidine, afforded the product in a 99% yield (Scheme 10, product **16**). As with the allylation, a range of substitution patterns on both coupling partners was tolerated (Scheme 10, **17**-**24**), even allowing for the formation of the rather hindered secondary benzylic sites (as in **25**). In the case of thiophene- and furane-containing sulfoxide, the protocol was rather similar to that of allylation and relied on TFAA as an electrophilic activation agent (Scheme 10, prod. **26**-**27**).[14b]



Scheme 10. *Ortho* propargylation of aromatic sulfoxides.

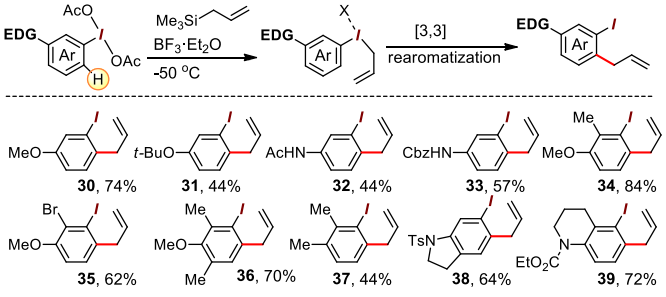
The Claisen-type rearrangement in this case takes place through a cationic allenyl sulfonium species, which could be observed by NMR and even isolated. The sequence would consist, therefore, of a fast formation of the allenyl sulfonium cation followed by its slower rearrangement to form the new C-C bond.

The *ortho*-propargyl sulfide pattern thus obtained proved to be synthetically versatile. Through a series of dealkylative cyclization protocols, the authors could access a wide range of benzothiophenes, and the transformation was applied to the synthesis of an array of organic materials potentially relevant in material design and solar panel applications (Scheme 11, A).[15] For example, through double propargylation of naphthalene bis-sulfoxide **27**, followed by cyclization, a new aromatic material **28** was obtained featuring an extended aromatic bis-benzothiophene unit. Another interesting feature of the sulfoxide *ortho*-functionalization is its *single-shot* nature: the sulfoxide gets reduced in the process, and will not promote a second *ortho* coupling unless reoxidized. This feature could be exploited to sequentially introduce two different propargyl fragments, as shown in Scheme 11, B for the synthesis of **29**.[14b]



Scheme 11. Synthetic potential offered by sulfoxide as a hypervalent *ortho*-directing group in multi-step transformations.

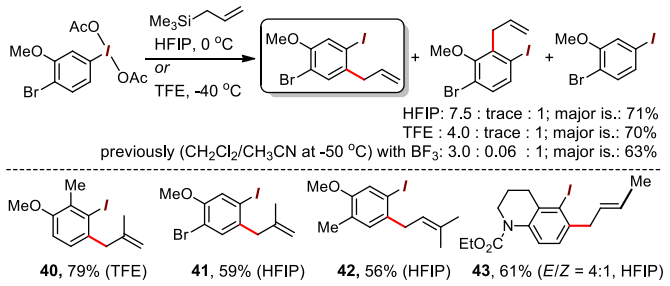
If the parallelism between the reactivities of the hypervalent sulfur and iodine species holds, it may be expected that a good deal of the allylation and propargylation chemistry should be valid for λ^3 iodanes; of course, some of this has already been established in earlier works.[10] This was further developed in a series of publication by Zhu and coworkers,[16, 17] who in 2012 showed that $ArI(OAc)_2$ undergoes *ortho*-allylation with allyl silanes, provided that an electron-donating substituent (methoxy, amino) is present *para* to the potential coupling site (and hence *meta* to iodine, Scheme 12),[16a] with the requisite $ArI(OAc)_2$ substrates synthesized mainly by the mild oxidation of the ArI with sodium perborate in acetic acid. The presence of this *meta*-releasing substituent was crucial: while the *meta*-methoxy phenyl iodine diacetate could be allylated in an 86% combined yield (Scheme 12, prod. **30**), only small amounts of product was achieved for the parent $PhI(OAc)_2$. This limitation may, at first, appear unexpected, since the first examples of this iodonio-Claisen process involved the allylation of the parent iodosobenzene in 36% yield (see Scheme 4). Due PIDA's relatively high oxidation power, it is likely that competing oxidative processes becoming rampant in substrates with a higher barrier for the desired [3,3] rearrangement. As in the case of aryl sulfoxide, an acidic activating agent (here $BF_3{\cdot}Et_2O$) was crucial. The allylation proceeded smoothly at -50 °C, indicating a very low activation barrier for the [3,3] rearrangement. As seen in Scheme 12 (prod. **31**-**39**), the allylation was applied to a range iodoarene diacetates, with the activating alkoxy (or an amido) assisting in enhancing the regioselectivity of the transformation.



Scheme 12. An *ortho*-allylation of aryliodine diacetates, $ArI(OAc)_2$.

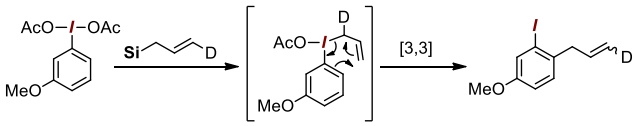
The process, however, still left room for improvement, both in terms of the regioselectivity (between the *ortho* CH sites) and in view of the unproductive reduction of $ArI(OAc)_2$. Some inroads were made by conducting the reaction in fluorinated alcohols,[17] with several of the earlier examples improved using trifluoroethanol (TFE) at -40 °C or in hexafluoroisopropanol

(HFIP) at 0 °C (Scheme 13). The use of fluoroalcohols also facilitated the introduction of substituted allyl components, with some examples shown Scheme 13 (prod. **40**-**43**).



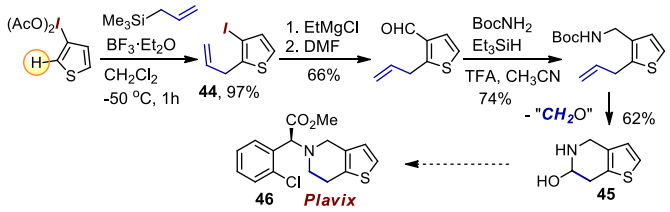
Scheme 13. An *ortho*-allylation of aryliodine diacetates, $ArI(OAc)_2$ in fluorinated alcohol medium.

The mechanism of the reaction was probed using the allylsilane deuterated *trans* to the CH_2Si group. The deuterium label in the resulting *ortho*-allyl product was scrambled between two terminal olefinic position, which is fully consistent with a double allylic inversion achieved through an allyliodane intermediate and a [3,3] iodonio-Claisen rearrangement (Scheme 14).[16a]



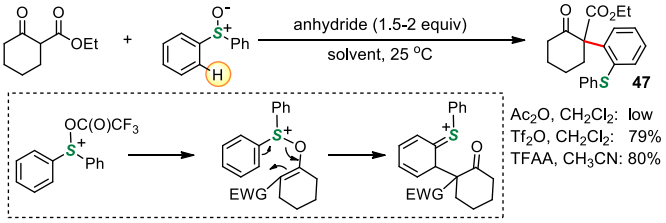
Scheme 14. A double allylic inversion in the redox arylative C-C coupling.

Given the evident mechanistic similarities between the allylation of the hypervalent sulfur and iodine reagents, the usage of the π-excessive heteroaryl iodides (*i.e.* azoles, thiophenes) in this iodonio-Claisen transformation should not only be possible, but even favoured in comparison with iodobenzenes. This held true for the 2- and 3-iodothiophene diacetates, which coupled with allyltrimerthylsilane in just 1h in 93% and 97% yield, respectively, with the latter exclusively at the C2 position (see prod. **44** in Scheme 15).[16b] Unfortunately, attempts to extend the methodology to the related pyrazole derivatives failed, affording the parent iodopyrazole along with its *ipso* allylation products. It remains to be seen, therefore, whether heterocycles other than thiophene are feasible in this allylation procedure. Nevertheless, even for the examples at hand, the mutual *ortho* disposition of the reactive allyl and iodine substituents provided an ample playground for the synthesis of a variety of heterocycles, as illustrated in Scheme 15 by the concise formal synthesis of Plavix® (clopidogrel, **46**),[16b] a thienopyridine-class antiplatelet agent used to reduce the risk of heart attack.



Scheme 15. Heterocycle *ortho* allylation in the synthesis of Plavix.

Enolizable ketones constitute another class of potential coupling partners with sulfoxides and λ³ iodanes.[5,6] Some of the more recent work involved the use of alkynes as enol equivalents through Au(I) catalysis.[8,9] However, in 2011 Maulide *et al.* reported a *bona fide* metal-free redox α-arylation of activated ketones using aryl sulfoxide in the presence of a stoichiometric acid anhydride additive.[18] By the logic of a Pummerer-type process, the anhydride likely activates the sulfoxide, assisting in in the formation of a sulfonium enolate; the latter is then proposed to undergo a [3,3]-sigmatropic rearrangement. The concept is shown in Scheme 16 with a reaction between a cyclic β-ketoester and diphenyl sulfoxide to give the α-aryl cyclohexanone **47** in 80%.



Scheme 16. An example of α-arylation of a β-ketoester with diphenylsulfoxide.

The method was found to be applicable to several cyclic 5- and 6-membered β-ketoesters and β-diketones, with a selection of examples seen in Figure 2 (prod. **48**-**56**).[18a] In the case of a substrate bearing a *t*Bu group at the C4 position, the reaction was 9:1 diastereoselective in favor of the *trans* Ar-*t*Bu disposition (prod. **52**). Finally, for the open-chain 2-Me malonate, the reaction, albeit sluggish, nevertheless furnished a 41% yield of the target α-aryl species **57** after 2 days.

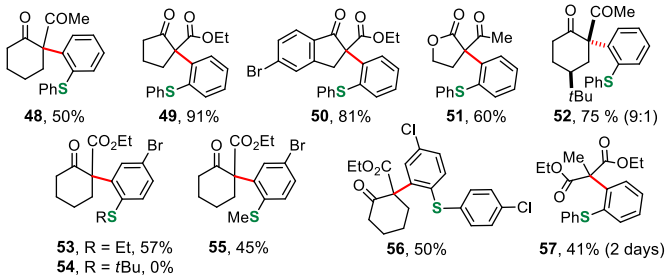
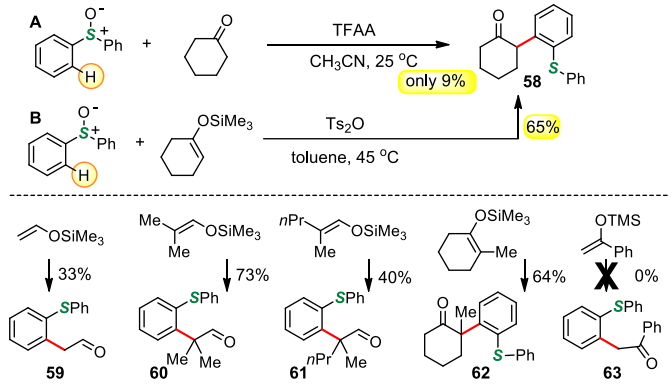


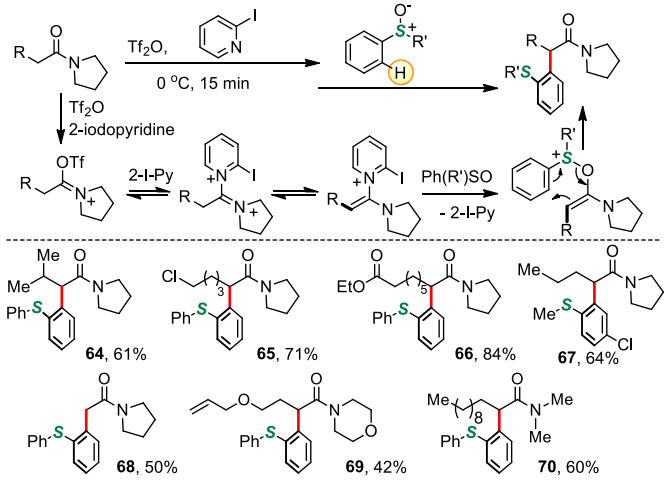
Figure 2. Examples of metal-free α-arylation of β-dicarbonyl substrates with aryl sulfoxides.

In a follow-up study, the process was further extended both in terms of scope and its mechanistic understanding; for ketones with an α-CH_2 group, a competing formation of sulfur ylides is also discussed.[18b] As part of this work, the usage of silyl enol ethers as coupling partners was investigated. As one of the more striking findings, while the previous protocol largely failed for non-activated ketones, such as cyclohexanone, the corresponding silyl enol ether was now arylated in a 65% yield (Scheme 17, **58**). This was further exploited to achieve formal α-arylation of aldehydes (**59**-**61**) and the regioselective α-arylation of 2-Me cyclohexanone at the sterically more hindered site (**62**); unfortunately, the method failed for the acetophenone-derived enol. These results might show the way for further selectivity control. For example, whether the arylation of the 2-Me cyclohexanone can also be achieved (through the appropriate enol ether) at the less hindered (*i.e.* CH_2) site?



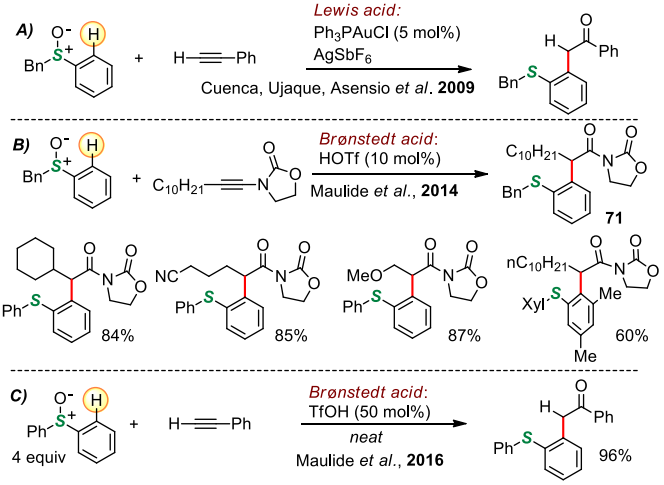
Scheme 17. The use of silyl enol ether in redox arylation with aryl sulfoxides.

Finally, in 2014 the methodology was applied to the α-arylation of amides using a combination of Tf_2O in conjunction with 2-iodopyridine.[19] The choice of the latter was conditioned by the need of a species basic/nucleophilic enough to activate the amide, while at the same time constituting a good leaving group in the presence of a sulfoxide. Operationally, the protocol consists in exposing the amide to a mixture of 2-I-Py with Tf_2O for 15 min, and then adding the aryl sulfoxide. Mechanistically, the coupling would, once again, involve a [3,3] rearrangement, this time of an sulfonium *O*-amidate rather than *O*-enolate.[19a] This species would arise from a series of equilibria leading to an electrophilic iodopyridinium enamine species, which is then attacked by the sulfoxide displacing 2-iodopyridine (Scheme 18). The method was tolerant towards certain potentially sensitive functional groups, such as those containing a chloroalkane and an ester moieties (**65**, **66**) problematic under the basic conditions associated with metal-catalyzed α-arylation of amides. The scope also included a simple acetamide (**68**) and amides derived from amines other than pyrrolidine (**69**, **70**).



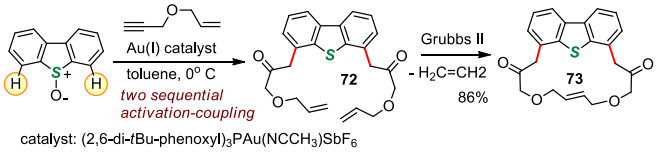
Scheme 18. Redox α-arylation of amides by Maulide *et al.*

The group also disclosed an operationally simpler version of this coupling employing ynamides as dehydrated amide synthon.[19b] The α-aryl amides were thus obtained by exposing a mixture of an ynamide and an aryl sulfoxide to catalytic amounts (10 mol%) of TfOH (Scheme 19, B, **71**). Though mechanistically distinct, this reaction is reminiscent of the Au(I)-catalyzed coupling of aryl sulfoxides with simple alkynes[9a] (Scheme 19, A, also Scheme 3), and in a way constitutes a gold-free variant of that earlier protocol. In fact, while this Digest was under review, Maulide *et al.* reported that simple alkynes can indeed be engaged (Scheme 19, C) in the coupling with aryl sulfoxides in the presence of triflic acid (50 mol%).[20] Due to a strong dependence on the concentration, the coupling was carried out in neat aryl sulfoxide (4 equiv) affording up to quantitative yields of the target α-aryl ketones.



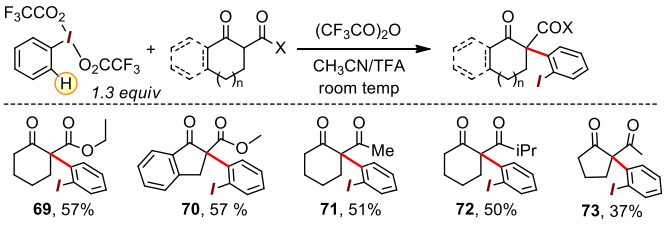
Scheme 19. Synthesis of α-aryl amides employing ynamide substrates, and a comparison with a Au(I)-catalyzed coupling.

At the same time, Barrett, Davies and Grainger applied a modified Au(I) catalyst in the C-H functionalization of dibenzothiophenes.[21] Pointing to the challenge of favoring "the key aromaticity-disrupting [3,3]-sigmatropic rearrangement" over a number of competing processes, the authors developed a hindered $(ArO)_3P$-Au(I) catalyst (2-5 mol%) competent in delivering up to 91% yields in the coupling of dibenzothiophene-*S*-oxides with alkynes. This method was applied to the preparation of a benzothiophene-based macrocycle (**73**, Scheme 20).



Scheme 20. An application of Au-catalyzed double C-H functionalization of benzothiophene.

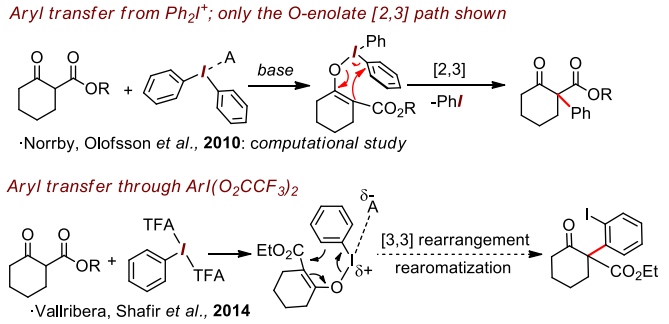
Completing the last corner of the reactivity "square" shown in Figure 1, in a 2014 report Vallribera, Shafir and coworkers described a reaction between phenyliodine bis(trifluoroacetate), PIFA, and a range of activated ketones.[22] Under acidic conditions, such combination gave rise to α-arylketones with iodine retained *ortho* to the new C-C bond. The initial work involved the arylation of cyclic β-diketones and cyclic β-ketoesters, with the coupling products produced in moderate yields (Scheme 21).



Scheme 21. Redox α-arylation of β-dicarbonyls using $ArI(O_2CCF_3)_2$.

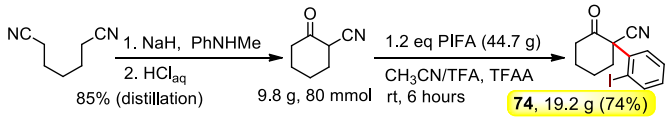
The reaction employed trifluoroacetic acid as co-solvent, and the usage of the TFAA additive is reminiscent of the Tf_2O employed by Maulide *et al.*[18] The absence of regioisomeric side products pointed towards an intermediate iodonium *O*-enolate and a [3,3]-sigmatropic (*i.e.* iodonio-Claisen) rearrangement. This arylation

pattern contrasts with that of diaryliodonium salts, which act as formal electrophilic arylating agents through *ipso* substitution. Interestingly, iodonium *O*-enolate intermediates have been invoked with both classes of hypervalent reagents, and the difference, therefore, appears to reside in the preferred class of rearrangement for each type of intermediate.[23] Thus, for the diaryliodonium species a [1,2] rearrangement dominates leading to an *ipso* substitution, while in the present case a [3,3] rearrangement leads to *ortho* products (Scheme 22).



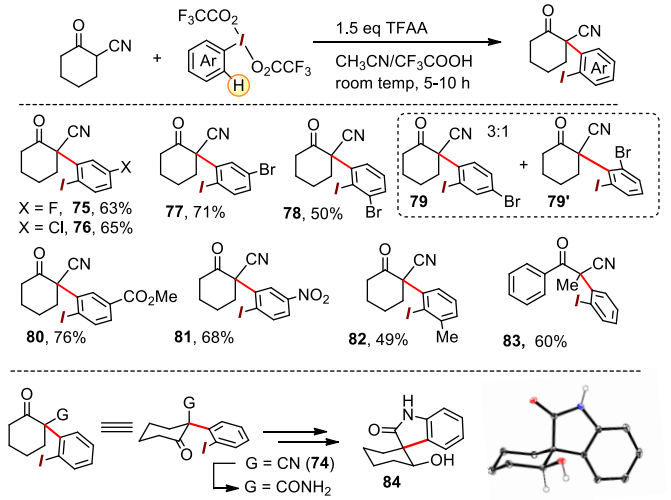
Scheme 22. A difference in α-arylation using Ph_2I^+ *vs* $PhI(O_2CCF_3)_2$.

While the yields were moderate using β-dicarbonyl substrates, the process was found to be rather efficient with cyanoketones. Under the optimized conditions, a reaction between PIFA and 2-cyanocyclohexanone required 6h at room temp, affording the α-cyano-α-(2-iodophenyl) cyclohexanedione **74** in 80%. The reaction was also performed on a multigram scale with comparable yields (Scheme 23). The process was equally efficient for the 5 and 7-membered cyanoketone analogues.



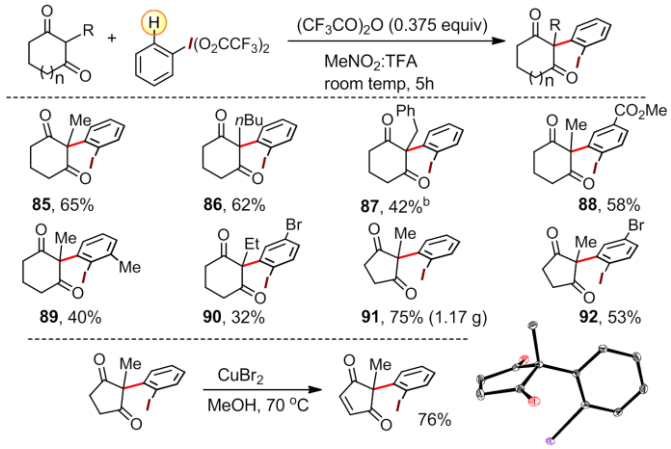
Scheme 23. A multigram synthesis of the 2-(2´-iodophenyl)-2-cyanocyclohexanone *via* redox arylation.

The authors then proceeded to synthesize a series aryliodine bis(trifluoroacetates) *via* an oxone-based oxidation developed by Zhdankin *et al.*[24] These species were then employed as aryl transfer agents in redox arylation of 2-cyanocyclohexanone (Scheme 24, **75**-**83**). Indicative of the synthetic potential such redox arylation was the formation of species **77**-**79** bearing two differentiated halogen on the transferred Ar group. In addition, the presence of an iodoaryl and cyano groups allowed for facile conversion of the new arylketones into heterocycles, including the hydroxyl-spiroxindole **84**.



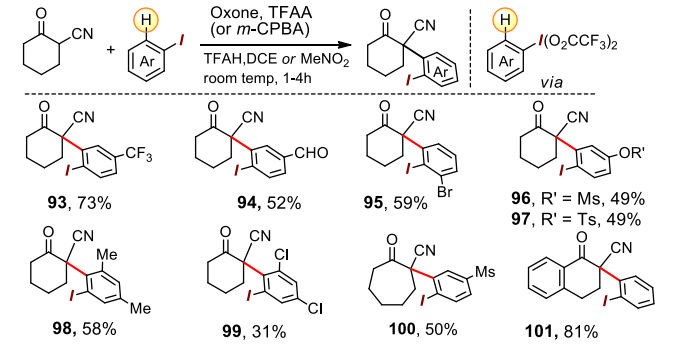
Scheme 24. Redox arylation of 2-cyanoketones using $ArI(O_2CCF_3)_2$.

In a subsequent publication, the protocol was also found to be applicable to 2-methylcyclohexane-1,3-dione and related cyclic diones, constituting an α-arylation manifold complementary to the metal-catalyzed variants (Scheme 25, **85**-**92**).[25] The newly formed products could be further diversified, as in the Cu-catalyzed dehydrogenation of the arylcyclopentane dione **91** (for examples of cross-coupling, see below).



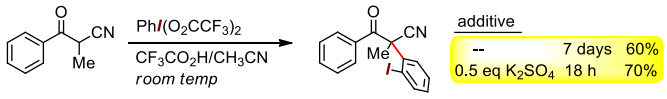
Scheme 25. The redox α-arylation of cyclic β-diketones using $ArI(O_2CCF_3)_2$.

Interestingly, unlike the related *ortho*-allylation (see Scheme 12),[16] the reaction in this case did not require an electron-rich aromatic ring, and proceeded at room temperature with reagents derived from electron-neutral and electron-poor iodoarenes. In fact, it was electron-rich ArI, such as iodoanisole, that proved most challenging due to their incompatibility with oxidizing conditions needed to obtain the corresponding λ^3 iodane. In order to overcome some of these limitations, the authors developed a protocol whereby the iodoarene could be used directly in the presence of Oxone as terminal oxidant.[25] The new protocol thus avoids having to isolate and handle the hypervalent reagent, and represents a metal-free α-arylation complement, in terms of ArI scope and regioselectivity, to the normal catalytic *ipso*-selective arylation. The ArI scope in the arylation of cyanoketones was thus successfully extended, with selected results shown in Scheme 26 (prod. **93**-**101**). Of particular interest are the formation of the sterically hindered quaternary centers observed in species **98** and **99**, and the incorporation of the protected *p*-iodophenols (**96** and **97**).



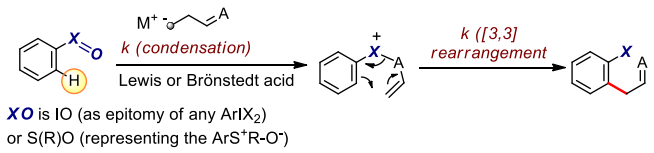
Scheme 26. Direct redox α-arylation of 2-cyanoketones with ArI.

One of the remaining challenging for further applicability of the method is the need for the more reactive λ^3 trifluoroacetic acid derivatives, which limits the types of the ArI fragments that can be employed, since the formation of ArI(O_2CCF_3)$_2$ is largely confined to electron-deficient and electron-neutral Ar moieties. Though this remains a challenge, the authors did address some potential strategies for process enhancement. For example, the coupling between ArI(O_2CCF_3)$_2$ and cyanoketones was greatly accelerated by the addition of simple sulfate salts. Thus, the arylation of the challenging propiophenone 2-nitrile, previously requiring a week at room temperature (Scheme 24, prod. **83**), could now be accomplished in just 18 hours in the presence of 0.5 equiv of K_2SO_4 (Scheme 27).



Scheme 27. Sulfate-promoted acceleration in redox arylation.

In order to provide a unifying view of the processes discussed in this Digest, it is stressed, once again, that there is convincing evidence that all of them proceed *via* a [3,3]-sigmatropic rearrangement. Specifically, two key steps can be identified, the initial acid-promoted condensation at the hypervalent center, and the subsequent rearrangement. For propargylic substrates, the condensation step, which involves the acetylenic carbon, may lead either to a propargyl or an allenyl iodonium intermediate. In fact, a third step should be considered, that of rearomatization, but such process is likely to be rather fast. The rates of the condensation and the rearrangement steps will thus determining the overall rate and the selectivity (Scheme 28). Only in the case of the allylation and propargylation of the sulfoxides does the rearrangement step appear to be rate limiting, or at least slow enough for the intermediate allyl (or allenyl) sulfonium species to be observed.[13] Nevertheless, even in this case the barrier for the subsequent [3,3] rearrangement is significantly lower than what is seen in the "normal" Claisen rearrangement of allylphenols. In most other cases, the condensation step appears to be slow(er), precluding the observation of the condensed intermediates. The acceleration of this step is thus likely the role of the acidic additive employed in virtually all examples, including the usage of the acid anhydrides (Tf_2O or TFAA), $BF_3{\cdot}Et_2O$ and/or the trifluoroacetic acid.[26]



Scheme 28. The two key step in redox arylation

One of the most interesting mechanistic aspects is the exact electronic nature of the putative [3,3] rearrangement. For enol coupling, this step was assessed by the DFT calculation by the groups of Maulide (for sulfoxides) and Shafir (for iodanes).[18b, 25] Specifically, for the rearrangement of the cationic sulfoxy-*O*-enolate **I-A**, a boat-like transition state **ts-A** was identified leading to the Wheland intermediate **II-A**; **ts-A** lies approx. 2 kcal/mol above **I-A** (Figure 3).[18b]. In contrast, the rearrangement of the cationic iodonium *O*-enolate **I-B** to **II-B** was found by Shafir *et al.*to involve a chair-like transition state **ts-B** residing barely 1 kcal/mol above **I-B**.[25,27] With the DFT parameters same as those used for **I-B**, the closely related allyliodonium species ***I-C*** was found to rearrange *via* a chair-like ***ts***-C with a barrier of ~8 kcal/mol, leading to the non-aromatized *ortho*-allyl intermediate ***II-C***.[25] An additional DFT calculation was recently reported for the coupling of alkynes with aryl sulfoxides, as seen in Scheme 19C. Here, the barrier for the [3,3] rearrangement was found to have $\Delta G^{\ddagger}$ =13.7 kcal for the Ph_2SO, a value that was somewhat higher when using Ph(Me)SO.[20] Despite the apparent similarity of these redox arylation processes to a classical Claisen rearrangement, important differences are also evident between these two classes of reactions. Thus, the rearrangement barriers for the processes covered here are relatively low, which translates into rather mild reaction temperatures. These reactions, therefore, fall under the umbrella of the "cationic Claisen rearrangements", a concept that was recently reviewed in this context by Maulide *et al.*[28] The nature of the non-aromatized intermediate arising immediately upon the rearrangement is also interesting. In the case of the classical aromatic Claisen rearrangement, this stage in the process corresponds to a dearomatized ketone (*i.e.* cyclohexadienone) intermediate. By analogy, the Wheland intermediates such as ***II-A*** and ***II-B*** have been frequently drawn with a C=S and C=I double bonds.

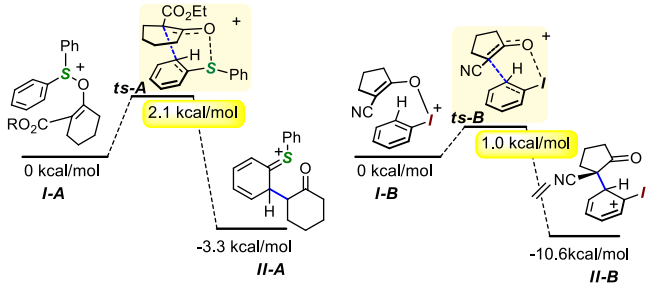


Figure 3. Results from DFT optimization and analysis of the putative [3,3] rearrangement for sulfoxides and λ^3 iodanes .

Nevertheless, these are probably better described as singly bonded: the calculated C-I bond distance in ***II-B*** is 2.06 Å, close to the normal single bond (with the positive charge largely on the carbon atom); a similar situation was computed by Ujaque *et al.* for a sulfoxide-based C-C coupling.[9a] Finally, while the exclusive *ortho*-selectivity is consistent with a [3,3] rearrangement, these transformations do appear to exhibit a pronounced electronic "Friedel-Crafts" component. To account for these observations, we put forward a model that may, at least operationally, reconcile the S_EAr and the Claisen phenomena. For the hypervalent iodonium, this model consists in deconstructing the intermediate *O*-enolate species into iodobenzene and the enol cation. This key intermediate is then reconstituted with the lone pair on the PhI iodine interacting with the LUMO of the enol cation at the oxygen, thus placing an electrophilic (carbocationic) component of the enol in a position to add to the *ortho* PhI site (Figure 4). The model thus depicts an "iodine-guided electrophilc aromatic substitution". Further study will likely place the mechanism in each instance of this transformation somewhere along the continuum between a *bona fide* [3,3] rearrangement and a special case of a "guided" Friedel-Crafts manifold shown in Figure 4.

"Guided" is used here to distinguish this phenomenon from the classical "direction" associated, in the case of the S_EAr processes, with electron-donating or electron-withdrawing substituents.

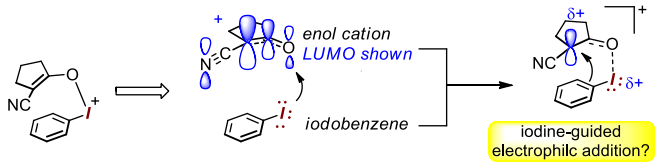
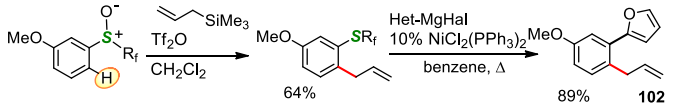


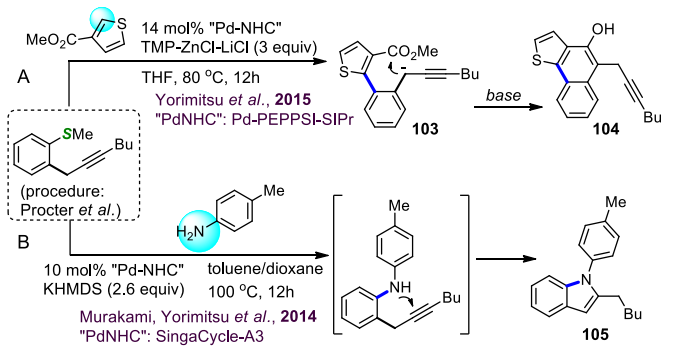
Figure 4. A model proposed here for Iodine-Guided Electrophilc Aromatic Substitution (*IGEAS*).

The product families obtained through the use of the redox arylation discussed in this Digest are highly versatile as building blocks. Some of this has already been highlighted throughout the text, and includes the efficient formal synthesis of Plavix® by Zhu *et al.* (Scheme 15),[16b] or the synthesis benzothiophene-based extended π systems reported by Procter and coworkers (Scheme 11).[15] Nevertheless, perhaps one of the more attractive features of this chemistry is the possibility of metal-catalyzed cross-coupling through C-I or C-S bond cleavage. Although *a priori* the Ar-I precursors would appear more suitable for this purpose, the Ar-S core has also been shown to undergo a variety of bond-forming processes. Thus, early on, Maulide *et al.* showed that the sulfoxide moiety can serve as a removable directing group in α-arylation by applying a subsequent hydrogenative Ar-S bond cleavage.[18a] At the same time, Procter *et al.* applied $NiCl_2(PPh_3)_2$ as an efficient catalyst in the Kumada-Corriu arylation of the aryl sulfide (in a protocol previously reported by Wenkert *et al*[29]), as shown in Scheme 29 for the synthesis of **102**.[13a]



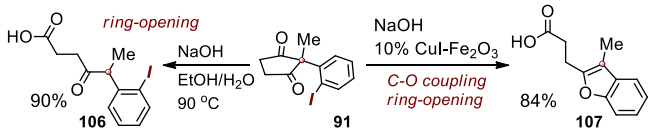
Scheme 29. The application of the Kumada-Corriu coupling to the *ortho*-allyl aryl sulfides.

More recently, Yorimitsu, Murakami and coworkers reported that the new generation of Pd-NHC complexes can be used to carry out cross-coupling with aryl sulfides.[30] Thus, Pd-PEPPSI-SIPr was used to carry out C-H arylation of heteroarenes through the activation of the Ar-S bond in the *ortho*-propargyl aryl sulfide, in turn obtained by the method of Procter *et al.*[14a] (see Scheme 30, A, prod. **103**); the presence of the propargyl group then allows for the synthesis of a new aromatic system **104** .[30a] Another Pd-NHC species was used to carry out a related C-N coupling, ultimately leading to *N*-aryl indoles (Scheme 30, B, **105**).[30b]



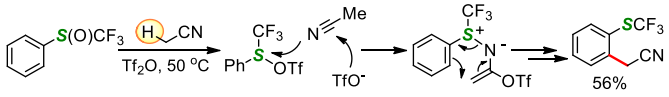
Scheme 30. NHC-Pd-catalyzed cross-coupling of *ortho* propargyl aryl sulfides.

Finally, as expected, the newly synthesized iodoarenes undergo straightforward inter- and intramolecular metal-catalyzed cross-coupling reactions. Some examples include the Suzuki-Miyaura and the Sonogashira C-C bond formation reported by Vallribera, Shafir *et al.* for the α-(2-iodophenyl)ketones shown in Scheme 21. Furthermore, the synthesis of the spiroxindole **84** from the α-(iodoaryl) ketones **74** (Scheme 24) relied on an intramolecular Cu-catalyzed Goldberg-type cyclizative C-N bond formation.[22] In 2015 Shafir *et al* showed that an intramecular cross-coupling can be combined with ring opening to give a series of interesting polar building blocks (Scheme 31). Thus, while basic treatment of the 5-membered cyclic dione **91** afforded the linear carboxylic acid **106** bearing a 2-iodophenyl substituent, conducting the same reaction in the presence of catalytic CuI/Fe_2O_3 led to a cross-coupling/ring opening sequence and a new benzophenone carboxylic acid **107**.[25]



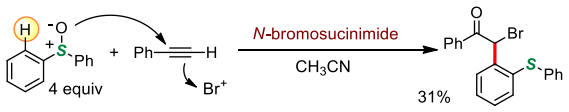
Scheme 31. Complementary ring opening protocols applied to **91**.

As a final note, work in the last 5 years has shown that redox arylation using aryl sulfoxides and λ^3 iodanes is proving to be a highly valuable tool in organic synthesis, likely to continue gaining in prominence. Challenges still remain, however. For the hypervalent iodine manifold, the method's applicability will hinge upon the ability to conjugate the oxidizing property of the I(III) center with potentially reducing coupling partners. Further development will also require a deeper mechanistic understanding of the reactions steps, including the key Claisen-type rearrangement. From a synthetic point of view, a particularly attractive prospect is the identification of coupling partners beyond those showed in Figure 1. As already discussed, known examples include the engagement of amides and ynamides developed by Maulide *et al.*[19] Also noteworthy is the possibility of engaging simple aliphatic nitriles as coupling partners, demonstrated in 2009 by Magnier *et al.*[31] The method relied on a Claisen-type rearrangement of fluoroalkyl acylsulfilimines obtained *via* a Ritter-type activation of nitriles (Scheme 32). Although only MeCN and *n*-PrCN were coupled in meaningful yields, this work nevertheless serves as a proof of concept.



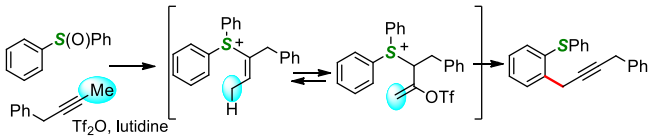
Scheme 32. Proof-of-concept coupling between aryl sulfoxides and alkylnitriles.

Of potential interest is the observation by Maulide *et al.* of a 31% yield of an α-arylated 2-bromoketone, produced by a manifold akin to that in Scheme 19C but using a Br^+ species (rather than H^+ or LAu^+) to activate the alkyne (Scheme 33).[20]



Scheme 30. The use of a Br^+ source in alkyne activation.

Another exciting development has just been reported by Procter *et al.* on the use of non-metallated alkynes as coupling partners, thus broadening the method's applicability (Scheme 34).[32]



Scheme 34. The direct engagement of non-metallated alkynes in redox arylation.

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