The Power of Iodane-Guided C-H Coupling: A Group Transfer Strategy in Which a Halogen Works for Its Money.

Wei W. Chen,^[a,b] Ana B. Cuenca,^{*[b]} and Alexandr Shafir^{*[a]}

Dedicated to Professor Gregorio Asensio as a tribute to his outstanding scientific career

Frontispiece Graphic
(18.5 cm in diameter)

Abstract: Hypervalent organoiodane reagents are ubiquitous in organic synthesis, both as oxidants and as electrophilic group transfer agents. In addition to these hallmark applications, a complementary strategy is gaining momentum that exploits the ability of λ^3 -iodanes to undergo iodine-to-arene group transfer, e.g. via iodonio-Claisen-type rearrangement processes. This Minireview discusses recent advances in the use of this method to access a variety of the C-H functionalized iodoarenes. While Section 2 is focused on the *ortho* C-H propargylation, allylation and the more unusual *para* C-H benzylation, Section 3 is devoted to the C-arylation of enol and phenol substrates. The accompanying

discussion includes the mechanistic considerations, and goes into the synthetic applications of the final iodoarene cores. The Minireview concludes with further conceptual extensions of the method, including the use of non-conventional coupling partners (e.g. cyanoalkylation), improved access to λ^3 -iodane building blocks or the development of iterative approach to access polysubstituted iodoarenes.

1. Introduction

The iodo-, bromo- and chloroarenes occupy an important role in organic chemistry, both as intermediates and as target structures in a variety of applications, including the preparation of bioactive molecules.^[1] The importance of such haloarenes has motivated a continuous search for new methods for their synthesis, with recent advances that include the metal-catalyzed halogen exchange,^[2] or the coordination-directed catalytic C-H halogenations reactions.^[3,4] With respect to the latter strategy, an interesting “inverse” approach involves the use of the iodine substituent in iodoarenes as a director group for selective C-H functionalization of the supporting arene core. This reactivity is enabled by the formation of certain types of reactive hypervalent iodine derivatives,^[5,6] and their ability to undergo an iodine-to-carbon group transfer.

As early as 1998, Oh and coworkers reported that exposing a mixture of PhIO and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to allyl(trimethyl)silane led to an unexpected formation of up to 36% of *ortho*-allyliodobenzene (Scheme 1, A).^[7] Given that this combination of reagents was expected to produce, via umpolung, an electrophilic allyl(phenyl)iodonium reagent, this result was attributed to a concerted allyl transfer process taking place via a “stable six membered-ring transition state” (see Scheme 1-A for the original drawing). Just a few years later, this type of transformation was baptized as [3,3]-sigmatropic or “iodonio-Claisen” rearrangement during the independent studies by the groups of Ochiai and Norton on a closely related reaction of λ^3 -iodanes with silyl- and stannyl-propargylic species to give the *ortho*-propargyl iodobenzene, **1** (Scheme 1, B).^[8]

Wei W. Chen obtained his degree in Chemistry from the University of Barcelona. He then completed his coursework in the Master of Pharmaceutical Chemistry at the Institut Químic de Sarrià (IQS, Barcelona). He is currently engaged in a master thesis project at the Institute of Advanced Chemistry of Catalonia (IQAC-CSIC) and IQS under the supervision of A. Cuenca and A. Shafir. His project involves new iodane-directed C-H coupling reactions.

Ana B. Cuenca graduated from the U. of Valencia, joining the group of Prof. G. Asensio to carry out her PhD in enantioselective protonation. She completed two postdoctoral stays, first at IRCOF-CNRS (Rouen), and then at MIT under the supervision of Prof. S. L. Buchwald. She served as an assistant professor, first at the U. Valencia and then at the University Rovira i Virgili (Tarragona, Prof. E. Fernández). In 2016, Cuenca joined the faculty at IQS-School of Engineering (University Ramon Llull) in Barcelona, where she is now a professor of Organic and Pharmaceutical Chemistry.

Alexandr Shafir completed his undergraduate studies at Hunter College and earned his Ph.D. at UC Berkeley under the direction of John Arnold. He then moved to the Mass. Institute of Technology for postdoctoral training with Stephen L. Buchwald. He began his academic career in Spain, first at the Autonomous University of Barcelona, and then at the Institute of Chemical Research of Catalonia (ICIQ, Tarragona). Since 2018, Shafir is a tenured scientist at the Institute of Advanced Chemistry of Catalonia (IQAC-CSIC), Barcelona.

A. Early *ortho* C-H allylation of a λ^3 -phenyliodane (Oh *et al.*, 1988)

B. Early *ortho* C-H propargylation of a λ^3 -phenyliodane (Ochiai *et al.*, 1991)

Scheme 1. Earliest examples of the iodonio-Claisen manifold.

[a] W. W. Chen, Dr. A. Shafir
Dept. of Biological Chemistry
Institute of Advanced Chemistry of Catalonia (IQAC-CSIC)
c/Jordi Girona 18–26, 08034 Barcelona (Spain)
alexandr.shafir@iqac.csic.es

[b] W. W. Chen, Dr. A. B. Cuenca
Dept. of Organic and Pharmaceutical Chemistry, Institut Químic de Sarrià, Universitat Ramon Llull
Via Augusta 390, 08017 Barcelona (Spain)
anabelen.cuenca@iqs.url.edu

As part of the latter effort, the authors proposed that such process would take place through an allenyl(phenyl)iodonium intermediate **Int-1**, produced via the transmetalation of the propargylsilane precursor to the iodine(III) center. The resulting “iodonio-Claisen” reactivity model, as laid out in these seminal publications, has since served as the framework for most subsequent iodane-guided C-H coupling processes. In contrast, despite the ability of this reaction to produce potentially valuable *ortho*-propargylated haloarenes, this carbon-carbon coupling method did not initially attract much attention as a synthetic tool, arguably because of its seemingly (at the time) limited scope and, perhaps, the method's overly “exotic” appearance. In the meantime, however, evidence for related iodonio-Claisen processes has cropped up over the next two decades, in the form of certain iodophenyl-containing quinone species reported from time to time as side products of oxidative dearomatization of phenolic scaffolds using λ^3 -iodanes. Examples of this phenomenon include an attempted generation of papaverine metabolites, or efforts towards valorization of resorcinol (Scheme 2, structures **2** and **3**).^[9] Most notably, Porco and coworkers reported that the use of $\text{PhI}(\text{O}_2\text{CCF}_3)_2$ in a related dearomatization sequence led to the undesired C-arylated azaphilone **4** in 46% yield. The formation of this side-product was once again attributed to a [3,3]-sigma tropic rearrangement of the putative iodonium phenolate **5** (Scheme 2).^[10]

Scheme 2. Examples of C-arylated side products observed during attempted oxidative dearomatization of phenolic cores with hypervalent iodine species.

Recently, renewed interest has led to a rapid renaissance of this area, as reflected in the discovery of several carbon-carbon bond-forming reactions capable of furnishing a wide variety of structurally diverse iodoarenes, with some illustrated in Scheme 3. In most cases, the coupling event takes place at the C-H site *ortho* to the iodine substituent. The operational resemblance of these reactions to the better known *ortho*-directed C-H functionalization has led us to use the term “iodane-guided C-H functionalization” (or “C-H coupling”) throughout this Minireview, alongside the earlier “iodonio-Claisen” descriptor.

Scheme 3. Selected recent examples of C-H functionalized iodoarenes obtained by iodane-directed coupling, to be discussed throughout this Minireview.

It should be noted that the development of this family of transformations has taken place alongside the closely related C-H functionalization manifold promoted by arylsulfonides,^[11] with differences and similarities between the two types of processes discussed in a recent highlight piece.^[12] In addition, insightful recent reviews, e.g. from the groups of Dauban, Nachtsheim or Hyatt have covered some aspects of this iodane-based chemistry in a broader context of atom-efficient and iodine-retentive transformations.^[13] Nevertheless, key recent advances in iodane-guided C-H coupling suggest the time is ripe for a first dedicated Minireview on the topic.

Following this introduction, the main discussion in this review has been divided into two parts, Sections 2 and 3, which have been grouped around the type of the iodonium intermediate involved in each case. Hence, Section 2 discusses recent advances in iodane-directed C-H coupling via C-I-C-type arylidene(III)-C_{group} intermediates, i.e. the propargylation and the allylation, as well as the benzylation. Section 3, summarizes recent advances in the iodonio-Claisen transformations relying on the enol- and phenol-based C-I-O intermediates to produce the corresponding α -arylation products. In the final outlook part (Section 4), additional recent discoveries are presented among those we feel have the potential to further expand the synthetic applicability of the iodane-directed coupling manifold. The include the possibility of engaging the I-N type intermediates, latest new strategies to obtain the λ^3 -precursors, as well as progress in iterative C-H coupling approaches. The discussion is complemented with key example showcasing the potential of the newly formed iodoarenes as building blocks in downstream functionalization.

2. C-H propargylation, allylation and benzylation

As mentioned in the Introduction, the earliest studies of the “iodonio-Claisen” reactivity were based on the formation and subsequent rearrangement of the C-I-C intermediates containing an iodine(III)-bound allenyl fragment. This section, therefore, will pick up on the chemistries enabled by such reactive λ^3 -allenyl- and the related λ^3 -allyl-iodonium structures, denoted here as **Int-1** and **Int-2** (Scheme 4). While these reactions will involve mainly the better-understood *ortho* coupling, this Section will

conclude with a brief discussion of the recently developed *para*-C-H benzylation, placing such rearrangement processes in a broader class of intramolecular iodine-guided group transfer reactions.

The C-I-C species **Int-1** and **Int-2** are presumed to be highly reactive, and although as of writing of this review their observation has not been reported,^[14] their involvement could be surmised from the ensuing reactivity,^[8,15] and their structure ascertained by DFT calculations.^[16] As mentioned earlier, these intermediates would arise upon a reaction between a metallated (e.g. silylated) propargyl or allyl reagent with a trivalent ArIX₂ precursor.

Scheme 4. Transient reactive λ^3 -iodonium species generated in the iodonio-Claisen C-C coupling involving silylated propargyl and allenyl nucleophiles.

The iodane-guided propargylation thus serves as a convenient platform from which to begin this foray into the field of iodane-guided coupling reactions. Despite subsequent advances in the more challenging allylation reaction (*vide infra*), the original propargylative coupling received very little attention up until 2018. That earlier 1990's efforts from the Ochiai and Norton laboratories, however, provided a good operational understanding of most key features of the "iodonio-Claisen" manifold.^[8,15] As shown in Scheme 5-A, both the iodosobenzene, PhIO, and its acetate derivative PhI(OAc)₂, **6**, reacted readily with propargylic silanes, stannanes and germanes to give the *ortho*-propargyl iodobenzene derivatives. The Ochiai variant required the addition of BF₃·Et₂O as an activator, while the use by the Norton group of the highly electrophilic Zefirov's (PhIOTf)₂O dimer circumvented the need for further additives. The original reaction scope included both the terminal propargylsilane **7** and the internal propargylic substrates capped with simple aliphatic and trimethylsilyl groups.^[8] The subsequent of this class of reactions has relied largely on the silylated reagents (but see section 4 for an exception), as seen in the archetypal reaction between **6** and **7** to give the *ortho*-propargyl iodobenzene **1** (Scheme 5-B). Although the allenyl(aryl)iodane **Int-1** was not detected,^[14] a lack of cross-over reactivity in control experiments, coupled with exclusive *ortho*-C-H selectivity, were fully consistent with the iodonio-Claisen hypothesis in which **Int-1** would undergo a [3,3] sigmatropic rearrangement to the propargylic species **Int-3**. Although the latter structure has been at times represented with a C=I double bond (due to the parallelism with the classical Claisen rearrangement), the C-I single bond resonance form (see Scheme 5-B, right resonance structure) is currently favored (*vide infra*). A final deprotonation step restores the aromaticity to give the target iodoarene **1**.

A. General scheme

B. Reaction prototype

Scheme 5. The reactivity framework for the "iodonio-Claisen" propargylation of λ^3 -iodanes.

In some cases, the coupling was accompanied by an unproductive reduction of the high-valent iodine precursor to iodoarene. This was proposed by Ochiai *et al.* to occur through a reaction of the highly electrophilic allenyl group in **Int-1** with external nucleophiles, e.g. AcOH, ROH or even CH₃CN (the latter *via* a Ritter-type manifold). The authors argue that this *umpolung* process, which yields oxidized propargylic derivatives (Scheme 6), is enabled by the excellent leaving group ability of the [ArI] unit, and was thus particularly relevant for ArI substrates based on electron-deficient arene cores. Although the nucleophilic attack could in principle occur directly at the iodine-bound allenyl fragment in **Int-1**, a later study by Ochiai *et al.* suggested a dissociative (S_N1) mechanism involving the free allenyl/propargyl cation. To support this hypothesis, a more detailed analysis revealed that the relative extent of this reaction, assessed as a molar fraction of the side product produced with different Ar-I(OAc)₂ substrates, positively correlates with the solvolysis rates of the corresponding aryl vinyliodonium species.^[15,17] This suggests that electron-withdrawing substituents on the iodoarene can indeed favor the dissociative process by enhancing the leaving group ability of the iodoarene core.

non-productive side process

Scheme 6. The unproductive S_N1 propargylsilane oxidation as a competing process in *ortho*-propargylation.

In addition, the *ortho* propargylic group in certain types of the rearranged intermediate **Int-3** can undergo a [1,2]-shift to the adjacent *meta* position, as seen for substrates in which both *ortho* positions have been previously substituted (Scheme 7: prod. **8**).^[8a] This is in contrast to the classical aromatic Claisen

rearrangement, in which such situations are resolved through a subsequent Cope-type rearrangement to the *para* proposition.^[18] In a related phenomenon, the presence of a donating -OMe substituent *para* to the iodane favors a dehalogenative [1,2] shift to form the *ipso*-propargyl species (Scheme 7: prod. **9**).^[8b]

Scheme 7. The possible evolution paths of *Int-3* via propargyl [1,2] shift.

Despite these early advances in understanding the iodonio-Claisen process, the original C-H propargylation remained, with few exceptions, largely overlooked as a synthetic method.^[19] This situation is now changing thanks to a wider access to the bis-acetoxy-iodoarene substrates, and owing to the growing importance of C-H coupling strategies. Recently, Shafir and coworkers applied the group's prior experience in the field of iodonio-Claisen processes to explore the limits and the synthetic applicability of the C-H propargylation.^[16] The group's initial re-optimization of the model C-H propargylation of the 2,5-substituted λ^3 -iodane **10** to give **11** revealed that the unproductive reduction of the λ^3 -iodane can be significantly suppressed by conducting the reaction in a $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ mixture at -78°C (Scheme 8). The authors also confirmed that no coupling took place in the absence of $\text{BF}_3\cdot\text{Et}_2\text{O}$ or another acidic additive, such as TMSOTf .

Scheme 8. The model propargylation of substrate **6** under the newly optimized reaction conditions.

The C-H propargylation under these new conditions was extended to a wider collection of arylidanes, most of which were obtained by the oxidation of an iodoarene precursor with NaIO_4 or NaBO_3 .^[20] As illustrated in Table 1, this C-H coupling was found to be rather efficient for a range of electronically diverse iodoarene cores (examples **12–23**), including iodonaphthalenes and iodothiophenes (**22**, **23**). For *meta*-substituted iodoarenes, such as *m*-iodoanisole, the coupling afforded two regioisomeric products, generally favouring the sterically less hindered position (examples **18–20**). As an exception, products **21** and **22**, as well as the 3-iodothiophene derivative **23** were obtained as a single regioisomer despite the presence of two differentiated *ortho* C-H positions. Importantly, the method's efficiency was largely maintained with arene substrates bearing moderately electron-withdrawing substituents. In fact, even the *para*- NO_2 and *para*- CN substituted λ^3 -iodanes

afforded the corresponding *ortho*-propargyl targets **25** and **26** albeit in modest yields.

Table 1. Selected examples illustrating the iodoarene scope in the C-H propargylation with silane **7**.^[a]

[a] With 1.0 equiv $\text{ArI}(\text{OAc})_2$, 1.5 equiv **2** and 1.2 equiv $\text{BF}_3\cdot\text{Et}_2\text{O}$;

[b] single regioisomer formed

The use of a series of internal propargylsilanes was also well tolerated. In fact, the C-H propargylation involving the 1,3-bis(trimethylsilyl)alkyne, **26** was found to be more efficient than the corresponding reaction using the terminal propargylsilane **7**. This reactivity enhancement observed for **26** was reflected in faster reactions using this internal substrate (down to <5 min at -78°C according to ReactIR) and higher yields in a number of cases (see Table 2, **27–29**), including a nearly quantitative yield of **27** on a 10 mmol scale. Additional functional substituents on the propargylsilane substrates included the $-\text{CH}_2\text{OH}$, -Bpin and the iodo groups (products **30–32**). While the presence of a capping phenyl group in the propargylic partner was detrimental, the coupling efficiency could be largely restored by switching to an aryl substituents bearing electron-withdrawing groups (compare **33** vs **34**). For reactions involving **26**, controlled desilylation of the coupling product could provide the corresponding *ortho*-allenyl iodoarenes, such as seen in the conversion of **35** to **36**; a failure to tightly control the reaction conditions resulted in the thermodynamically favorable arylalkyne, the formation of which could be seen as the result of a formal *ortho*-C-H alkylation reaction (Table 2, bottom).

Table 2. Iodine-guided C-H coupling using internal propargylic silanes.

Selected internal propargylsilane derivatives tested

While the propargylation reaction relies on an allenyl iodonium species (i.e. **Int-1**), a closely related allylation can also be conceived, provided that an analogous allylic structure **Int-2** could be generated (see Scheme 4). Although the observation of small amounts a C-H allylation species upon treatment of $\text{PhI}(\text{OAc})_2$ with allyl(trimethyl)silane was first reported in late 1980's,^[7] it's only recently that this manifold was explored as a potential synthetic method. Hence, Zhu and coworkers reported that the iodane-directed *ortho* C-H allylation was indeed viable using allyl(trimethyl)silane **37**, although the process' efficiency showed strong dependence on the electronic nature of the iodoarene core.^[21] In fact, the simplest λ^3 -iodane precursor $\text{PhI}(\text{OAc})_2$ produced only small quantities of the *ortho*-allyl iodobenzene **38**, with most of the hypervalent precursor reduced to iodobenzene. In contrast, the use of a λ^3 -iodane derived from *meta*-OMe iodobenzene led to an 86% yield of the corresponding allylarene **39**, obtained as a mixture of the *ortho/ortho'* isomers (Scheme 9).^[21a] The need for a Lewis acid additive in this case was fulfilled through the use of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, with best results achieved by conducting the reaction in a 1:1 $\text{CH}_3\text{CN} : \text{CH}_2\text{Cl}_2$ solvent mixture.

Scheme 9. A comparison between the reactivity of activated and non-activated iodoarenes cores in the *ortho* C-H allylation.

Despite this inherent electronic limitation, the method could be used to obtain a series of structurally interesting examples of *ortho*-allyl iodoarenes employing *meta*-activated precursors

(Scheme 10). Particularly noteworthy is the formation *meta*-aniline derivatives **41** and **42** as well as the doubly halogenated bromo / iodo species **43**. In addition, substrates containing the *meta* activating group as part of a cycle led to the synthetically valuable allylated cores such as **45** and **46**. For substrates with differentiated *ortho* C-H sites, the coupling products were typically obtained as a ~6:1 to 3:1 isomeric mixture favoring the sterically less hindered site. In a separate publication, Zhu and coworkers also showed that the π -excessive iodothiophene cores allowed for a highly efficient and regioselective formation of the corresponding allyl-thiophene cores (Scheme 10, **47** and **48**).^[21b] However, the coupling proved more difficult for allylsilanes bearing substituents at the 2 or the 3-positions (the α -alkyl substitution was not reported), as illustrated with a modest 43% yield for the 2-Me-allylthiophene **49**. To showcase the synthetic potential of the newly formed allylarenes, the 2-allyl-3-iodothiophene, **47**, obtained in a 97% yield from 3-(bis-acetoxyiodo)thiophene, was transformed in 4 steps into the bicyclic heterocycle **50**, a key precursor on route to the antiplatelet drug clopidogrel (Plavix®, Scheme 10, bottom).^[22] Transformations such as this one, with both the iodine and the newly introduced *ortho* substituent engaged in a cyclizative transformation, likely constitute one of the most best examples of the synthetic versatility of products obtained via iodine-guided *ortho* coupling.

Scheme 10. Selected examples of iodine-directed C-H allylation, as reported by Zhu and coworkers.

Valuable stereo- and regio-chemical insight into this *ortho* C-H allylation reaction was obtained using the *E*-deuterated allylsilane **51**. The use of this precursor in the coupling reaction afforded **39-d**, which contained the deuterium at the terminal position with a 1:1 *E:Z* stereochemistry (Scheme 11).^[21a] In

addition to confirming the identity of the allylic carbon that forms the C-C bond, the full scrambling of the double bond geometry is consistent with the expected loss of stereo information in the allyliodonium intermediate such as **Int-4**. Indeed, once formed, the two possible reactive forms A and B of **Int-4** should each evolve, selectively, to the *Z* and *E* isomers of **39-d**, respectively, leading to the observed positional deuterium scrambling.

Scheme 11. The stereochemical hypothesis of iodane-guided *ortho*-allylation and its effects on the double bond geometry.

Although the use of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as a Lewis acid activator was necessary for these initial studies, a subsequent reassessment by the same group revealed that the use of fluorinated alcohol solvents 2,2,2-trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP), allows in certain cases for the *ortho* C-H allylation to take place in the absence of additional activators.^[21c] In particular, switching to the fluorinated alcohol medium led to an improvement in the coupling of certain Me-substituted allylsilanes (Scheme 12, prod. **52**).

Scheme 12. The *ortho*-C-H allylation in a fluorinated alcohol medium.

This ability to forego an acid activator in fluorinated alcohol medium is best understood in a more general context of the so-called acid activation of hypervalent species, and particularly the simplest $\text{ArI}(\text{OAc})_2$. In general, BF_3 or other acid additives are believed to bind to one of the carboxylate groups in such λ^3 -iodanes, thus weakening the corresponding I-OAc bond. In a recent study, Shafir and coworkers provided experimental evidence for the archetypal adduct of $\text{PhI}(\text{OAc})_2$ with BF_3 .^[23] Specifically, a single crystal X-Ray structure (Scheme 13, left-center) confirmed the elongation of the $\text{I} \cdots \text{OAc} \cdot \text{BF}_3$ bond, and the complementary shortening of the I-O bond in the non-activated I-OAc unit. DFT calculations showed that one of the effects of this activation is to lower the energy of the iodine-centered LUMO, thus making the iodine(III) center even more acidic. Supporting the intermediacy of such species in iodane-

directed coupling, the preformed $\text{PhI}(\text{OAc})_2 \cdot \text{BF}_3$ adduct reacted smoothly with propargylsilane **7** in the absence of additional additives to give the C-H coupling product **1** in 72% yield. In this context, a recent study by Donohoe, Compton and coworkers suggests that a similar activation phenomenon may take place in fluorinated alcohol solvents *via* weak hydrogen-bonded adducts, such as $\text{PhI}(\text{OAc})_2 \cdot \text{HFIP}$, as shown in Scheme 13 (right).^[24]

Scheme 13. An illustration of two experimentally observed acid-activated forms of $\text{PhI}(\text{OAc})_2$.

Returning to the challenge of the C-H allylation of electron-deficient and even electron-neutral iodoarene cores, Shafir and coworkers recently observed a highly efficient iodane-directed C-H allylation by employing the sulfonated allylic silane **53**.^[25] Hence, exposing $\text{PhI}(\text{OAc})_2$ to **53** in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ afforded the *ortho*-allylated iodobenzene **54** in a 92% yield (Scheme 14-A). In a control experiment, less than 15% of the corresponding C-H allylated species was achieved using the parent allylsilane **37**. The substrate **53** likely reacts *via* the tosyl-substituted allyliodonium intermediate **Int-5** through a [3,3]-sigmatropic rearrangement, and so from a mechanistic point of view it will be highly informative to find out how exactly the structural differences between **Int-5** and allylsilane-derived **Int-2** translate into such a superior reactivity of the sulfone-containing substrate. Incidentally, similarly efficient reactions were also achieved using the benzothiophene-S-dioxide substrate **55**. This cyclic allylsilane underwent efficient C-H coupling with a diverse set of iodoarene cores, including the somewhat electron-deficient arene groups (Scheme 14-B, products **57-59**), as well as with the idonaphthalene and iodothiophene cores (**60**, **61**). The use of λ^3 -aryliodane bearing substituents at both *ortho* positions led to the coupling taking place with *meta* selectivity, as seen in the formation of prod. **62**. According to the earlier model (e.g. see Scheme 7),^[8a] the *meta* selectivity would arise from an initial [3,3]-sigmatropic rearrangement followed by a [1,2] allyl migration.

A) Iodane-directed C-H coupling with Ts-substituted allylsilane 53

B) Iodane-directed C-H allylated with benzothiophene-based substrate 55

Scheme 14. C-H allylation using sulfonylated allylsilanes.

Interestingly, two independent attempts, one by Hyatt and coworkers^[26] and another by Shafir and coworkers,^[25] to extend the scope of the iodonio-Claisen reactivity to a benzylic precursor, such as benzyl(trimethyl)silane, **63**, led to a surprising selectivity switch, as seen in the formation of >70% of the *para*-benzyl iodobenzene, **64** (Scheme 15). While the reaction clearly deviates from the archetypal *ortho*-selective process, the cross-over experiments conducted independently by the two groups succeeded in ruling out a simple *umpolung* Friedel-Crafts benzylation. Hence, just as in the earlier allylation and propargylation processes, this new reaction too appears to proceed *via* an internal group delivery from a hypervalent iodine center to an iodoarene C-H position. Although the exact origin of this *para*-selectivity is yet to be elucidated, two alternative hypotheses were put forward. Hence, Hyatt and coworkers tentatively proposed an interruptive benzyl transfer sequence, whereby an attractive $\text{Si}\cdots\text{O}$ interaction between the benzylic substrate and the I-OAc group would direct the benzylic CH_2 group to develop an attractive interaction with the *para* C-H position of the ArI ring (see **Int-6**).^[26,13b] As an alternative explanation, Shafir and coworkers proposed that the initial Si-to-I benzyl transfer would produce a “head-to-tail” cationic π -complex **Int-7**, which, according to the DFT calculation, could undergo a low-barrier C-C bond formation. Both hypotheses, resembling a formal a [5,5]-rearrangement, would expand the realm of iodine-directed coupling reaction beyond a [3,3]-type rearrangement motif.

Scheme 15. Iodane-directed *para* C-H benzylation of Ph-I(OAc)_2 and two possible mechanistic scenarios to rationalize the *para* selectivity.

This *para* C-H benzylation reaction proved to be rather sensitive to the substitution pattern on either partner. Nevertheless, the reaction proceeded efficiently with a number of substituted iodoarene precursors, as illustrated with the isolation of the benzylated arenes **65–67** in Table 3; in some cases the reaction was accompanied by the observation of a *meta*-benzyl side product. Certain substituted benzylic reagents were also tolerated, as reflected by the formation of the substituted iodoarenes **68** and **69**. Notably, benzylation at the *meta* C-H position was observed for iodoarene cores with a blocked *para* position (Table 3, prod. **70**).

Table 3. Selected examples of iodane-directed C-H benzylation.^[a]

[a] Reactions conducted between ArI(OAc)_2 and $\text{Ar'CH}_2\text{SiMe}_3$ in $\text{CH}_2\text{Cl}_2 / \text{CH}_3\text{CN}$ in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$; [b] regioisomer ratio indicated.

3. Iodane-directed coupling of enols and phenols

As mentioned in the introduction, the “iodonio-Claisen” manifold is also possible in reactions between λ^3 -iodanes and enolic or phenolic substrates. Indeed, the binding of this type of O-nucleophiles to an iodine(III) center could produce an I-O (ph)enolate species structurally similar to the previously invoked allyliodonium cations. Although the iodine(III)-enol and iodine(III)-phenol intermediates have been previously postulated in numerous oxidative and dearomatization strategies,^[27] a [3,3]-sigmatropic rearrangement of such intermediates provides access to α -aryl ketones and *ortho*-aryl phenols or quinones (Scheme 16).

Scheme 16. A general “iodonio-Claisen” framework for the iodane-directed coupling between enols or phenols and λ^3 -iodanes.

Indeed, as mentioned in the introduction, arylated quinone species (Scheme 2, also Scheme 16, path A), observed at times as side products in the oxidative dearomatization of phenols with λ^3 -iodanes, constitute some of the earlier evidence for the existence of the iodo-[3,3]-sigmatropic rearrangement. Interestingly, however, the first synthetic application of this manifold relied not on phenols, but rather on the more robust enolic substrates. The sequence was reported in 2014–2015 by Shafir, Vallribera and coworkers, and consisted in the α -arylation of activated carbonyl compounds using the hypervalent bis-trifluoroacetate reagents, $\text{ArI}(\text{O}_2\text{CCF}_3)_2$.^[28] In a model reaction between $\text{PhI}(\text{O}_2\text{CCF}_3)_2$ and 2-cyanocyclohexanone, the α -(2-iodophenyl) ketone **71** was obtained in a ~25% yield using CH_3CN as solvent, while switching to a more acidic $\text{CH}_3\text{CN} / \text{CF}_3\text{CO}_2\text{H}$ medium in the presence of trifluoroacetic anhydride delivered **71** in 80% yield (Scheme 17, A).^[28a] The reaction was proposed to proceed *via* the iodonium O-enolate **Int-8**, which would undergo a [3,3] sigmatropic rearrangement *via* the 6-membered transition state **TS₈₋₉** to give the final cationic intermediate **Int-9**. Importantly, in this case the reaction appears to require the trifluoroacetate form of the λ^3 -iodane, with poor results obtained with an analogous $\text{PhI}(\text{OAc})_2 / \text{AcOH}$ system. The presence of an activating group, such as the 2-cyano substituent, proved important, as no coupling was observed with cyclohexanone (Scheme 17, B).

A) Arylation of an activated carbonyl species

B) Comparative attempt using cyclohexanone

Scheme 17. A) The model arylation of 2-cyanocyclohexanone with $\text{PhI}(\text{O}_2\text{CCF}_3)_2$; and B) a comparative attempt using cyclohexanone.

As shown in Table 4, this α -arylation protocol was found to be applicable to the 5–7 membered cyclic cyanoketones (prod. **71–73**), and tolerated a series of substituted $\text{ArI}(\text{O}_2\text{CCF}_3)_2$ precursors, including those bearing a second halogen, the $-\text{CO}_2\text{R}$ and the $-\text{NO}_2$ groups (**74–79**). Finally, the coupling was extended to β -ketoesters and β -diketones, albeit with somewhat lower yields (**80–82**). The reaction could be conducted on larger scales, including an 80 mmol run to give a 19.2 g batch of the α -aryl product **71**. Incidentally, a recent publication by Christoffers and coworkers describe an expedient conversion of the α -arylated β -ketoester **80** to a benzo[*b*]azocinone *via* a Cu-catalyzed amination and an immediate ring opening of the intermediate (see last product in Table 4).^[29]

Table 4. Examples of the α -arylation of activated carbonyl compounds *via* iodonio-Claisen rearrangement of iodonium enolates.

The need for the bis-trifluoroacetate coupling partners was found to limit the original scope to the electron-neutral and electron-deficient iodoarene cores, in part due to the practical difficulties of accessing the (bis-trifluoroacetoxy)iodo derivatives of donor-substituted and π -excessive (hetero)arenes. The situation may soon change thanks to conceptually different alternative approaches to access such species (see Section 4). In fact, the authors also addressed the possibility of carrying out the coupling with *in-situ* generated λ^3 -iodanes. As an example of this one-pot approach, exposing a mixture of the 2-cyanocyclohexanone and iodobenzene to a mixture of Oxone and trifluoroacetic anhydride led to the formation of the α -arylketone **71** in yields comparable to those obtained using the

isolated $\text{PhI}(\text{O}_2\text{CCF}_3)_2$ (Scheme 18).^[28b] The same simplified approach was then demonstrated in the preparation of a series of additional arylated products, with both Oxone and *m*-CPBA used as convenient terminal oxidants (Scheme 18, **83–88**). Particularly noteworthy is the successful coupling of 3,5-iodoxylene, underscoring the method's potential to generate highly hindered quaternary carbon center (product **85**).

Scheme 18. The one-pot iodane-directed arylation of cyclic 2-alkyl-1,3-diketones.

In a surprising twist, the authors discovered that the one-pot coupling reactions involving Oxone were consistently faster than their counterparts based on premade bis-trifluoroacetoxy iodanes. To shed light on this phenomenon, it was found that the initial oxidation of iodoarenes to the λ^3 -iodane was rather fast, taking as little as 5–10 min in some cases. More importantly, the sulfate salts, present as an integral part of Oxone's triple salts composition ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$), exerted an accelerating effect on the reaction between $\text{ArI}(\text{O}_2\text{CCF}_3)_2$ and cyanoketones. Based on these observations, Oxone appears to act both as an oxidant in the initial oxidation of the ArI , and then as the sulfate promoter of the subsequent C–H coupling. This effect was exploited by the authors to improve the particularly sluggish arylation of the acyclic cyanoketone **89** with PIFA (Scheme 19). In the absence of a sulphate additive, this reaction required 7 days at room temp., leading to the target arylketone **90** in 60% yield. The addition of 0.5 equiv of K_2SO_4 allowed for the reaction to complete in just 18 h, affording **90** in a 70% of yield. Although the origin of this accelerating effect remains unclear,^[30] it was tentatively suggested that the sulfate anion may be involved in facilitating the formation of the initial iodonium enolate intermediates.

Scheme 19. Accelerating effect of K_2SO_4 in a sluggish α -arylation of an open-chain cyanoketone.

In the same report, the α -arylation approach was extended to cyclic 1,3-diones.^[28b] Although the reaction failed for the parent cyclohexane-1,3-dione, the use of its α -Me derivative allowed for this coupling to proceed in a 65% yield (Scheme 20, prod. **91**). This ability to generate a quaternary, but not a tertiary, carbon center was rationalized by the propensity of unsubstituted intercarbonylic CH_2 groups to favor the formation of iodonium ylides, such as $\text{ArI}=\text{C}(\text{COR})_2$.^[31] The protocol was applied to certain substituted dione and iodoarene cores, with some examples shown in Scheme 20 (**92–95**). Although the yields were generally moderate, the arylation of the 2-Me-cyclopentane-1,3-dione with $\text{PhI}(\text{O}_2\text{CCF}_3)_2$ could be carried out on a 5-mmol scale in a 75% yield (prod. **94**).

Scheme 20. The iodane-directed arylation of cyclic 2-alkyl-1,3-diketones.

Just as seen with the allyl- and propargyl-iodonium species (e.g. **Int-1** and **Int-2**), the iodonium *O*-enolates, proposed as intermediates in this process, appear to represent fleeting and hard to detect (let alone isolate) molecular entities. It should be noted, however, that Szpilman and coworkers recently reported an NMR observation of a related iodine-bound *O*-enolate species at -78°C , generated by a reaction between Koser's λ^3 - $\text{PhI}(\text{OH})\text{OTs}$ and the silyl enol ether form of acetophenone. Although both the C- and O-bound isomers are in principle possible, experimental evidence suggests that the only species present “is the one in which the hypervalent iodine is bound to oxygen” (Scheme 21-A).^[32] Considering the electrophilic character of the resulting enolic moiety, the term “enolonium” rather than “enolate” was suggested to properly describe such species. Although this experimental data may lend support to the feasibility of such enolonium species in the iododio-Claisen manifold, it should be emphasized that this data was obtained in a context not conducting to the α -arylation described in this section.

Coming back to the α -arylation manifold, DFT calculations by Shafir and coworkers support the iodonio-Claisen path, outlined in Scheme 21-B. In fact, the [3,3]-sigmatropic rearrangement of the 2-cyanocyclopentanone-derived *enolonium* species species **Int-10** to give **Int-11** was computed to proceed *via* a 6-membered transition state (**TS₁₀₋₁₁**) with a very low activation

barrier of < 2 kcal/mol (Scheme 21-B).^[28b] It is likely, therefore, that the slow step in this process is the initial formation of the requisite iodine-bound enolonium precursors.

A) Observation of an I-O "enolonium" by Szpilman and coworkers

B) DFT profile for the [3,3]-sigmatropic rearrangement on route to 72

Scheme 21. The iodane-directed arylation of cyclic 2-alkyl-1,3-diketones.

The chemistry covered thus far in this section operates on enols activated by α -electron-withdrawing groups capable of entering into conjugation with the enol. Recently, Wang, Peng and coworkers showed that the α,α -difluorinated acetophenone, in its silyl enol form **96**, could also react with λ^3 -iodanes to give the corresponding α -arylated species.^[33] Conditions were thus identified that allowed for the coupling between **96** and $\text{PhI}(\text{OAc})_2$ to take place at -78°C , leading to the α -aryl ketone **97** in 83% in just 5 min (Scheme 22). Importantly, one of the keys to this efficient coupling was the use of TMSOTf as the acid activator of the λ^3 -iodane precursor. Based on a detailed DFT study, the proposed mechanism sequence involved a general iodono-Claisen sequence, although with special features associated with the use of a silylated enol precursor. In a simplified mechanistic diagram (Scheme 22, bottom), the oxygen atom of the silyl ether group would bind to the electrophilic iodine center of the activated λ^3 -iodane PhIX_2 . The resulting **Int-12** then undergoes a low-barrier rearrangement via a 6-membered transition state (**TS**₁₂₋₁₃, $\Delta G^\ddagger \sim 3\text{--}4$ kcal/mol) to give **Int-13**, which, after the desilylation and rearomatization steps, produce the α -arylketone **97**. Interestingly, the desilylation step was suggested to occur *after* the rearrangement, and not prior to it as had been proposed in the case of the allyl- and propargylsilanes. It would be of interest, therefore, to see how the energy profile computed for this reaction is affected in a scenario where the SiMe_3 group in **Int-12** is removed (e.g. as TMSOTf) prior to the key C-C bond-forming step. Conversely, the energy landscape of the earlier cyanoketone arylation (e.g. Scheme 21-B) should probably be reexamined using the analogous *O*-protonated iodine-bound enols. Another interesting aspect is the nature of the reactive λ^3 -iodane, produced in this case by the activation of $\text{ArI}(\text{OAc})_2$ with TMSOTf. With regard to the key role played by TMSOTf, the authors suggest the formation of an extremely electrophilic $\text{PhI}(\text{OTf})_2$ as the reactive intermediate. It should be noted, however, that although this bis-triflate had indeed been postulated in prior publications by a

number of groups, a recent reassessment of the $\text{PhI}(\text{OAc})_2$ / TMSOTf system by Dutton and coworkers points towards the formation of a mixed λ^3 -iodane $\text{PhI}(\text{OTf})(\text{OAc})$, which appears to persist (as per NMR) even in the presence of excess TMSOTf.^[34] This mixed ligand species, in fact, was recently isolated and characterized by X-ray crystallography by Shafir and coworkers,^[23] and it would be of interest to assess whether starting the DFT calculation of this α -arylation reaction from this mixed λ^3 -iodane would have much effect on the final energy profile in Scheme 22.

Scheme 22. Model iodane-directed α -arylation of the α,α -difluorinated silyl enol ether **96** and a simplified mechanistic outline.

The silyl enol ether **96** proved to be highly reactive towards a wide range of $\text{ArI}(\text{OAc})_2$ precursors, with >30 examples included in the scope section. Some of these are shown in Scheme 23, and cover the electronically activated and deactivated iodoarenes cores (**98–107**). The reaction was compatible with a fairly broad range of substitution patterns, providing a series of *ortho*-iodo α,α -difluorinated derivatives, including those bearing the $-\text{NO}_2$, $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{Br}$ and olefin-containing substituents. The method was also applicable to the iodonaphthalene and the iodothiophene cores (**105** and **106**). As part of the method's versatility, the carbon-carbon bond of the $\text{F}_2\text{C}-\text{C}(\text{O})\text{Ph}$ group could be cleaved under basic conditions to give the corresponding *ortho*-difluoromethyl iodoarenes, such as prod. **108** in Scheme 23. This cleavage, in fact, could take place concomitantly with a metal-catalyzed cross-coupling reaction, as in the formation of the arylboronate **109** via the C-H coupling / Miyaura borylation sequence.

Scheme 23. Examples and applications of the iodane-directed α -arylation of α,α -difluorobenzophenone

This beautiful transformation appears to represent a fairly small oasis of reactivity, with most attempts to alter either the CF₂ group (i.e. replacing F with other substituents), or to replace the Ph group with an *n*-Bu or –OMe groups resulting in complete shut down the arylation process. Nevertheless, the methodology could be extended to the CF₃-substituted silyl enol ether **110**. Due to the highly electron-deficient nature of the carbonyl group, the α -arylation product in this case was isolated as the hydrate **111**·H₂O (52% yield), which underwent a facile base-promoted C-CF₃ bond cleavage to give the carboxylic acid **112**. Although the coupling in this case could not be extended to electron-deficient iodoarene cores, a series of difluorocarboxylic acids were prepared in moderate yields for the more reactive λ^3 -iodanes (see prods. **113–115**, Scheme 24).

Scheme 24. The formation of *ortho*-iodinated 2,2-difluoro-2-arylacetic acids via the α -arylation /C-CF₃ bond cleavage sequence.

Based on DFT calculations, the authors propose that the strict requirement for the two fluorine atoms of the CF₂ group in substrates **96** and **110** is due to the initial interaction of the silyl enol ether with the iodine(III) center. Although binding through either the O- and the C- termini of the enol moiety is possible, only the O-bound intermediate would lead to the desired C-C coupling pathway, while the C-binding would lead to non-productive enol oxidation. A comparison of the C- vs O-binding energies for a series of non-*gem*-difluoro enol substrates was found to heavily favor the non-desired C-binding in almost all cases (Scheme 25). This situation is only reversed in the presence of the strongly electron-withdrawing CF₂ group, which allowing for the formation of the requisite I-O species *Int-12*.

Scheme 25 The initial interaction rationale for the unique reactivity of the α,α -difluoroderivatives **84** and **98**.

As mentioned earlier, the low-barrier rearrangement of enolonium species *Int-10* or *Int-12* ties in with the idea that an iodonio-Claisen rearrangement of related “phenolonium”-type intermediate should also be viable. In fact, phenols and naphthols have long been postulated to form transient iodine(III) phenolonium structures, *Int-14*, known to undergo trapping with nucleophiles. This manifold, is at the origin of certain phenol and naphthol dearomatization processes (Scheme 26, right).^[22] A priori such naphtholonium intermediates could also undergo a [3,3]-iodonio-sigmatropic rearrangement (Scheme 26, left), and in such case, the resulting cationic intermediate could either engage in a double rearomatization to form an arylated naphthol, or stop at the α -arylquinone stage, as reported by in Porco and coworkers for species **4** (Scheme 2^[9,10]).

Scheme 26. Hypervalent iodine mediated oxidative dearomatization reactions of phenols (right). Dehydrogenative coupling of λ^3 -iodanes with naphthols (left).

Converting this idea into a useful synthetic method, however, did not prove trivial due to the ease with which the phenolonium species engage in non-arylate dearomatization paths. Nevertheless, in 2018 Yorimitsu and coworkers showed that the iodonio-Claisen path can be activated in the coupling of 2-naphthols with certain ring-activated ArI(OAc)₂ to give 1-aryl-2-naphthol products. Most of the λ^3 -iodanes used in this work were accessible by *in situ* oxidation of various iodoarenes with dry *m*-CPBA, and could be submitted without further isolation to the coupling with 2-naphthols (Scheme 27).^[35] Using this method, the model coupling between 2-iodonaphthol and the hypervalent form of 2-iodonaphthalene afforded the 2,2'-substituted 1,1'-binaphthalene **116** in 64% yield. The process was also suitable for 2-naphthols bearing electron withdrawing substituents, such as the -Br, -CN and carbonyl derivatives (see products **117–120**). On the iodoarene side, the presence of electron releasing groups appears to have a positive effect, as seen in the rather efficient synthesis of products **122** and **123**. Noteworthy is the selective monoarylation obtained with the 2,6-diiodonaphthalene (**121**), which the authors note is maintained even in the presence of larger excess of *m*-CPBA. Finally, the use of certain *meta*-substituted iodoarenes led to the expected mixture of the *ortho,ortho'* regioisomers, favoring the sterically less hindered position (e.g. **124**).

Scheme 27. Selected scope of the dehydrogenative coupling of aryl iodides with naphthols.

The 2-hydroxy-2'-iodo substitution pattern in the new biaryls derivatives opens the door to an expedient synthesis of π -extended dinaphthofurans under basic conditions (Scheme 28, prod. **125**). On the other hand, converting the hydroxyl substituent into the triflate leaving group enabled a cross-coupling / light-assisted ring closure sequence to furnish the

dorsally benzo-fused [5]helicene **126** in 33% yield (Scheme 28).^[35,36]

Scheme 28. Downstream functionalization of 2-hydroxy-2'-iodobinaphthalene derivatives.

4. New opportunities and future outlook

As we have strived to illustrate throughout this Highlight, the so-called iodonio-Claisen manifold provides an expedient and convenient access to a wide variety of valuable iodoarene building blocks. In fact, applications shown thus far may represent only the tip of the iceberg the method's full potential. From a point of view of further putting this area to the service of the synthetic community, interesting objectives in this field include, among other targets, the search for new classes of the "nucleophilic" coupling partners, as well as the drive to engage increasingly more complex λ^3 -iodanes.

A conceptually fruitful approach to discovering iodane-directed reactions involve the identification of a broader array of possible intermediates capable of undergoing the iodane-based rearrangement manifolds. To illustrate this idea, very recently Wang, Peng and coworkers proposed that the realm of the currently known processes, all best on the I-C and I-O intermediates, could be extended through the generation of the analogous I-N structures. This idea was reflected in the development of the iodine-guided *ortho* C-H cyanoalkylation, a process reminiscent of the C-H propargylation but in which the former acetylenic -CCH moiety is now replaced with a cyano group. Key to this reactivity was the discovery that while the (more logical) α -silylated acetonitrile was a rather poor substrate, the corresponding α -stannyl reagent led to the *ortho*-cyanomethyl iodobenzene **127** in an 83% yield in the presence of TMSOTf (Scheme 29).^[37] The iodonio-Claisen rearrangement in this case is presumed to proceed from a ketenimine-type iodonium *Int-15*, a direct I-N analogue of the allenyl iodonium I-C species *Int-1* involved in the propargylation.

Scheme 29. Structural comparison between the *ortho* C-H propargylation (left) and the *ortho* C-H cyanoalkylation (right) of (diacetoxyiodo)arenes.

The new method showed good tolerance to a wide variety of additional substituents α to the nitrile group. In most cases, the product formation took place in 5 min at $-78\text{ }^{\circ}\text{C}$, and led to synthetically meaningful yields of several cyanoalkylated iodoarene cores (Scheme 30). Among notable results is an efficient coupling of nitrile reagents bearing the reactive $-(\text{CH}_2)_n\text{Y}$ moieties, where X could be a halogen, OTs or a OTBTPS group (Scheme 30, **128–140**). Although the quaternary carbon center in the α,α -cyclopropyl spiro derivative was reasonably well tolerated, the more sterically demanding spiro-cyclohexyl motif led to an erosion in the coupling efficiency (for comparison: **141** vs **142** in Scheme 30). In addition, nitrile reagents bearing certain oxidation-sensitive moieties (thienyl, vinyl) were also compatible with this protocol (**143–145**). The method's applicability extends to iodoarene cores with deactivating electron-withdrawing groups, including $-\text{CO}_2\text{Me}$, CF_3 and even a $-\text{NO}_2$ substituent (Scheme 30, **146–148**). Unfortunately, as is common to iodine-directed C-H functionalization, this coupling shut down for the iodopyridine core, either as a result of the basicity of the nitrogen atom, or due to the highly π -deficient nature of the pyridine ring (structure **149**).

Scheme 30. Selected examples for the iodine-guided *ortho* C-H cyanoalkylation of arenes.

The synthetic value of an aromatic core bearing the iodine and nitrile groups was nicely illustrated by the authors with a high-yielding two-step conversion of **127** to the anti-inflammatory drug Diclofenac through a sequence involving a nitrile hydrolysis followed by Cu-catalyzed C-N coupling reaction (Scheme 31).

Scheme 31. Synthetic utility of the iodine-guided *ortho* C-H cyanoalkylation of arenes.

On the basis of DFT calculations, the reaction would involve the formation of a keteniminyl(phenyl)iodonium intermediate **Int-15** (see Scheme 29) followed by a low-barrier ($\Delta G^\ddagger \sim 2\text{ kcal/mol}$) [3,3]-sigmatropic rearrangement. Although the overall sequence is analogous to the earlier iodane-directed reactions, the presence of the nitrile group is expected to alter the initial substrate-iodine interaction in favor of the end-on I-N coordination, which is in contrast to the edge-on mode proposed for propargyl silanes (see Scheme 32 for comparison).

Scheme 32. Different binding modes of the activated phenyl iodane depending of the nucleophile employed.

Considering that the recent surge in this area is likely spurred, at least in part, by a wider accessibility of the requisite λ^3 -iodanes, valuable lessons could be learned from synthetic advances produced in the context of positron emission tomography (PET). Indeed, one of the better studied methods for the synthesis of ^{18}F -labeled aromatic compounds involves the radiofluorination of diaryliodonium salts.^[38] Therefore, considerable efforts in this field are centered on the search for new approaches to access densely functionalized λ^3 -iodanes, and this fact has greatly contributed to making such reagents more readily available to the broader synthetic community. It should be noted that although the synthesis of λ^3 -iodanes of certain functionalized cores has proven challenging, it is often hard to tell whether this is caused by the intrinsic instability of the target λ^3 -iodane, or by the incompatibility of the ArI precursor with the oxidizing reaction conditions. In this context, an interesting recent report Yoshino, Matsunaga and coworkers describes the preparation of high-valent iodine building blocks using iodine(III) tris-carboxylate precursors.^[39] The new method is conceptually related to the recent work by Wirth and coworkers^[40] on the generation of

$\text{ArI}(\text{OAc})_2$ via electrophilic C-H iodination using $\text{I}(\text{OAc})_3$ and $\text{I}(\text{O}_2\text{CCF}_3)_3$ (the latter as an adduct with nitrosonium trifluoroacetate).^[41] In order to exert a greater control of the introduction of the iodine(III) substituent, in the latest procedure these reagents were used to prepare a wider range of $\text{ArI}(\text{O}_2\text{CCF}_3)_2$ and $\text{ArI}(\text{OAc})_2$ reagents via the *ipso* iodination of the readily accessible aryl-germanium and -tin precursors.^[39] In contrast with the common iodoarene oxidation routes, this new iodination approach allows for the critical iodine oxidation step, in this case $\text{I}_2 \rightarrow \text{I}(\text{OAc})_3$, to be performed away from the potentially sensitive aromatic cores. The method's utility is illustrated by a one-pot two-step sequence in which the initial *ipso*-iodination of an aryl(trimethyl)germane is followed by *in situ* iodane-directed C-H coupling. Here, the coupling partners for the newly generated λ^3 -iodanes include the $\text{Bu}_3\text{SnCH}_2\text{CN}$ (cyanomethylation), 2-naphthol and 2-cyanocyclohexanone (Scheme 33).

Scheme 33. Selected examples for the one-pot transformation of Ar-GeMe_3 to $\text{Ar-I}(\text{O}_2\text{CCF}_3)_2$ followed by *ortho* C-H coupling.

An interesting aspect of the iodine-directed C-H coupling is the fact that the iodine atom in the resulting products could in principle be re-oxidized, enabling a new C-H coupling event. In fact, the concept had been previously illustrated with sulfoxide-based *ortho*-C-H propargylation.^[42] Such iterative strategy was recently reported by Shafir and coworkers by combining the *para* and *ortho*-directed iodane-directed C-H coupling events *para* decorate the iodobenzene ring with up to three differentiated alkyl fragments.^[25] As an illustration, iodobenzene was converted to the tri-functionalized iodoarene **151** using a sequence involving the initial *para*-C-H benzylation, followed by two successive *ortho* C-H allylation steps (Scheme 34). The iodine substituent in the resulting multi-substituted arene could finally be used as a leaving group in cross-coupling, as seen in the synthesis of the densely substituted arene **152** bearing four distinct carbon substituents. It should be noted that the latter sequence was made possible, in large part, thanks to the very mild Selectfluor-based iodoarene oxidation protocol developed by Shreeve and coworkers, and well as its later modification from the laboratory of DiMaggio.^[43]

Scheme 34. A sequence illustrating the iterative iodine-directed C-H alkylation to access multiply substituted iodoarene.

The developments illustrated in Schemes 33 and 34 suggest that in the future the iodane-directed C-H functionalization can be used to access increasing complex molecular entity, be that via complex late-stage hypervalent precursors, or perhaps through a stepwise diversity-oriented iterative buildup. In fact, the latter iterative approach can in principle be combined with other iodine-retentive transformation based on λ^3 -iodane reactivity.^[13,44]

Acknowledgements

This work was funded by MINECO (CTQ2013-46705-R, CTQ2017-86936-P) and AGAUR (2017 SGR 1051, 2017 SGR 00294). Financial support from URL (2019-URL_Proj-034) and IQS-Obra Social La Caixa (2017-URL-Intermac-010) is also gratefully acknowledged.

Keywords: haloarenes • hypervalent iodine • rearrangements • C-H functionalization • iodane-directed coupling

- [1] For selected examples, see: a) P. Auffinger, F. A. Hays, E. Westhof, P. Shing Ho, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 16789-16794; b) L. A. Hardegger, B. Kuhn, B. Spinnler, L. Anselm, R. Ecabert, M. Stihle, B. Gsell, R. Thoma, J. Diez, J. Benz, J.-M. Plancher, G. Hartmann, D. W. Banner, W. Haap, F. Diederich, *Angew. Chem. Int. Ed.* **2011**, *50*, 314–318.
- [2] For an earlier example of copper-catalyzed Br-to-I exchange, see: A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 14844-14845.
- [3] For a review on metal-catalyzed carbo-halogen bond formation, see: D. A. Petrone, J. Ye, M. Lautens, *Chem. Rev.* **2016**, *116*, 8003-8104.
- [4] For selected examples on metal-catalyzed *ortho* C-H iodination, see: with Pd a) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 2300-2301; b) D. Sarkar, F. S. Melkonyan, A. V. Gulevich, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2013**, *52*, 10800; with Rh: c) with Rh: d) N. Schröder, J. Wencel-Delord, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 8298-8301; d) E. Erbing, A. Sanz-Marco, A. Vázquez-Romero, J. Malmberg, M. J. Johansson, E. Gómez-Bengoia, B. Martín-Matute, *ACS Catal.* **2018**, *82*, 920-925.
- [5] a) A. Varvoglis, *Hypervalent Iodine in Organic Synthesis*; Academic Press: London, **1997**; b) A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328-3435.
- [6] a) *Hypervalent Iodine Chemistry*, Editor: T. Wirth, Springer 2016; b) *The Chemistry of Hypervalent Halogen Compounds*; B. Olofsson, I.

- Marek, Z. Rappoport, Eds.; Wiley Interscience: 2019; c) L. F. Silva, B. Olofsson, *Nat. Prod. Rep.* **2014**, *28*, 1722–1754.
- [7] K. Lee, D. Y. Kim, D. Y. Oh, *Tetrahedron. Lett.* **1988**, *29*, 667–668.
- [8] a) M. Ochiai, T. Ito, Y. Takaoka, Y. Masaki, *J. Am. Chem. Soc.* **1991**, *113*, 1319–1323; b) M. Ochiai, T. Ito, Y. Masaki, *J. Chem. Soc., Chem. Commun.* **1992**, 15–16; c) D. A. Gately, T. A. Luther, J. R. Norton, M. M. Miller, O. P. Anderson, *J. Org. Chem.* **1992**, *57*, 6496–6502.
- [9] a) G. C. Reddy, *Tetrahedron Lett.* **1995**, *36*, 1001–1002; b) R. W. Van De Water, C. Hoarau, T. R. R. Pettus, *Tetrahedron Lett.* **2003**, *44*, 5109–5113.
- [10] J. L. Zhu, A. R. Germain, J. A. Porco, *Angew. Chem. Int. Ed.* **2004**, *43*, 1239–1243.
- [11] For a review on sulfoxide-directed C–H coupling, see: a) A. P. Pulis, D. J. Procter, *Angew. Chem. Int. Ed.* **2016**, *55*, 9842–9860. For selected examples, see: b) S. Akai, N. Kawashita, Y. Wada, H. Satoh, A. H. Alinejad, K. Kakiguchi, I. Kuriwaki, Y. Kita, *Tetrahedron Lett.* **2006**, *47*, 1881–1884; c) A. B. Cuenca, S. Montserrat, K. M. Hossain, G. Mancha, A. Lledós, M. Medio-Simón, G. Ujaque, G. Asensio, *Org. Lett.* **2009**, *11*, 4906–4909; d) X. Huang, N. Maulide, *J. Am. Chem. Soc.* **2011**, *133*, 8510–8513; e) A. J. Eberhart, D. J. Procter, *Angew. Chem. Int. Ed.* **2013**, *52*, 4008–4011.
- [12] A. Shafir, *Tetrahedron Lett.* **2016**, *57*, 2673–2682.
- [13] a) G. Grelier, B. Darses, P. Dauban, *Beilstein J. Org. Chem.* **2018**, *14*, 1508–1528; b) A. Boelke, P. Finkbeiner, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **2018**, *14*, 1263–1280; c) I. F. D. Hyatt, L. Dave, N. David, K. Kaur, M. Medarda, C. Mowdawalla, *Org. Biomol. Chem.* **2019**, DOI: 10.1039/c9ob01267b.
- [14] However, a footnote in ref. 8b (Ochiai *et al.*) alludes to a personal communication from J. R. Norton regarding variable temperature ^{13}C NMR detection of allenylodane(aryl)iodonium intermediates.
- [15] M. Ochiai, M. Kida, T. Okuyama, *Tetrahedron Lett.* **1998**, *39*, 6207–6210.
- [16] S. Izquierdo, S. Bouvet, Y. Wu, S. Molina, A. Shafir, *Chem. Eur. J.* **2018**, *24*, 15517–15521.
- [17] T. Okuyama, T. Takino, T. Sueda, M. Ochiai, *J. Am. Chem. Soc.* **1995**, *117*, 3360–3367.
- [18] A. M. Martín Castro, *Chem. Rev.* **2004**, *104*, 2939–3002.
- [19] Only a handful of reports make use of this C–H propargylation reaction. In two notable cases, the propargyl group is introduced as an allyl precursor: a) E. Negishi, C. Copéret, S. Ma, T. Mita, T. Sugihara, J. M. Tour, *J. Am. Chem. Soc.* **1996**, *118*, 5904–5918; b) A. T. Hopper, D. T. Witiak, J. Ziemniak, *J. Med. Chem.* **1998**, *41*, 420–427.
- [20] a) P. Kazmierczak, L. Skulski, L. Kraszkiewicz, *Molecules* **2001**, *6*, 881–891; b) A. McKillop, D. Kemp, *Tetrahedron* **1989**, *45*, 3299–3306; c) M. D. Hossain, T. Kitamura, *J. Org. Chem.* **2005**, *70*, 6984–6986.
- [21] a) H. R. Khatri, J. Zhu, *Chem. Eur. J.* **2012**, *18*, 12232–12236; b) H. Nguyen, H. R. Khatri, J. Zhu, *Tetrahedron Lett.* **2013**, *54*, 5464–5466; c) H. R. Khatri, H. Nguyen, J. K. Dunaway, J. Zhu, *Front. Chem. Sci. Eng.* **2015**, *9*, 359–368.
- [22] L. Wang, J. Shen, Y. Tang, Y. Chen, W. Wang, Z. Cai, Z. Du, *Org. Process Res. Dev.* **2007**, *11*, 487–489.
- [23] a) S. Izquierdo, S. Essafi, I. del Rosal, P. Vidossich, R. Pleixats, A. Vallribera, G. Ujaque, A. Lledós, A. Shafir, *J. Am. Chem. Soc.* **2016**, *138*, 12747–12750; b) for an earlier DFT calculation on the PIDA-BF₃ adduct, see: A. Jobin-Des Lauriers, C. Y. Legault, *Molecules* **2015**, *20*, 22635–22644.
- [24] I. Colomer, C. Batchelor-McAuley, B. Odell, T. J. Donohoe, R. G. Compton, *J. Am. Chem. Soc.* **2016**, *138*, 8855–8861.
- [25] Y. Wu, S. Bouvet, S. Izquierdo, A. Shafir, *Angew. Chem. Int. Ed.* **2019**, *58*, 2617–2621.
- [26] C. Mowdawalla, F. Ahmed, T. Li, K. Pham, L. Dave, G. Kim, I. F. D. Hyatt, *Beilstein J. Org. Chem.* **2018**, *14*, 1039–1045.
- [27] For a recent review on asymmetric dearomatization of phenols, including with chiral hypervalent iodine reagents, see: W. T. Wu, L. Zhang, S. L. You, *Chem. Soc. Rev.* **2016**, *45*, 1570–1580.
- [28] a) Z. Jia, E. Gálvez, R. M. Sebastián, R.; Pleixats, A. Álvarez-Larena, E. Martín, A. Vallribera, A. Shafir, *Angew. Chem. Int. Ed.* **2014**, *53*, 11298–11301; b) Y. Wu, I. Arenas, L. M. Broomfield, E. Martín, A. Shafir, *Chem. Eur. J.* **2015**, *21*, 18779–18784.
- [29] A. Dierks, J. Tönjes, M. Schmidtman, J. Christoffers, *Chem. Eur. J.* **2010**, *16*, 1002–1003.
- [30] The authors report no changes in the NMR when exposing PhI(O₂CCF₃)₂ to sulfate salts, which is taken as evidence against the formation of iodonium sulfate species.
- [31] For an early report on iodonium ylides, see: a) E. Gudriniece, O. Neiland, G. Vanags, *Zh. Obsch. Khim.* **1957**, *27*, 2737–2740; for selected additional examples, see: b) X.-C. Huang, Y.-L. Liu, Y. Liang, S.-F. Pi, F. Wang, J.-H. Li, *Org. Lett.* **2008**, *10*, 1525–1528; c) S. Chelli, K. Troshin, P. Mayer, S. Lakhdar, A. R. Ofial, H. Mayr, *J. Am. Chem. Soc.* **2016**, *138*, 10304–10313.
- [32] S. Arava, J. N. Kumar, S. Maksymenko, M. A. Iron, K. N. Parida, P. Frstrup, A. M. Szpilman, *Angew. Chem. Int. Ed.* **2017**, *56*, 2599–2603.
- [33] X. Huang, Y. Zhang, C. Zhang, L. Zhang, Y. Xu, L. Kong, Z.-X. Wang, B. Peng, *Angew. Chem. Int. Ed.* **2019**, *58*, 5956–5961.
- [34] A. Aprile, K. J. Iversen, D. J. D. Wilson, J. L. Dutton, *Inorg. Chem.* **2015**, *54*, 4934–4939.
- [35] a) M. Hori, J.-D. Guo, T. Yanagi, K. Nogi, T. Sasamori, H. Yorimitsu, *Angew. Chem. Int. Ed.* **2018**, *57*, 4663–4667.
- [36] The latter methodology was based on the group's earlier report: Y. Kurata, S. Otsuka, N. Fukui, K. Nogi, H. Yorimitsu, A. Osuka, *Org. Lett.* **2017**, *19*, 1274–1277.
- [37] J. Tian, F. Luo, C. Zhang, X. Huang, Y. Zhang, L. Zhang, L. Kong, X. Hu, Z.-X. Wang, B. Peng, *Angew. Chem. Int. Ed.* **2018**, *57*, 9078–9082.
- [38] X. Deng, J. Rong, L. Wang, N. Vasdev, L. Zhang, L. Josephson, S. H. Liang, *Angew. Chem. Int. Ed.* **2019**, *58*, 2580–2605 and references cited therein (section 3.2.2.).
- [39] a) N. Komami, K. Matsuoka, A. Nakano, M. Kojima, T. Yoshino, and S. Matsunaga, *Chem. Eur. J.* **2019**, *25*, 1217–1220; b) K. Matsuoka, N. Komami, M. Kojima, T. Yoshino, S. Matsunaga, *Asian J. Org. Chem.* **2019**, *10*, 1002–1003.
- [40] T. Hokamp, L. Mollari, L. C. Wilkins, R. L. Melen, T. Wirth, *Angew. Chem. Int. Ed.* **2018**, *57*, 8306–8309; *Angew. Chem.* **2018**, *130*, 8438–8442.
- [41] a) R. C. Cambie, D. Chambers, P. S. Rutledge, P. D. Woodgate, *J. Chem. Soc., Perkin Trans. 1* **1977**, 2231–2235; b) T. Birchall, C. S. Frampton, P. Kapoor, *Inorg. Chem.* **1989**, *28*, 636–639. For earlier syntheses of I(OR)₃ reagents see: c) F. Fichter, S. Stern, *Helv. Chim. Acta* **1928**, *11*, 1256–1264; d) M. Schmeißer, K. Dahmen, P. Sartori, *Chem. Ber.* **1967**, *100*, 1633–1637.
- [42] A. J. Eberhart, H. J. Shriver, E. Álvarez, A. Carrër, Y. Zhang, D. J. Procter, *Chem. Eur. J.* **2015**, *21*, 7428–7434.
- [43] a) C. Ye, B. Twamley, J. M. Shreeve, *Org. Lett.* **2005**, *7*, 3961–3964; b) L. Qin, B. Hu, K. D. Neumann, E. J. Linstad, K. McCauley, J. Veness, J. J. Kempinger, S. G. DiMagno, *Eur. J. Org. Chem.* **2015**, 5919–5924.
- [44] a) B. Lu, J. Wu, N. Yoshikai, *J. Am. Chem. Soc.* **2014**, *136*, 11598–11601; b) Y. Wu, S. Izquierdo, P. Vidossich, A. Lledós, A. Shafir, *Angew. Chem. Int. Ed.* **2016**, *55*, 7152; c) D. P. Hari, J. Waser, *J. Am. Chem. Soc.* **2016**, *138*, 2190–2193; d) J. Buendia, G. Grelier, B. Darses, A. G. Jarvis, F. Taran, P. Dauban, *Angew. Chem. Int. Ed.* **2016**, *55*, 7530–7533.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

REVIEW

The iodine in Ar-I bonds is commonly conceived as a leaving group. This review discusses a powerful alternative reactivity by which λ^3 -iodoarenes direct C-H coupling events at the corresponding aromatic ring.

Wei Wen Chen, Ana
B. Cuenca,* and
Alexandr Shafir*

Page No. – Page No.

The Power of Iodane-Guided C-H Coupling: A Group Transfer Strategy in Which a Halogen Works for Its Money