Shafir Reseach Group

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Abstract

We are interested in developing new chemical transformations, with particular focus on methodsthat allow rapid complexity build up from simple and inexpensive precursors. During 2016, our main emphasis has been on the new reactivity patterns promoted by a hypervalent iodine group, and which allows for oxidative carbon-carbon and carbon-nitrogen and carbon-halogen bond-forming reactions with the retention of iodine as a “universal” diversification point. While our previous efforts involved reactions proceeding *via* iodonio-Claisen rearrangement (see the 2015 Report), in 2016 we reported a method for the construction of 1-aryl-5-iodoimidazoles which relies on a new concept of using an iodine(III) center as a directing tether group for the introduction of an aryl fragment (*ACIE* **2016**). The method offer an unusual solution to a long-standing chemical problem: while efficient coupling methods exists for preparing the 1,4-derivatives (e.g. the Buchwald-Hartwig N-arylation), the formation of the hindered 1,5 analogues remains challenging, hence limiting their applications, e.g. as drug candidates. Our new approach is made possible by a new family of imidazole-containing aryliodonium salts, and allows access to a range of 1,5-imidazole derivatives.

At the same time, we have continued exploring the iodonio-Claisen and mechanistically related metal-free transformations, now with the aim of introducing unsaturated hydrocarbyl fragments, including propargyl, homoally and benzyl groups. It appears that the range of mechanisms in this system may allow for selective CH functionalization *ortho*, *para* and even *meta* to iodine. Given that in all cases the $ArI(OAc)_2$ reagent is activated by $BF_3{\cdot}Et_2O$ or another acid, in 2016 we also reported a detailed study on the general phenomenon of acid activation of aryliodine dicarboxylates (*JACS* **2016**). In this report, we provide, for the first time, a range of NMR and solid state evidence for the putative $PIDA{\cdot}BF_3$ complex, assumed as active species in hundreds of transformations reported by groups around the world. A detailed DFT description of the orbital origin of the activation phenomenon is also provided. Finally, in 2016, the group also published a Highlight reviewing the growing synthetic importance and mechanistic parallelism of sulfur- and iodine-directed redox arylation processes (Tetrahedron let. **2016**).

Halogen-directed oxidative C-I and C-N bond formation.

In 2016, we sought to apply the ability of the hypervalent iodoarenes (ArI) to act as ***iodo-arylation*** agents as a strategy to solve a long-standing challenge in heterocyclic chemistry, namely that of selectively preparing 1,5-imidazole derivatives through the *N*-arylation of the imidazole *NH* group (*ACIE* **2016**). As an entry point, we discovered that imidazole reacts with $PhI(OAc)_2$ to form a new class of aryl/heteroaryl iodine(III) salts containing a free unprotected *NH* group.

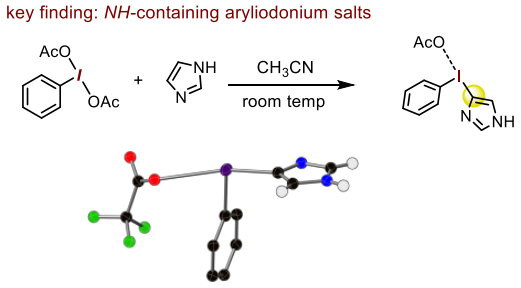

Fig. 1 – *The formation of imidazolyl-based aryliodonium species.*

This type, the iodine(III) center acted as a tether at the imidazole C4(5) position and directed the Cu-catalyzed Ar transfer to the proximal nuleophilic nitrogen, thus precluding the undesired arylation at the distal N3 site The method was applicable to a wide range of iodoarenes and heteroarenes. Particularly noteworthy was fact that the 1,5 selectivity (*vs* 1,4) was maintained even in the case of *N*-thienyl products (both 2- and 3-thienyl) allowing for the synthesis of unusual iodinated bis-heterocyclic building blocks. It is also interesting that derivative bearing the hindered *N*-aryl groups (including 1-naphthyl and mesityl) were also synthesized with high degrees of selectivity.

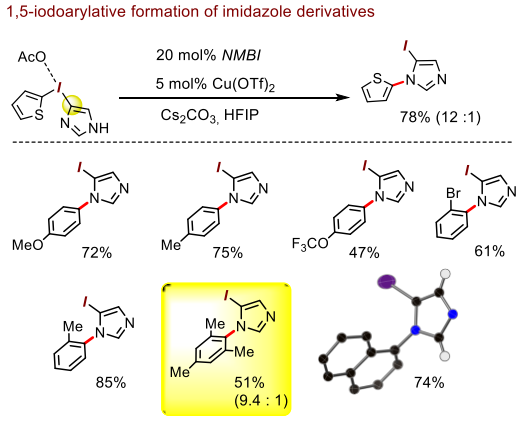

Fig. 2 – *Selected examples of the 1,5-imidazole derivatives obtained by the iodine-directed approach.*

Mechanistic studies suggest that that the true substrate is the betaine (ylide) type structure obtained through the deprotonation of the rather acidic NH site (pKa =10-11). The reaction would thus proceed through the coordination of a Cu(I) center to the target N site and a migration of the Ar group onto the metal center, followed by reductive elimination. The key neutral ylide was indeed isolated and found to be a valid substrate in this transformation.

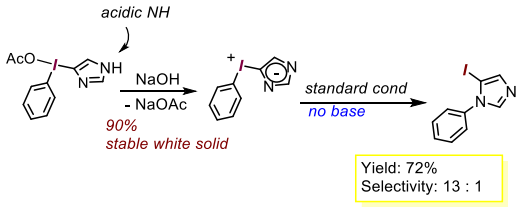

Fig. 3 – *Experimental evidence for NH deprotonation prior to aryl transfer.*

Uncovering mechanistic details in acid activation of aryliodine dicarboxylates

Finally, as part of our efforts on gaining a deeper mechanistic understanding of reactive hypervalent iodine species, we turned our attention on the phenomenon of acid activation prevalent iodine(III)-mediated oxidation processes. Indeed, frequently the hypervalent iodine (III) reagent is not sufficiently active, and accessing desired reactivity requires activation by an acid additive. For example, hundreds of transformations rely on the use of the simple $PhI(OAc)_2$ or $PhI(O_2CCF_3)_2$ but in the presence of $BF_3{\cdot}Et_2O$, H_2SO_4, TMSOTf or other Lewis or Brønsted acid. The $PhI(OAc)_2$ / BF_3 combination has been particularly prolific, with application ranging from the formation of λ^3-diaryliodanes and the oxidation of alcohols, the dehydrogenative arene−arene coupling, arene functionalization, olefin diacetoxylation, or a variety of rearrangement and C−O, C−N and C−S cyclization reactions. Interestingly, the exact mode of activation of iodine(III) by BF_3 has not been investigated. Hence, in 2016 report we have now shown that the coordination of BF_3 to one of the acetate ligands in $PhI(OAc)_2$ produces an activated complex more akin to a free hypothetic $PhI(OAc)^+$ cation.

To gain a complete picture, the mechanistic challenge of acid activation was tackled from four angles: spectroscopic, solid state, DFT and reactivity. Thus, initial direct evidence for an interaction between $PhI(OAc)_2$ and BF_3 was obtained through a downfield displacement of

aromatic resonances upon addition the Lewis acid.

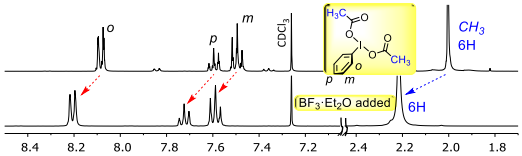

Fig. 4 – *NMR evidence for the formation of a BF_3 complex with aryliodine diacetates*

In fact, an NMR titration experiment confirmed that a dynamic 1:1 adduct forms in this system, prompting efforts to isolate and further characterize this key activated species.

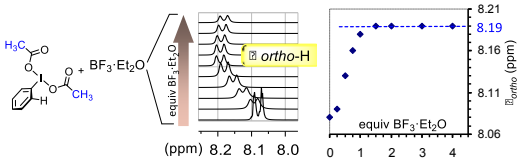

Fig. 5 – *NMR titration in the PIDA – BF_3 system.*

This was indeed possible by using a solvent system in which the newly formed adduct was insoluble. The addition of 1.5 equiv of $BF_3{\cdot}Et_2O$ to a solution of $PhI(OAc)_2$ in a 1:1 hexane/CH_2Cl_2 mixtures led, after 1 h, to the appearance of a white precipitate, which was isolated by filtration under N_2 atmosphere. The ^1H and ^{19}F NMR of this solid confirmed the formulation as $PhI(OAc)_2{\cdot}BF_3$, isolated in an 87% yield (Scheme 1). For the first time, crystals suitable for X-Ray diffraction were obtained as colorless needles from a CH_2Cl_2 solution via a slow diffusion exchange with *n*-hexane. The molecular structure presented discreet units of $PhI(OAc)_2{\cdot}BF_3$ with the BF_3 moiety bound to the "remote" O atom of one of the OAc ligands.

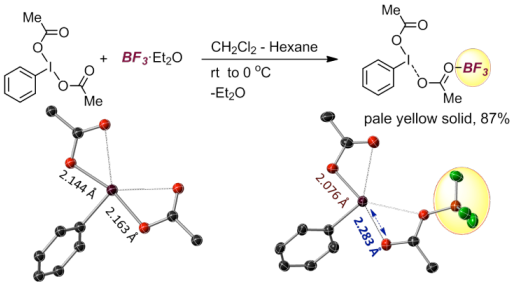

Fig. 6 – *Synthesis and structure of $PhI(OAc)_2{\cdot}BF_3$..*

Finally, the acid activation phenomenon was also rationalized from been rationalized from a molecular orbital point of view.

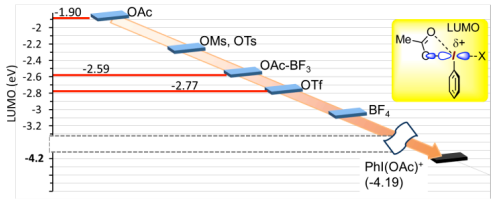

Fig. 7 – *Synthesis and structure of $PhI(OAc)_2{\cdot}BF_3$..*

Unifying the concept of the sulfur- and iodine-based Claisen manifolds

In the last 8 years the methodology for oxidative carbon-carbon bond formation has been amplified by the introduction of the so-called redox neutral arylation manifold. In this this new class of C-H functionalization a formal dehydrohenative C-C bond formation takes place *ortho* to a hypervalent sulphur or iodine substituents. 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.

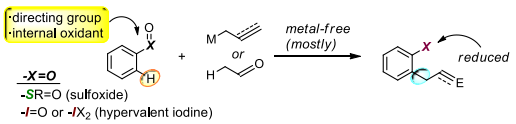

Fig. 8 – *Redox arylation employing a hypervalent sulfur or iodine-based ortho directing group.*

In this invited contribution (Tetrahedron Let. **2016**), A. Shafir reviews the progress main in this area, and provides, for the first time, a unifying view of the iodine- and sulfur-based processes. With all the data at hand, the author also puts forward a model that may, at least operationally, reconcile the SEAr and the Claisen rearrangement features that appear to operate simultaneously in this class of transformations. In this model, the intermediate *O*-enolate is broken down into an iodoarene and an cationic enolonium fragment. 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".

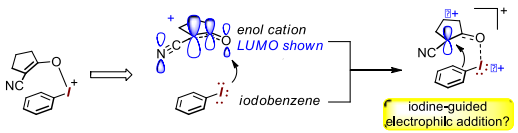

Fig. 9 – *A model proposed here for Iodine-Guided Electrophilc Aromatic Substitution (IGEAS).*

Proline as superior modulator in the formation of Zr-based (UiO-type) MOFs.

A second line of research in our laboratory is the development of catalytically active (or, in general, functional) materials based on porous metal-organic frameworks (MOFs). Hence, through funding from a 2014-2016 Marie Curie fellowship to Dr. O. Gutov we initiated a program on Zr-based MOF systems. In a first publication stemming from this research, we showed in 2015 that defects are present almost ubiquitously in the Zr MOFs such as UiO-66 and UiO-67, and that in the so-called "modulation approach" the defects are compensated by the remaining modulator acid (*Inorg. Chem.* **2015**; this work proved of interest to the scientific community, with some 40 citations in less than 2 years). Intrigued by the modulation phenomenon, we reported in 2016 (*Chem. Eur. J.* **2016**) that proline constitutes an excellent modulator in the formation of a wide variety Zr MOFs. Importantly, while the classical modulators (e.g. benzoic acid, formic acid) must be used in large excess (>30 equiv), *L*-proline was efficient at loadings of only 2-5 equivalents. The method was showcased in the synthesis of a muconate-based MOF network. Previously, this material was prepared from pre-formed Zr_6 clusters, and the structure was interpreted, based on powder X-Ray patterns, as identical to the high-symmetry UiO-66, through rotational disorder in the *cisoid* muconate fragment. Through proline modulation, the material can now be prepared directly from muconic acid. Interestingly, we now obtained a single crystal solid-state structure, which revealed an unusual lower symmetry network with the more stable *transoid* muconates.

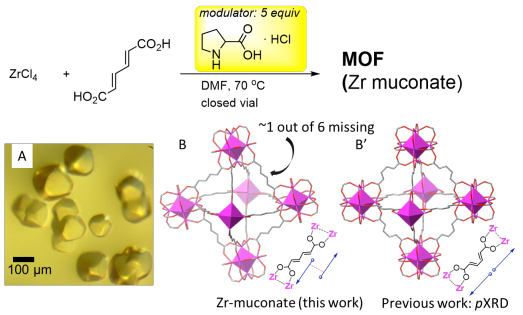

Fig. 10 – *Structure of the Zr-muconate obtained through proline modulation.*

Articles

"*NH*-Heterocyclic Aryliodonium Salts and their Selective Conversion into N1-Aryl-5-iodoimidazoles"
Angew. Chem. Int. Ed. (**2016**) *55*, 7152 –7156
Y. Wu, S. Izquierdo, P. Vidossich, A. Lledós, A. Shafir

"Modulation by Amino Acids: Toward Superior Control in the Synthesis of Zirconium Metal–Organic Frameworks"
Chem. Eur. J. (**2016**) *22*, 13582 – 13587
O. V. Gutov, S. Molina, E. C. Escudero-Adán, A. Shafir

"The emergence of sulfoxide and iodonio-based redox arylation as a synthetic tool"
Tetrahedron Lett. (**2016**) *57*, 2673–2682
A. Shafir

"Acid Activation in Phenyliodine Dicarboxylates: Direct Observation, Structures, and Implications"
J. Am. Chem. Soc. (**2016**) *138*, 12747–12750
S. Izquierdo, S. Essafi, I. del Rosal, P. Vidossich, R. Pleixats, A. Vallribera, G. Ujaque, A. Lledós, A. Shafir