

## Shafir Research Group



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### Abstract

At the Shafir laboratory we are interested in developing new chemical transformations, both in the context of fine chemical and commodity applications. In 2015, the principle direction involved the hypervalent activation of organoiodines for the oxidative carbon-carbon and carbon-nitrogen bond-forming reactions, with the emphasis in retaining the *iodine* functionality for downstream diversification. Along these lines, we discovered a method for the TM-free coupling of iodoarenes with ketones ( $\alpha$ -arylation). This unusual carbon-carbon coupling takes place *ortho* to the iodine, leaving the iodine untouched. The regioselectivity thus attained complements the ipso-selective metal-catalyzed (Pd, Cu)  $\alpha$ -arylation. The coupling allows for the synthesis highly hindered all-carbon quaternary centers. In another application, the group developed a relay route towards 1,5-imidazoles derivatives, a highly sought out compound family inaccessible by many common imidazole functionalization

approaches. As part of our work on heterocycle activation, we prepared a series of unusual aryl  $\lambda^3$  iodanes containing an unprotected *NH*-imidazole. A combination of the hypervalent iodine chemistry with Cu-catalyzed C-N coupling now offers the possibility to access the hindered *N*-aryl-5-iodomidazole core. The approach is highly divergent, as the iodine atom now ushers the synthesis of a wide variety of 1,5-imidazole derivatives.

The group has also initiated studying the application of Zr-based metal-organic frameworks (MOF), as highly promising catalyst platform. Given the crucial role played by the Zr MOF structure defects, we have developed a method for controlling the prevalence and chemical nature of such defects through controlled modulation. In a subsequent study, proline modulation has been introduced, offering a highly controlled growth of a wide variety of Zr metal-organic frameworks.

### New oxidative C-C and C-N coupling

Carbonyl compounds bearing an  $\alpha$ -aryl group are important targets in a wide range of chemical applications. Although their preparation is possible via the conventional  $S_NAr$  reaction of enolates, the  $\alpha$ -arylation approach became particularly practical in the late 90's with the introduction of efficient metal-catalyzed C-C coupling protocols. Alternatively, the uncatalysed arylation using diaryliodonium or aryl-lead species has also been applied in the synthesis of  $\alpha$ -arylketones. Despite all these advances, challenges remain, particularly with respect to the selectivity and to the transfer of the ortho-substituted aryl fragments. In 2015, our group developed an alternative arylation procedure which addresses several of these challenges. The method relies on hypervalent activation of iodoarenes, and leads to the carbon-carbon bond formation at the C-H site *ortho* to the iodine substituent (Fig. 1).

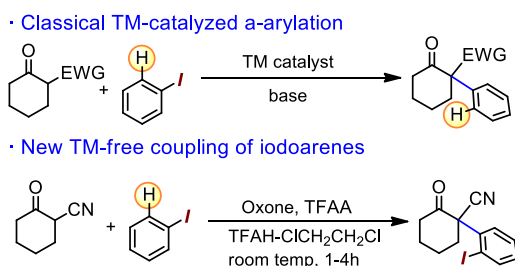


Fig. 1 – Classical TM-catalyzed  $\alpha$ -arylation vs. the new hypervalent activation approach.

The new transformation is performed by simply treating a mixture of the iodoarene and the cyanoketone substrates with an oxidant, preferably Oxone®, and is performed in air at room temperature in 1-4 hours. As a result, iodoarenes are coupled *ortho* to the iodine, leaving the iodine substituent as gateway for downstream diversification. As an unusual feature, the reaction provides access to highly hindered all-carbon quaternary centers unobtainable by common  $\alpha$ -arylation routes (Fig. 2).

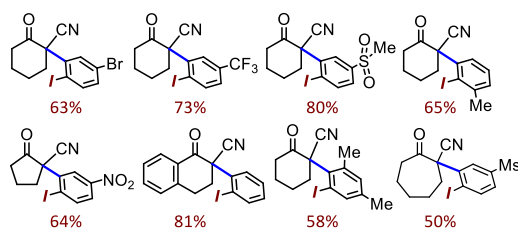


Fig. 1 – Selected examples for the TM-free  $\alpha$ -arylation C-C coupling.

Mechanistically, the reaction relies on the *in situ* oxidation of the iodoarene into the corresponding T-shaped hypervalent  $\lambda^3$  iodonium  $ArI(O_2CCF_3)_2$ . In the presence of an enol this species gives rise to an iodonium O-enolate which then undergoes a [3,3] sigmatropic rearrangement (Fig. 3)

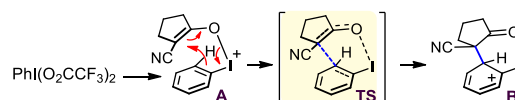


Fig. 3 – The key [3,3] sigmatropic rearrangement step.

In the same study, the industrially relevant formation of the cyclic 2-aryl-1,3-diones was also addressed, starting this time from pre-formed hypervalent derivatives (Fig 4). Such species are highly relevant as pesticides, but are generally inaccessible through common arylation techniques.

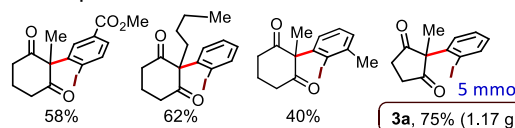


Fig. 4 – Selected examples of the 2-aryl-1,3-dione derivatives obtained by C-C coupling

Using the hypervalent activation of iodoarenes, we have also developed a general methodology to access the imidazoles with the challenging 1,5-substitution pattern. Indeed, for C4(5)-substituted imidazoles, both the Buchwald-Hartwig palladium-(or copper)-catalyzed *N*-arylation of the oxidative Chan-Lam *N*-arylation lead to coupling at the remote nitrogen, making the formation of 1,4 derivatives relatively straightforward. During our study on heterocycle activation, we established that  $PhI(OAc)_2$  can be used to introduce the hypervalent  $C_6H_5$ -iodo group at the C4(5) position of an unprotected imidazole (Fig 5).

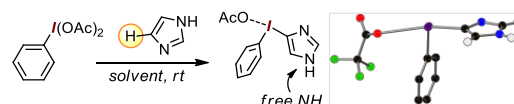


Fig. 5 – Formation of the  $PhI-(Imid)^+$  cation

With the iodine now acting as a stepping stone, the phenyl group could now be transferred to the proximal nitrogen with the help of a copper catalyst, affording selectively the *N*-phenyl-5-iodoimidazole. The method, therefore, is complementary to the existing imidazole *N*-arylation protocols by affording the 1,5 derivatives (Fig. 6).

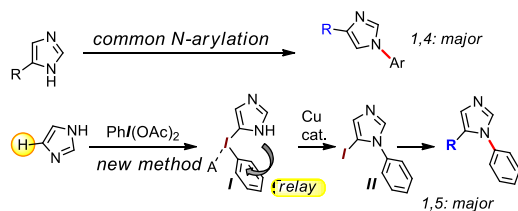


Fig. 6 – The classical *N*-arylation of imidazole vs the new iodoarylation.

Using the new approach, a series of *N*-aryl-5-iodo were readily obtained, in all cases with regioselectivities >8:1. Selected examples are shown in Fig. 7.

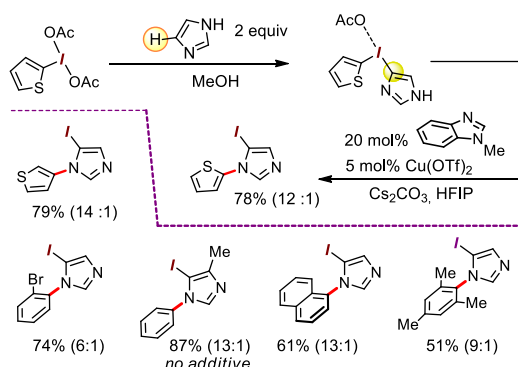


Fig. 7 – Selected example of the synthesis of the *N*-aryl-5-iodoimidazoles

Given that both the selectivity and the yield in the Cu-catalyzed Ph transfer were favored by the addition of a base ( $\text{Cs}_2\text{CO}_3$ ), the reaction was assumed to proceed through a neutral zwitterion obtained through the NH deprotonation of the imidazolium iodane. In agreement with this assumption, the preformed zwitterion proved an excellent substrate even in the absence of a base (Fig 8).

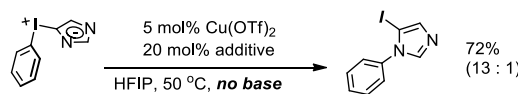


Fig. 8 – Neutral iodoimidazole zwitterion as substrate in copper-catalyzed Ph transfer.

DFT calculation have shown that the reaction likely begins with the coordination of a Cu(I) species to the proximal N atom, which allows for the Ph group transfer to the nitrogen in two steps via a Cu(III)-Ph intermediate.

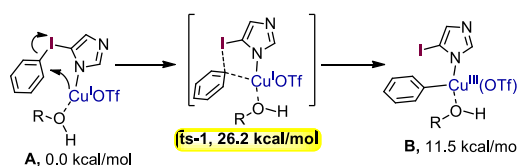


Fig. 9 – A proposed mechanistic sequence for Cu-catalyzed iodine-to-nitrogen transfer.

The drastic changes in the reactivity of the hypervalent iodine reagents, as a function of solvent polarity and acidic additives, have led us to explore the mechanistic basis for these changes. Particularly common is the use of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  to enhance the reactivity of  $\text{PhI}(\text{OAc})_2$  and related aryl iodine dicarboxylates. Interestingly, despite abundant mechanistic applications of such combination, we could find no data on the exact role played by the Lewis acid. Seeking to shed light on this phenomenon, we succeeded, for the first time to identify the reactive intermediate  $\text{PhI}(\text{OAc})_2 \cdot \text{BF}_3$  by NMR. Furthermore, the complex was isolated, and its structure was determined by single crystal X-Ray diffraction (Fig 10). The structure revealed the coordination of the  $\text{BF}_3$  unit to a distal oxygen atom of one of the acetate units, causing the weakening of the bond between this ligand and the iodine atom. The DFT calculations, this alteration was found to create a more Lewis acidic and more oxidizing iodine center (*unpublished*).

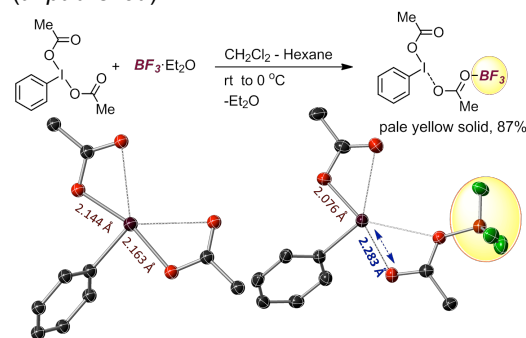


Fig. 10 – The formation and structure of  $\text{PhI}(\text{OAc})_2 \cdot \text{BF}_3$ .

### Control for the MOF structure via acid modulation

As part of our work on functional materials, we have initiated a program on the synthesis of Zr-based metal-organic frameworks, MOFs. This class of coordination polymers is built around an octahedral  $\text{Zr}_6$  cluster (node) connected to other cluster through ditopic (or multitopic) carboxylate linkers. The resulting materials are unique in its ultra-high degree of connectivity, with each  $\text{Zr}_6$  unit bound to 12 carboxylates. This feature helps contribute to the material's robustness, and also allows for the presence of high number of missing linker defects. In fact, in 2015 we have established that these missing linker sites are oftentimes the key to the reactivity of the Zr MOFs. In an initial study, we established a methodology to control the number and type of such defects present through the use of the so-called "modulated growth". We also showed that due to the dynamic nature of such defects,

functional groups can be easily introduced into the pre-formed material (Fig. 11).

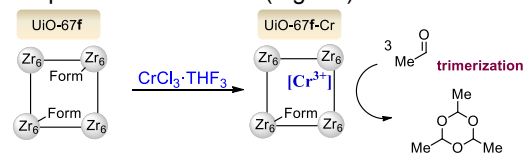


Fig. 11 – Defect-based functionalization of Zr-based UiO-type MOFs.

Building on these early results, we have also discovered that amino acids in general, and proline in particular constitute a superior modulating agent in the growth of a wide variety of Zr MOFs (Fig. 12). The use of L-proline as modulator was found to a) significantly simplify the MOF synthesis by lowering the amount of the modulator needed (up to 6-fold decrease), b) allow for a superior control on particle size and crystallinity, and b) generate single crystals of a wide range of Zr MOFs, allowing, for the first time in many cases, for exact structure determination.

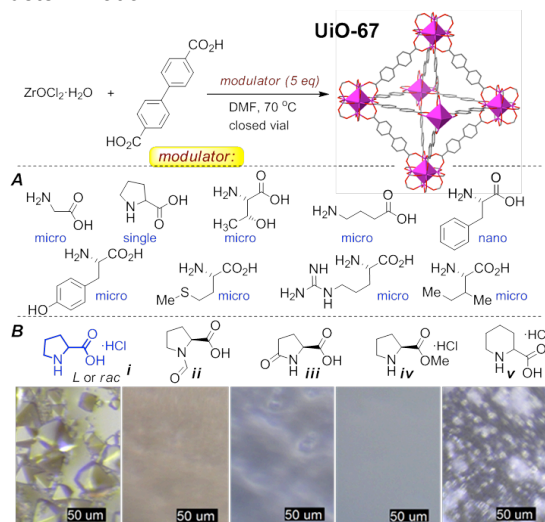


Fig. 12. A) Amino acid screen in UiO-67 synthesis; B). Proline vs analogues in modulated synthesis.

The latter feature has also allowed for the correction of the previously erroneous structure reported by another laboratory for muconate-based Zr MOF (Fig 13, *Submitted*).

## Articles

“Hypervalent Activation as a Key Step for Dehydrogenative *ortho* C-C Coupling of Iodoarenes”

*Chem. Eur. J.* (2015) 21, 18779–18784

Y. Wu, Ismael Arenas, L. M. Broomfield, Eddy Martin, A. Shafir

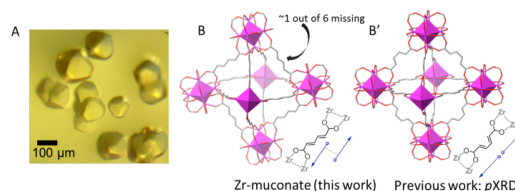


Fig. 13. Erroneous and corrected structure for Zr muconate-based MOF.

## Additional results

In 2015, the group also explored new catalytic system seeking to expand the scope and applicability of hydrogen transfer and hydrosilylation methodologies. A powerful catalytic system for the hydrosilylation of alkynes was thus developed based on the chemistry of Rh nanoparticles. The system allows for the synthesis of a wide range of vinyl silanes under extremely mild conditions using just 1% Rh loading (Fig 14). The articles was featured on as a VIP on the Front Cover of *Advanced Synthesis and Catalysis*

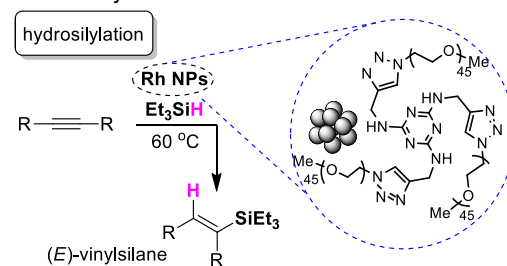


Fig. 14. Mild Rh-catalyzed hydrosilylation of alkynes.

Finally, we have explored the possibility of creating and optimizing catalyst systems through rapid high-throughput generation of ligand libraries. As an example, a series of aminophosphines were generated through in a high throughput manner by condensing a series of commercial mono- and bis-amines with chlorophosphines. The libraries proved highly efficient in designing a new efficient catalyst for Ru-catalyzed amination of alcohols *via* H<sub>2</sub>-borrowing.

“Metal–Organic Framework (MOF) Defects under Control: Insights into the Missing Linker Sites and Their Implication in the Reactivity of Zirconium-Based Frameworks”

*Inorg. Chem.* (2015) 54, 8396–8400

O. V. Gutov, M. Gonzalez Hevia, E. C. Escudero-Adan, A. Shafir

## 2015 Annual Scientific Report

“Phosphino-amine (PN) ligands for rapid catalyst discovery in ruthenium-catalyzed hydrogen-borrowing alkylation of anilines: a proof of principle”

*Adv. Synt. Catal.* (2015) 357, 3538-3548

L. M. Broomfield, Y. Wu, E. Martin, A. Shafir

“Water-Soluble Gold Nanoparticles: From Catalytic Selective Nitroarene Reduction in Water to Refractive Index Sensing”

*Chem. Asian J.* (2015), 10, 2437-2443

W. Guo, R. Pleixats, A. Shafir

“Rhodium Nanoflowers Stabilized by a Nitrogen-Rich PEG-Tagged Substrate as Recyclable Catalyst for the Stereoselective Hydrosilylation of Internal Alkynes”

W. Guo, R. Pleixats, A. Shafir, T. Parella

*Adv. Synth. Catal.* (2015), 357, 89-99