寄稿論文

Aryl(2,4,6-trimethoxyphenyl)iodonium Salts as Reagents for Metal-Free Arylation of Carbon and Heteroatom Nucleophiles

David R. Stuart*

Department of Chemistry, Portland State University, Portland OR 97201 United States
E-mail: dstuart@pdx.edu

Abstract: The use of aryl(2,4,6-trimethoxyphenyl)iodonium salts as novel arylation reagents is discussed. The reaction mechanism of diaryliodonium salts and nucleophiles is outlined and the advantage of using unsymmetrical aryl(auxiliary)iodonium electrophiles is highlighted. Auxiliaries (dummy ligands) that are derived from 1,3,5-trimethoxybenzene are a specific focus and general synthetic approaches to and synthetic applications of these compounds are detailed.

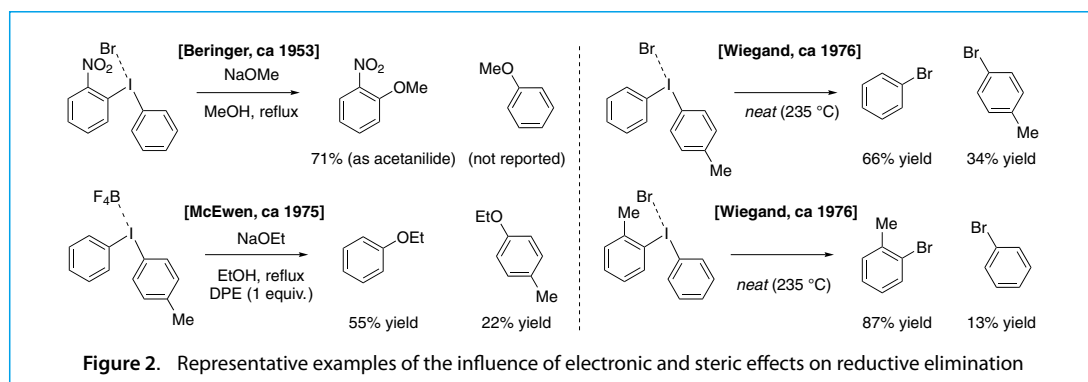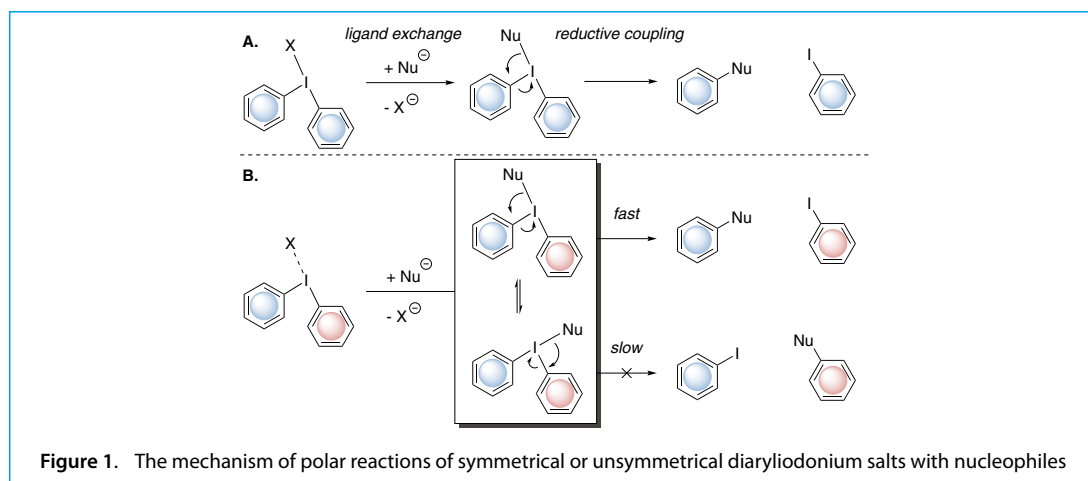**Keywords:** hypervalent iodine, diaryliodonium, arylation, metal-free

1 Introduction

Diaryliodonium salts, also referred to as diaryl-λ^3-iodanes, have been of interest to synthetic chemists since their discovery well over a century ago[1] and the chemistry of hypervalent iodine has been extensively reviewed.[2] Their popularity is largely due to diverse and intriguing reactivity, and utility in the synthesis of both polymers and small molecules. With respect to the latter, diaryliodonium electrophiles are novel arylation reagents for a wide range of nucleophiles and the use of a transition metal catalyst is not required in many cases. This strategy is attractive because it parallels the simplicity of classic nucleophilic aromatic substitution (S_NAr) but has the potential to achieve the broad scope of transition metal catalyzed reactions without the cost of designer ligands or the requirement to assay and remove trace metal impurities[3] from target compounds. Consequently, unsymmetrical diaryliodonium salts may prove incredibly useful in the synthesis of pharmaceuticals, agrochemicals, or functional materials as aryl groups appear incessantly in these molecules.

The generally accepted mechanism for polar reactions of nucleophiles with diaryliodonium salt electrophiles under metal-free conditions is shown in Figure 1A with a symmetric salt and consists of two steps: ligand exchange and reductive coupling.[2e,4] In the ligand exchange step a labile anion (typically triflate, tetrafluoroborate, tosylate, or halide) is displaced by a carbon or heteroatom nucleophile. In the reductive coupling step the resulting T-shaped λ^3-iodane intermediate undergoes a pseudo-reductive elimination of the nucleophile ligand and one of the aryl ligands to form a new aryl-nucleophile bond and an aryl iodide. The geometry of the T-shaped intermediate is inconsequential when symmetrical diaryliodonium salts are used because reductive elimination of the nucleophile with either aryl group leads to identical products. While this scenario is more straightforward it results in significant aryl waste when diaryliodonium salts that cannot be synthesized from their constituent simple arenes are employed. A potentially less wasteful approach is to use an unsymmetrical diaryliodonium salt (Figure 1B). However, in this approach two geometrically distinct T-shaped

intermediates are in equilibrium which may lead to four different products (two different aryl-nucleophile products and two different aryl iodide by-products) upon reductive elimination (Figure 1B). The synthetic utility of this approach is only realized if one of the reductive elimination steps is slower than the other thereby rendering one of the aryl groups an auxiliary or dummy ligand (Figure 1B, red group). Consequently, studies to elucidate the factors that influence and promote (or inhibit) reductive elimination have been an important part of research on diaryliodonium salt chemistry.

Two factors principally control the selectivity of reductive elimination from unsymmetrical T-shaped nucleophile-diaryl-λ^3-iodane intermediates: electronic and steric effects of the aryl groups (Figure 2).[5] Electronic effects have been noted since early reaction development with these reagents independently by Beringer,[5a] McEwen[5b] and Wiegand;[5c] steric effects have been noted in specific cases, most notably by Wiegand.[5c] Several decades of reactivity studies have been distilled down to the following general trends. Electronic effects favor reductive elimination of the nucleophile with the more electron deficient aryl group. Steric effects, in the form of *ortho*-substituents, may promote reductive elimination of the nucleophile with the more sterically congested aryl group and this has been termed the "ortho effect".[5c] However, while electronic effects appear to be general across most nucleophiles, steric effects appear to be dependent on the nucleophile and this trend has led to an emergence of the "anti-ortho effect".[5g] Moreover, when electronically disparate aryl groups are present on unsymmetrical diaryliodonium salt electronic effects are generally stronger than steric effects in promoting reductive elimination.[6] Given the greater generality of the electronic effect on reductive elimination, this has been a focal point of studies to develop general auxiliaries for unsymmetrical aryl(auxiliary)iodonium salts.[7]

Figure 1. The mechanism of polar reactions of symmetrical or unsymmetrical diaryliodonium salts with nucleophiles

Figure 2. Representative examples of the influence of electronic and steric effects on reductive elimination

2 Synthetic Approaches to Aryl(TMP)iodonium Salts

Aryl(2,4,6-trimethoxyphenyl)iodonium salts have emerged as promising reagents for chemoselective aryl transfer to nucleophiles because the trimethoxyphenyl (TMP) moiety is relatively more electron-rich than many other arenes and thus serves as a "dummy" ligand by exploiting the pronounced electronic effect on reductive elimination. Despite evidence for the utility of these reagents,[5g] their synthesis has remained relatively limited compared to other unsymmetrical diaryliodonium salts. Methods that have previously been employed to prepare aryl(TMP)iodonium salts are presented in Figure 3.[5g,7c,d,8] Notably, the majority of these approaches have used an aryl-λ^3-iodane (four of the six general approaches) which requires independent synthesis.[5g,7d,8a,b,d,e,f] This feature, though reliable, reduces the generality of these methods and as a result between 1988 and 2015 only eight different aryl(TMP)iodonium salts were described in the chemical literature for the synthesis of small molecules.[9] A more general strategy involves the use of aryl iodides as these are widely commercially available. Toward this end, a one-pot process that incorporates an aryl-λ^3-iodane formed *in situ* and reaction with trimethoxybenzene was described in pioneering work by Kita and co-workers in 2012.[8c] In this work phenyl(TMP)iodonium tosylate (85% yield) was the only iodonium salt incorporating a TMP auxiliary. Additionally, aryl iodides that contained strongly electron donating (methoxy) or electron withdrawing (nitro) substituents resulted in low yield under the standard reaction conditions with other auxiliaries; good yield with the nitro substituted aryl iodide could be achieved when HFIP was used as the solvent.

In 2015 we initiated a project to develop a one-pot synthesis of aryl(TMP)iodonium salts from readily available aryl iodides in an effort to substantially broaden the scope of aryl(TMP)iodonium salts and thereby stimulate the development of new reactions with these nascent arylation reagents.[8g] This work builds upon the previous work of Kita,[8b,c] Olofsson,[10] and Pike.[7c,d] A key feature of our experimental set up was the removal of halogenated solvents and we found that acetonitrile was an excellent substituted for both stages (oxidation of iodine and introduction of the auxiliary). The optimization of all continuous reaction variables over two stages (temperature, time stage 1, time stage 2, stoichiometry, and solvent volume) was accomplished by Design of Experiment (DoE).[11] These studies revealed that the reaction is fast and may be complete, from set-up to isolation, within one hour. Moreover, the reaction could be run under relatively concentrated conditions of 1 M and with equal stoichiometry of all reactants. Overall, the reaction conditions provided a broad scope of substrates that could be synthesized in short reaction time and the isolated yields range from 67-96% with an

Figure 3. Synthetic approaches to aryl(TMP)iodonium salts
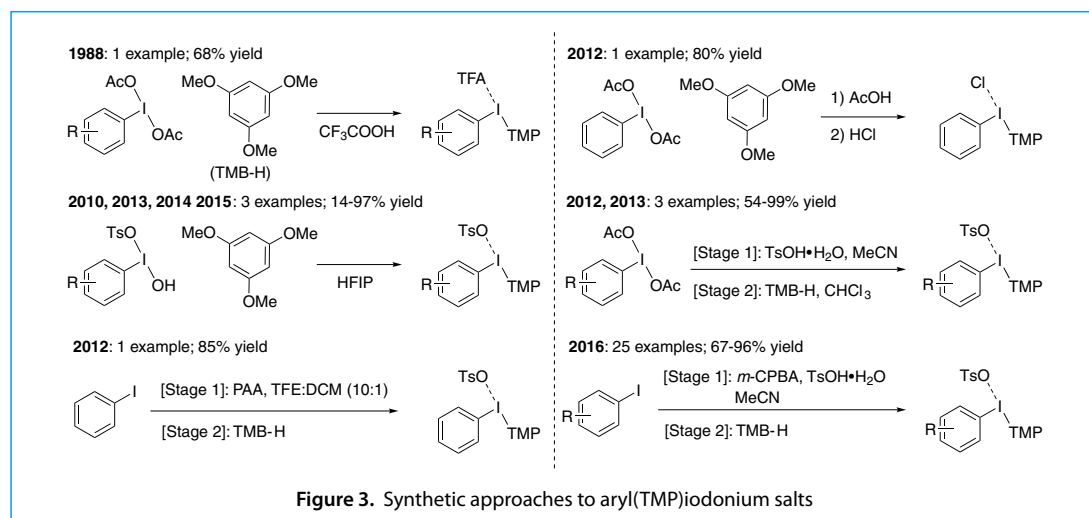
average of 87%. Strongly electron donating and electron withdrawing substituents on the aryl iodides are well tolerated as are potentially reactive functionality including benzyl bromide and free hydroxyl groups. These conditions were also compatible with azine heterocycles and more elaborate aryl moieties that underscore the use of an unsymmetrical diaryliodonium salt in subsequent arylation chemistry. The current scope, to the best of our knowledge, of all aryl(TMP)iodonium salts obtained from our work and all previous methods is presented in Figure 4.
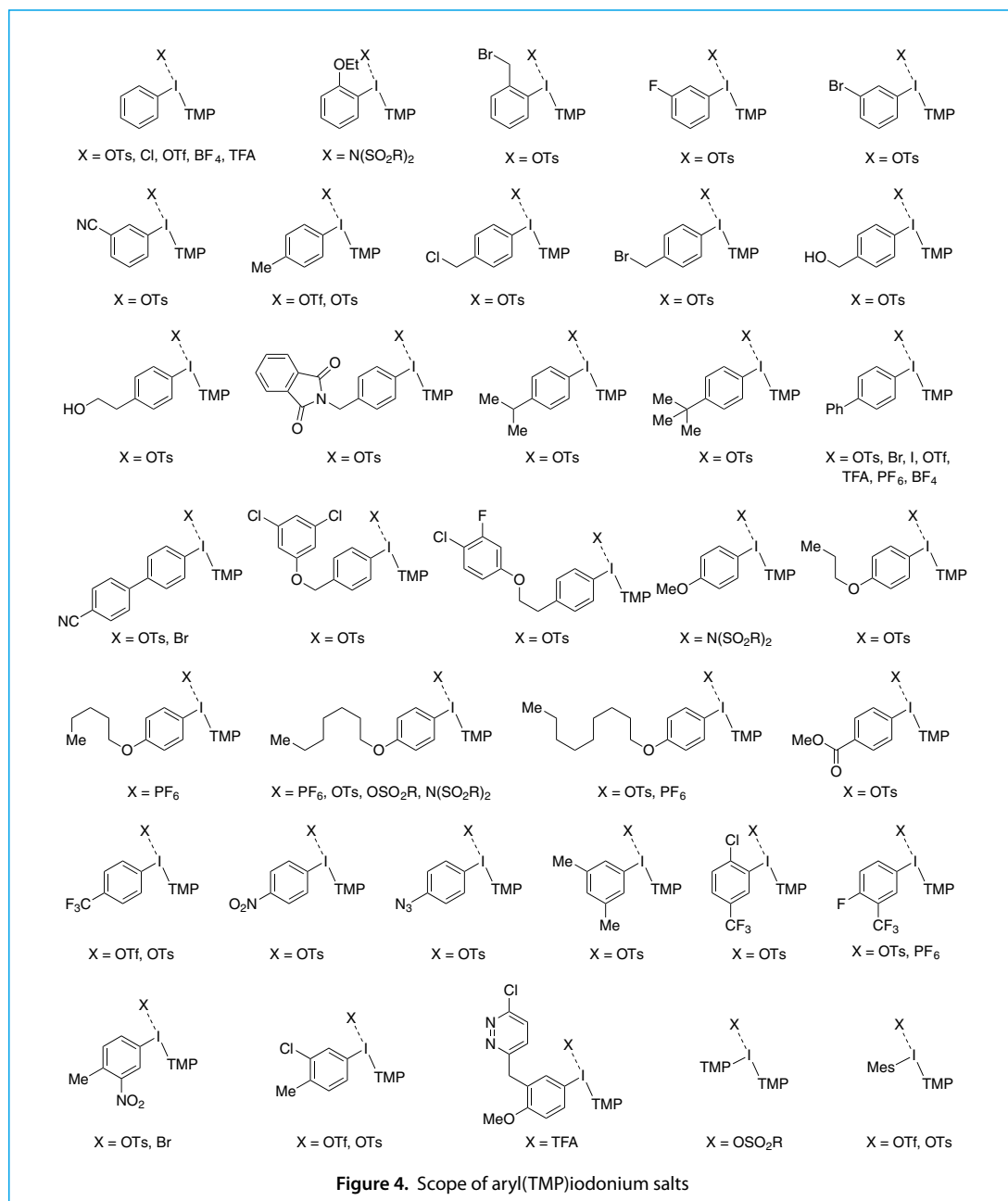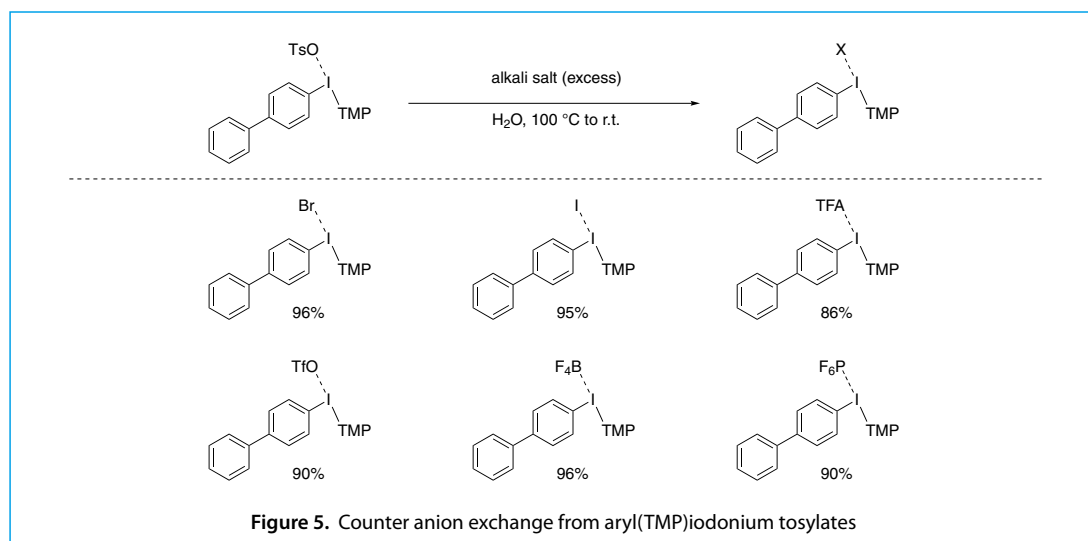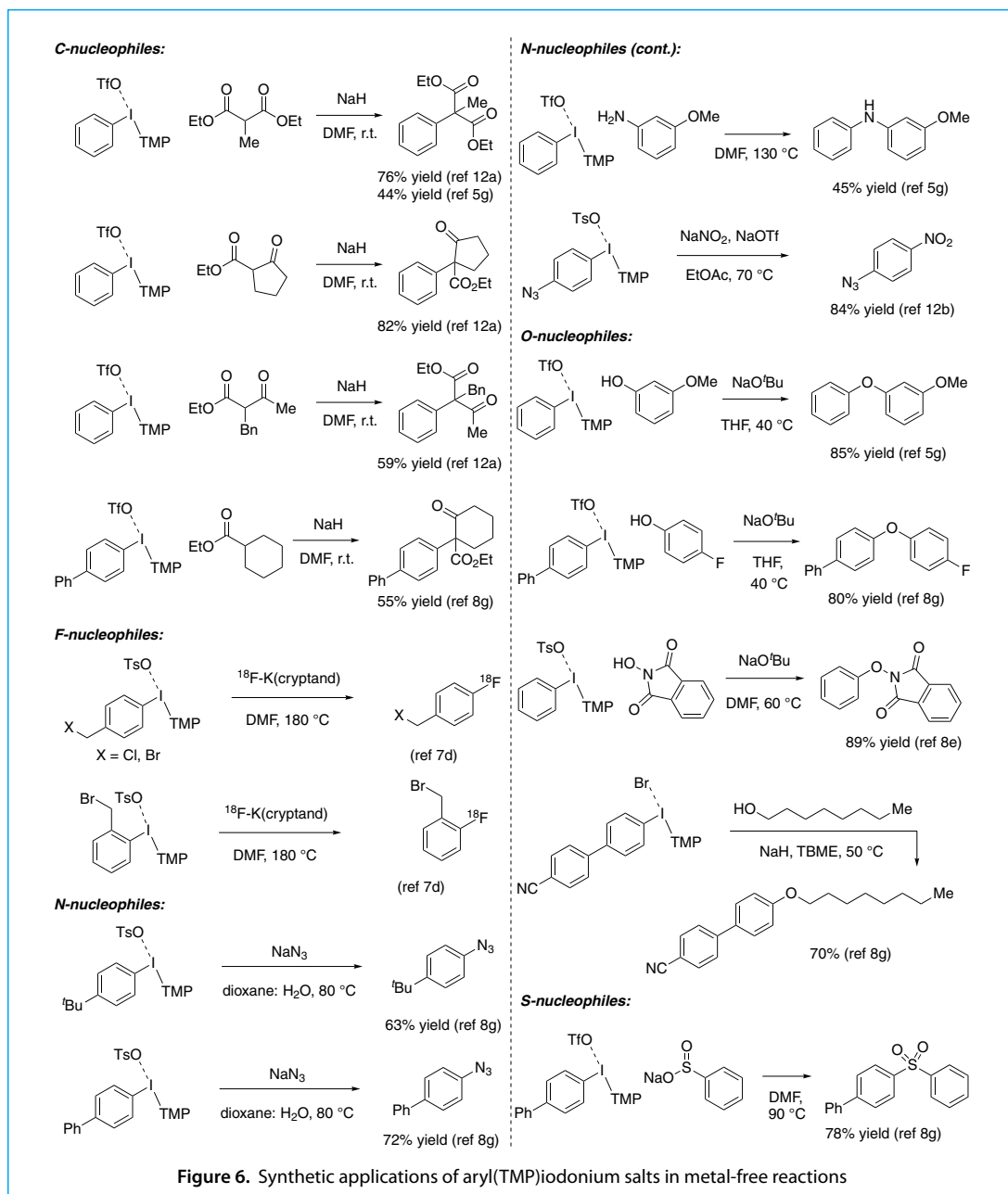

Figure 4. Scope of aryl(TMP)iodonium salts

The counter anion is a useful handle for reactivity of diaryliodonium salts and the ability to access diaryliodonium salts with a range of counter anions is a critical component of reaction development. The vast majority of aryl(TMP)iodonium salts outlined in Figure 4 are the tosylate salts which is a consequence of the method of synthesis (Figure 3). During our development of the one-pot synthesis of aryl(TMP)iodonium salts we found that the tosylate anion could be readily exchanged to other anions under aqueous conditions (Figure 5). Bromide, iodide, trifluoroacetate, triflate, tetrafluoroborate, and hexafluorophosphate were all introduced in good yield; essentially quantitative replacement of the tosylate was observed.

3 Metal-free Reactions of Aryl(TMP)iodonium Salts for the Synthesis of Small Molecules

The use of aryl(TMP)iodonium salts as metal-free arylation reagents for small molecule synthesis continues to grow and is outlined in Figure 6.[5g,7d,8g,e,12] The earliest reported case was the arylation of three malonate-type nucleophiles in 1999 (Figure 6, C-nucleophiles).[12a] For almost two decades these reagents received little attention and then, beginning in 2013, 14 more examples have emerged to include F-, N-, O-, and S-nucleophiles[5g,7d,8e,g,12b] with 7 of the examples reported in 2016.[8g,12b] The examples presented in Figure 6 highlight two exciting features of the aryl(TMP)iodonium reagents relative to other diaryliodonium salts: 1) aryl groups with electron-donating (e.g., t-Bu) and withdrawing (e.g., N₃) substituents are chemoselectively transferred to nucleophiles in good yield, 2) elaborate aryl groups (e.g., 4′-cyanobiphenyl) are chemoselectively transferred to nucleophiles. These features specifically indicate the potential utility and generality of these reagents for metal-free synthesis of small molecules.

Figure 5. Counter anion exchange from aryl(TMP)iodonium tosylates

Figure 6. Synthetic applications of aryl(TMP)iodonium salts in metal-free reactions

4 Conclusions and Outlook

Diaryliodonium salts are novel reagents for metal-free arylation of carbon and heteroatom nucleophiles. The aryl(TMP)iodonium derivatives are uniquely promising toward this end as we and others have demonstrated their use with *C*-, *F*-, *N*-, *O*-, and *S*-nucleophiles. As these reagents become more readily available through general synthetic methods and commercial vendors their application in the synthesis of small molecules is anticipated to increase. The surge of use of these reagents in the past year is evidence for that and I am excited to watch with field grow in years to come.

Acknowledgments

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執筆者紹介

David R. Stuart
Assistant Professor, Department of Chemistry, Portland State University, United States

[Education and employment] 2000-2005 B.Sc. (Chemistry Honors), University of Victoria, Canada; 2005-2010 Ph.D. (Chemistry), University of Ottawa, Canada (Supervisor: Prof. Keith Fagnou); 2010-2012 NSERC Postdoctoral Fellow, Harvard University, United States (Supervisor: Prof. Eric N. Jacobsen); 2012-present Assistant professor, Portland State University, United States.
[Specialties] Organic synthesis, hypervalent iodine, reaction discovery and development