# CYCLIC HYPERVALENT IODINE REAGENTS FOR OXIDATIVE FUNCTIONALIZATIONS

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## INTRODUCTION

Hypervalent iodine reagents are of particular interest in organic synthesis due to their ability to mimic the reactivity of transition metals while maintaining the minimal cost and toxicity common to many main group elements. Whereas hypervalent iodine reagents are commonly recognized as oxidants, over the past decade the scope of reactivity has broadened to include electrophilic functionalization. Hypervalent iodine reagents can serve as electrophilic synthons for normally nucleophilic functional groups (such as azides, nitriles, etc.), providing a complementary approach for functionalization. While many structural variations of hypervalent iodine reagents have been explored, cyclic reagents display enhanced stability compared to their acyclic counterparts, which is essential for broad application (**Figure 1**). Specifically, cyclic hypervalent iodine reagents have been developed for carbon transfers (primarily in the form of triflouromethylation and alkynylation) as well as oxygen, nitrogen, and halogen transfers.[1]

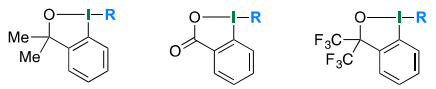
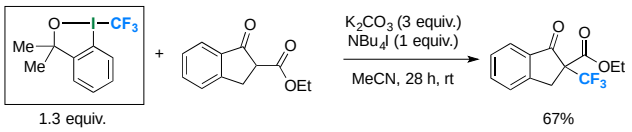



**Figure 1.** Cyclic hypervalent iodine reagents

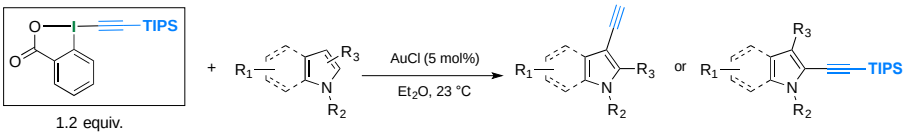
## CARBON TRANSFER

A key breakthrough in the use of cyclic iodinanes for functionalization was the development of Togni's reagents.[2] Togni's reagents were first reported for the trifluoromethylation of thiols and electron-deficient esters **(Scheme 1)**. Since this initial development, these reagents have been applied to many systems, including carbonyls, arenes, heteroarenes, alkynes, and alkenes.[3] In 2010, Sodeoka and coworkers applied Togni's reagents for copper-catalyzed trifluoromethylation of indoles. This method was used by MAP Pharmaceuticals in the synthesis of drug candidates for the treatment of Parkinson's Disease and migraines.[3] MacMillan and coworkers demonstrated that Togni's reagents could be used in the presence of a chiral organocatalyst to afford enantioselective trifluoromethylation of aldehydes.[5] In 2011, Buchwald and coworkers showed that Togni's reagents could be used for the trifluoromethylation of unactivated olefins.[4]




**Scheme 1.** Trifluoromethylation with Togni's reagent

Alkyne transfers with cyclic iodinane reagents have also been extensively studied. In a seminal work, Waser and coworkers demonstrated that TIPS-EBX could be used for the alkynylation of indoles and




**Scheme 2.** Alkynylation of indoles and pyrroles using TIPS-EBX

pyrroles. **(Scheme 2)**. TIPS-EBX has also shown utility for the α-alkynylation of electron-deficient esters, and this chemistry has been applied in several total syntheses.[1] A recent application by Nachtsheim and coworkers demonstrated that in the presence of a rhodium catalyst, TIPS-EBX can be used for the alkynylation of 2-vinyl phenols, enabling the facile synthesis of 1, 3 enynes.[6]

## HETEROATOM TRANSFER

Heteroatom transfer from cyclic iodinanes is much less established than carbon transfer, with most major developments having occurred in the past three years. Common hypervalent iodine reagents for heteroatom transfer are shown in **Figure 2**. Rao and coworkers reported that **1** could be used for amino-quinoline directed C-H oxidation.[7] The authors propose that **1** undergoes a ligand exchange with the solvent to form the terminal oxidant, enabling the formation of different ethers. Solvents that were combatable with these conditions included MeOH, EtOH, and *t*BuOH.

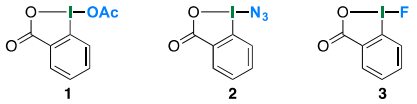



**Figure 2.** Cyclic iodinanes used for heteroatom transfer reactions.

Hartwig and Sharma demonstrated that **2** could be used for iron-catalyzed azidation of electron rich, tertiary C-H bonds.[8] This method proved to be highly functional group tolerant and demonstrated selectivity for the most electron-rich tertiary C-H bond on a variety of substrates.

A 2016 study by Szabó and coworkers demonstrated the use of **3** for rhodium-catalyzed geminal difunctionalization of diazoketones.[10] This reaction is thought to proceed via formation of a rhodium carbenoid that can undergo OH insertion of an alcohol, followed by trapping of a fluorine electrophile to afford a variety of different oxyfluorinated ketones.

## CONCLUSION AND OUTLOOK

Electrophilic functionalization with cyclic hypervalent iodine reagents provides an alternative to traditional functionalization through nucleophilic substitution of a leaving group. These reactions can often be perfomed under mild conditions, and their utility for late stage functionalization has been demonstrated. Future efforts will likely be aimed at expanding the applicability of these reagents for heteroatom transfer, as well as developing methods for enantioselective functionalization.

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