1. Introduction

Oxidation is one of the central reaction classes in organic chemistry and significant progress has been made in the development of reagents that are capable of oxidising complex molecules with high levels of selectivity. However, much remains to be achieved, and synthetic chemistry is not yet close to the levels of selectivity and efficiency that are achieved by enzymes. The use of small organic molecules to promote chemical reactions is an extremely competitive and timely area in which to work, with an increasing movement from the chemical and pharmaceutical industry towards more sustainable technologies.

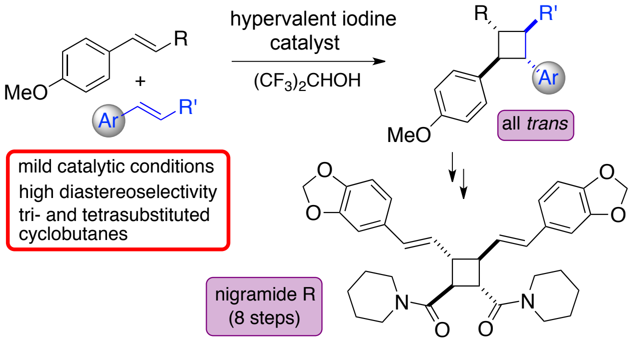
2. Hypervalent iodine reagents as metal-free SET oxidants

Hypervalent iodine reagents exhibit diverse reactivity and find widespread use in organic synthesis. Much of their chemistry is analogous to that found for transition metal complexes. As an extension of these properties, under suitable conditions they may be utilised as less toxic and safer replacements for heavy metal oxidants.

One of our objectives was the study of hypervalent iodine reagents and the contributions that they can make to organic synthesis. In particular, we wanted to explore hypervalent iodine reagents as promoters of single electron transfer (SET) processes, because it was an underdeveloped and underutilized area with significant potential for reaction discovery.

3. Synthesis of cyclobutanes via styrene homo- and cross-dimerization

We have developed a simple and powerful catalytic method for styrene dimerisation using hypervalent iodine reagents, with the use of hexafluoroisopropanol being essential, allowing the rapid formation of unsymmetrical tetra-substituted cyclobutanes. The products are formed with high diastereoselectivity (all *trans*) by a reliable head to head coupling process. Moreover, we have also illustrated the power of this methodology with a short synthesis of a tetrasubstituted natural product, nigramide R, in an efficient eight step protocol, thus confirming the identity of this natural product.



Scheme 1: Hypervalent iodine catalyzed synthesis of tri- and tetrasubstituted cyclobutanes via styrene dimerization.

4. Mechanistic studies towards elucidating the role of HFIP

As compared to many other solvents the properties of HFIP are extreme, it is highly polar, strongly hydrogen-bond donating and very weakly nucleophilic. The use of HFIP as a solvent or additive is known to kinetically enhance or alter the selectivity of a number of synthetically important reactions. Most notable is its use in combination with hydrogen peroxide for both epoxidations and Baeyer-Villiger oxidations, as well as a H-bond donor to epoxides or carbonyl compounds, therefore increasing their electrophilicity.

4.1. Electrochemical experiments

Voltammetric data demonstrates that the enhanced reactivity of the initiator phenyliodine(III) diacetate (PIDA) in HFIP is due to its greater oxidizing abilities in this fluorinated solvent. Such that in HFIP the reactivity of PIDA is comparable if not superior to its fluorinated analog phenyliodine(III) bis(trifluoroacetate) (PIFA). These results contrast with the often reported view that the role of the fluoroalcohol is to stabilize a radical cation formed by single electron transfer.

On average the voltammetric oxidation for the electron-rich styrenes studied within this work are found in HFIP to occur at a lower potential as measured against the ferrocene/ferrocenium redox couple potential as compared to ACN (average shift of ~140 mV as measured from 11 alkenes). This shift in the oxidative wave is attributed to the stabilization of the formed cation.

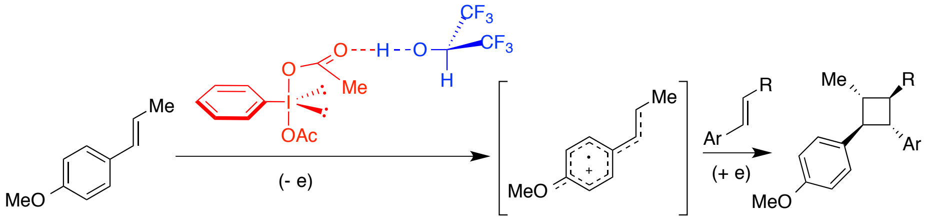
Although not insignificant this shift in potential is small in contrast to the reduction of PIDA in HFIP as compared to ACN, where the reduction wave is observed to shift cf. 850 mV. Hence, the difference between the voltammetric oxidation of *trans*-anethole and the hypervalent reagent PIDA is over a volt less in HFIP than in ACN.

4.2. NMR experiments

Moreover, NMR results reveal the formation of a strong H-bonded adduct between the solvent and oxidizing reagent, which is the physical origin of the observed altered synthetic reactivity.

The ^1H NMR spectra of the 1:1 complex of PIDA with HFIP shows a deshielded shift of the OH signal in HFIP. Such a shift in the OH signal is consistent with the formation of a H-bonded adduct between the HFIP and PIDA. To further evidence the presence of a H-bonded adduct nuclear Overhauser effect (nOe) and diffusion-ordered spectroscopy (DOSY) experiments were performed. On irradiating the PIDA Me signal of the equimolecular mixture of PIDA:HFIP significant nOes were observed with the HFIP broad OH signal.

The results of the DOSY experiments and the measured diffusion coefficients confirm the existence of a H-bonded species upon mixing both H-donor HFIP and H-acceptor PIDA.



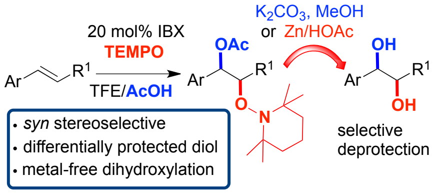
Scheme 2: Hydrogen bonding to hexafluoroisopropanol controls the oxidative strength of hypervalent iodine reagents

5. *syn*-Dihydroxylation of alkenes using TEMPO and fluorinated alcohols

Olefin dihydroxylation is one of the most powerful tools in organic chemistry. The functionalization of vicinal carbons via double C-O bond formation can be achieved in a single step and established dihydroxylation methods give high levels of stereospecificity. In particular, OsO_4 has been used extensively in organic synthesis for the *syn* dihydroxylation of olefins, although its toxic nature is well recognized. The development of new methods to overcome the use of toxic reagents is of great interest and many groups have been devoted to finding new metal-free dihydroxylation procedures.

Following the above-described results on the stereoselective synthesis of cyclobutanes via oxidation of styrenes to their radical cation, we became intrigued with the idea of trapping this radical cation intermediate using TEMPO. This has led to the discovery of a new metal-free dihydroxylation process with the incorporation of both TEMPO and an external nucleophile (or the solvent in its absence). Orthogonally protected *syn* 1,2-diols were obtained with high levels of diastereocontrol,

The ability of TEMPO to disproportionate in acidic solvent (TFE or HFIP) could generate hydroxylamine and an oxoamonium cation. Electron rich olefins may react with oxoamonium cation to form benzylic cation intermediate, which will then be trapped by a nucleophile (either an external carboxylic acid or HFIP). The beneficial role of hypervalent iodine reagents in this reaction may then be to generate an oxoamonium cation *in situ*, therefore improving the yield. The high levels of diastereocontrol displayed when using fluorinated solvents may be related to their larger dielectric constant (ε = 26 for TFE and ε = 18 for HFIP) compared to AcOH (ε = 6.2), which may influence the conformation and reactivity of a cationic intermediate. Finally in order to demonstrate the synthetic utility of this new metal-free dihydroxylation method we addressed the selective deprotection of both hydroxy groups. The orthogonally protected *syn* 1,2-diols were further selectively functionalized into useful compounds.



Scheme 3: Metal-free olefin syn-dihydroxylation