1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP): more than a polar protic solvent

Ignacio Colomer,* Anna E. R. Chamberlain,# Maxwell B. Haughey,# Timothy J. Donohoe*

Department of Chemistry, Chemistry Research Laboratory
University of Oxford, OX1 3TA, UK

# These authors contributed equally

Abstract

Hexafluoroisopropanol (HFIP) has recently become a very popular solvent with uses in many different applications; analysis shows that it possesses a wide range of interesting and unique properties. In this Perspective we detail the main uses of HFIP in the natural sciences and disclose the underlying principles that give it such wide appeal. Accordingly, we will show the broad usage and beneficial effects of HFIP in different fields such as organic, inorganic or physical chemistry, chemical biology and polymer science.

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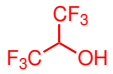
1. Introduction

While reviewing the use of a solvent is not a very common undertaking, the role of HFIP [$(CF_3)_2CHOH$] in promoting different and diverse chemical processes means that in this case it is informative and useful to draw together the many applications of this extraordinary solvent. HFIP presents very particular physical and chemical properties that facilitate unique modes of reactivity and make it an exceptional solvent worth considering in detail.



HFIP

Firstly, it is necessary to review the fundamental physical and chemical properties of HFIP, showing examples that will highlight some of its under-appreciated capabilities. We will then use these properties to explain the reactivity observed in the fields of organic and inorganic chemistry, using examples to extend into other fields, such as electrochemistry. Finally, some interesting applications in the field of chemical biology and polymer science will exemplify the role of HFIP beyond small molecule chemistry. In this review, we have decided to focus on contributions made in the last decade, with a particular emphasis on work published in the last five years.

2. Physical and chemical properties of HFIP

In this section we will explore the physical and chemical properties of HFIP that underpin the diverse range of applications discussed later in this Perspective. Whether the application concerned is relevant to the field of organic synthesis, electrochemistry, chemical biology or polymer chemistry, it is the physical and chemical properties of HFIP that allows us to explain and rationalise the reactivity observed.

a) Physical properties HFIP does not absorb UV light, is thermally stable and is also miscible with water and most common polar organic solvents.[1] The low boiling point (59 °C)[2] permits facile recovery by distillation, resulting in reduced solvent waste and offsetting the initial expense (HFIP can be purchased at ca. £99/kg). Moreover, industrial procedures for HFIP recovery on large scale have been developed involving co-distillation with heptanes and separation of the immiscible distillate.[3]

b) Enhanced Acidity The negative inductive effect as a consequence of fluorination results in a significantly enhanced acidity for HFIP in aqueous solution (pK_a = 9.3)[2] than observed for ^{i}PrOH (pK_a = 17.1).[4] In seminal work by Carre, an acidity scale (the range of acidities achievable in a given solvent) was constructed for HFIP.[5] As shown below (box 1b), the overall range of the scale for HFIP is very similar to that of water, but shifted considerably towards more acidic conditions due to the low basicity of HFIP. Remarkably, the range of acidities achievable in HFIP is more directly comparable to that of formic acid.[6]

c) Reduced Nucleophilicity A comparison of the solvent nucleophilicity parameters (N_{OTs}) for ^{i}PrOH and HFIP highlights the dramatically decreased nucleophilicity of fluorinated alcohols compared to their non-fluorinated counterparts (box 1c). N_{OTs} is a logarithmic scale representing the strength of a given solvent derived from the solvolysis of MeOTs and ranges from -5.56 (CF_3COOH) to +0.2 (^{i}PrOH). Note that HFIP has been reported to act as a nucleophile, but only in the presence of highly reactive cationic electrophilic species.[7,8]

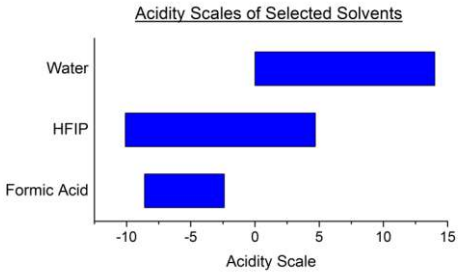
d) Hydrogen Bond Donating Ability A striking example of the hydrogen bond donating ability of HFIP has been reported by Lindsey, where HFIP (bp 59 °C) and THF (bp 66 °C) were observed to form a stable, equimolar complex with a boiling point of 100 °C (see **1** in box 1d).[9] Work by Anderson investigated the effect of mixing HFIP with tertiary amines.[10,11] With increasing amine basicity, enthalpies of hydrogen bond formation become increasingly exothermic, approaching a maximum of –31 kJ mol^{-1} for quinuclidine.[11]

Box 1 | Key physical and chemical properties of HFIP

a) ***Physical properties***

bp(HFIP)[2] = 59 C; bp(^{i}PrOH)[110] = 82.2 C

b) ***Enhanced Acidity***[5,6]

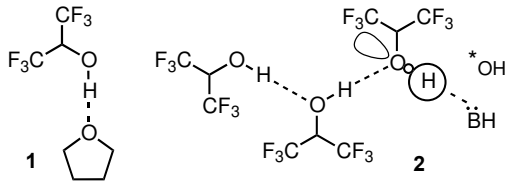


c) ***Reduced Nucleophilicity***

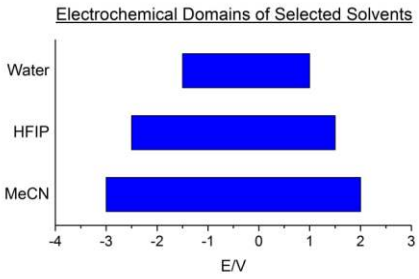
N_{OTs}(HFIP)[19] = -4.23

N_{OTs}(^{i}PrOH)[111] = 0.2

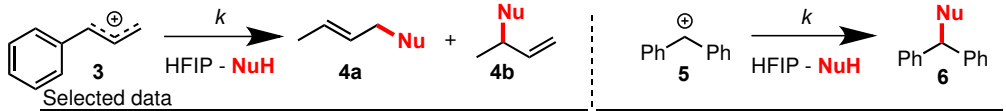
d) ***Hydrogen Bond Donor Ability***



e) ***Redox Stability***[47,112]

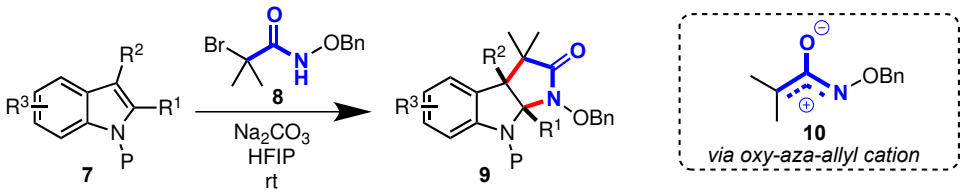


f) ***Cation Stabilisation***



Selected data

HFIP	k (s^{-1}) = 2.2 x 10^4	HFIP- **H_2O (98-2)**	k (s^{-1}) = 2.0 x 10^4
HFIP - **H_2O**	k (M^{-1} s^{-1}) = 9.5 x 10^4	HFIP - **H_2O (95-5)**	k (s^{-1}) = 1.7 x 10^5
HFIP - **MeOH**	k (M^{-1} s^{-1}) = 1.8 x 10^6	HFIP - **H_2O (90-10)**	k (s^{-1}) = 1.0 x 10^6
HFIP - **Br^-**	k (M^{-1} s^{-1}) = 1.5 x 10^{10}	HFIP - **H_2O (70-30)**	k (s^{-1}) = 7.5 x 10^6



bp = boiling point.

N_{OTs} is the solvent nucleophilicity parameter (the higher the value, the greater the nucleophilic strength of the solvent).[110] Electrochemical domains are measured using glassy carbon working electrodes and referenced against a saturated calomel electrode for water, and an Ag/Ag^+ reference electrode for HFIP and MeCN. The supporting electrolyes were: $HClO_4$ (Water); Bu_4NPF_6 (HFIP); Bu_4NPF_6 (MeCN).

More recently, Berkessel has reported single-crystal X-ray structures of HFIP showing infinite helices of hydrogen bonded aggregates. Using these X-ray structures as a basis, the hydrogen bonding properties of HFIP in solution were evaluated using Density Functional Theory (DFT). An aggregation-induced hydrogen bonding enhancement of HFIP was demonstrated (see **2** in box 1d), and it was concluded that the upper limit of this effect was a trimer of HFIP monomers.[12]

e) Redox Stability The oxidative stability of HFIP makes it an ideal solvent for electrochemical investigations.[13] Also, as described below, chemical reactions in highly oxidising environments, such as the hydrogen peroxide epoxidation of olefins, may be conducted in HFIP where other non-fluorinated alcohol solvents would be incompatible. As shown above (Box 1e), when measured using a glassy carbon working electrode, the electrochemical domain of HFIP is greater than that for water, and very comparable to acetonitrile.[14]

f) Cation Stabilisation The reasonably high dielectric constant (ε= 15.7) and low nucleophilicity mean that HFIP is an ideal solvent in which to generate and study cations. Different studies have demonstrated the strong solvent effect of HFIP on the stabilisation of allyl[15] and benzylic[16] cations (**3** and **5** in box 1f) with nucleophiles including MeOH, H_2O and tetrabutylammonium bromide. The first-order decays of cations become faster with the addition of nucleophiles, while the rate constant in neat HFIP appeared to be the smallest.

Very recently, Jeffrey[17] and Wu[18] have exploited this property, reporting the first [3+2] cycloaddition of indoles **7** using aza-oxyallyl cation (see **10** in box 1f) generated *in-situ* from bromoamide **8**. Wu speculates that azaoxyallyl cation formation occurs by a hydrogen bond mediated tautomerisation followed by unimolecular ionisation of bromide. DFT calculations indicate that strong hydrogen bond donor solvents lower the transition state energy and stabilise the intermediate, thus accelerating the rate of the reaction.

3.HFIP in organic chemistry: from traditional functional group activation to more sophisticated chemistry.

Although most of the traditional reactions whereby HFIP activates organic molecules pertain to carbonyl and epoxide substrates,[19,20] recent developments involving other reactive functional groups such as alcohols, halides and sulfonates have been reported. For some of the most recent examples, the actual role of HFIP is still unknown and mechanistic studies are required for a complete understanding and further development of these synthetic methods.

Activation of H_2O_2 in HFIP HFIP has been extensively employed as a solvent for the epoxidation of olefins with hydrogen peroxide since 1977 when it was first used in the presence of transition metal catalysts.[21] Recently, Neumann has reported the electrophilic activation of hydrogen peroxide by HFIP in the absence of transition metal catalysts, permitting both the epoxidation of alkenes and the Baeyer-Villiger oxidation of ketones (Figure 1).[22] Detailed work by Berkessel employing catalytic Brønstead acids in HFIP has revealed a unique mechanism for the Baeyer-Villiger oxidation of cyclic ketones in which a spiro-bisperoxide intermediate (**13**) was identified (Figure 1a).[23,24] It is clear that the use of HFIP has a dramatic effect on reaction course with a non-Criegee mechanism being identified. In later work, Berkessel explored the origin of the ca. 100,000-fold rate increase for the epoxidation of olefins by hydrogen peroxide in HFIP relative to 1,4-dioxane.[25] Kinetic studies investigating the epoxidation of *Z*-cyclooctene revealed a first order rate dependence on the concentration of olefin and hydrogen peroxide, and a third order dependence with respect to HFIP.[12,25] Combined with a strongly negative entropy of activation, $\Delta S^{\ddagger} = -163$ J K^{-1} mol^{-1}, this suggested a highly ordered transition state involving three molecules of HFIP (See Box 1d).[25] DFT calculations supported these findings, and it was stated that aggregation of HFIP molecules led to polarisation of the oxygen-oxygen bond therefore activating hydrogen peroxide towards nucleophilic attack. The implications of this work are significant as several authors have independently reported reactions proceeding when performed in CH_2Cl_2 with just a few equivalents of HFIP used as an additive, without decrease in yield or selectivity, thereby making the widespread use of this solvent more affordable.[26]

Although macroscopically HFIP-H_2O mixtures are homogeneous, recent molecular dynamics simulations of alkenes, aq. H_2O_2 and HFIP have shown the possibility of forming a microheterogeneous structure. This has a triphilic character, having three separate microphases (the oxidant H_2O_2 in water, fluorinated HFIP and the hydrocarbon starting material), [27]

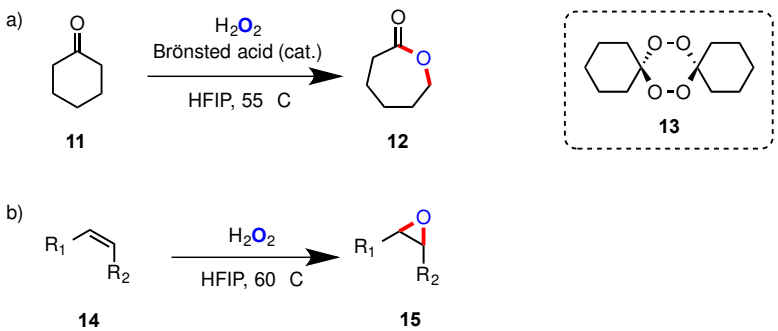


Figure 1: Use of HFIP with H_2O_2 in: a) Baeyer-Villiger oxidation of ketones. b epoxidation of olefins) .

We have opted to organise the following section based on the organic functional group that HFIP activates.

a) Carbonyl and acetal activation As an example of the exciting new applications of HFIP, Aubé has reported the intramolecular Schmidt reaction using catalytic Lewis acid (10 mol% of $TiCl_4$) in HFIP, see **16→17** (Figure 2a). Use of this solvent overcomes one of the previous limitations of the reaction, namely the requirement for excess Lewis or Bronsted acid in order to achieve complete conversion, because of strong product binding and reaction inhibition.[28] In this case, inhibition was not observed due to competitive and strong hydrogen bonding of the amide product to HFIP itself. More recently, this methodology has been extended to an intermolecular Schmidt reaction with triflic acid employed as the optimal catalyst.[29]

The same group has also reported the HFIP promoted intramolecular Friedel-Crafts reaction of acyl chlorides **18** requiring no additional catalyst (Figure 2a).[26] Mechanistic experiments supported acyl chloride activation promoted via hydrogen bonding to HFIP. In the intermolecular version, electron rich arenes, including pyrrole, indole and benzothiophenes were used to good effect.[30]

The Hosomi-Sakurai allylation of dimethyl acetals **20**, studied by Smit, represents an example of hydrogen bonding of acetals to HFIP, leading to an enhanced electrophilic species via polarised intermediates (Figure 2a).[31] While stabilisation of the polar transition state by HFIP is invoked, similar results were obtained when using 2-5 equivalents of HFIP in dichloromethane, suggesting a cooperative hydrogen bonding effect similar to that investigated by Berkessel.

b) Imine activation The addition of alkynes to imines in HFIP has been reported by Tehrani, leading to β-amino-ketones (see **23** in Figure 2b)[32] or allylic amines (not shown)[33] depending on the imine protecting group. The presence of the α,α-dichloro moiety is crucial for the intermediate to be sufficiently electrophilic in this solvent. Mechanistic experiments suggest protonation of the imine, followed by alkyne addition to afford a stabilised vinyl cation, which may be trapped by HFIP, before being hydrolysed to the final product.

c) Epoxide activation In an effort to find alternative ways of functionalising epoxides, Qu investigated the intra- and intermolecular Friedel-Crafts alkylation of electron rich arenes with epoxides **24** being activated by HFIP (Figure 2c). Remarkably, no catalyst was required and no reaction is observed in other commonly used solvents including toluene, acetone or acetonitrile.[34] The authors proposed an acid catalysed pathway involving concerted C–O bond cleavage and C–C bond formation, supported by an inversion of stereochemistry.

Later on the same group applied their methodology to epoxide initiated cation olefin polycyclisation reactions (see **26** to **27** in Figure 2c). Although HFIP promotes the reaction, the use of an excess of Ph_4PBF_4 resulted in an increased yield, from 40% to 60%, and rate of reaction, from 1 hour to 5 minutes. It is noteworthy that other fluorinated solvents, such as trifluoroethanol (TFE) or per-fluoro-*tert*-butyl alcohol (PFTB) do not catalyse this reaction at all.[35] The authors postulated that in HFIP the linear polyene adopts a more ordered conformation due to hydrophobic interactions.

d) Alcohols The metal-free substitution of allylic alcohols **28**, reported by Baeza and Nájera in 2012, represents one of the first examples of alcohol activation in HFIP (Figure 2d).[36] Nucleophiles including amines, sulfonamides and carbamates were used, affording allylic amines with modest to good yields. Additionally, C-C bond formation was achieved using allyl silanes, 1,3-dicarbonyl compounds or electron-rich aromatic compounds, in a Friedel-Crafts-type reaction. Note that identical products were obtained when different alkene geometries were used, suggesting double-bond isomerisation via an allyl cation intermediate.

Qu has applied the same concept to an intramolecular variant, reporting several examples of polyene cyclisation reactions using HFIP or a mixture of HFIP and water; for example a tertiary alcohol **30** was used to initiate the reaction (Figure 2d).[37]

e) Halides Although the effect of HFIP on activating halides had some precedent, the reported examples relied on a neighbouring activating group, e.g. a β-thioether.[38] However, Paquin has recently shown a very interesting Friedel-Crafts arylation of benzyl fluorides **32** with electron-rich arenes, via selective C-F bond activation using HFIP as a H-bond donor (Figure 2e).[39]

f) Sulfonates Denmark has studied the configurational stability of enantiopure bromonium and chloronium ions (see **36** in Figure 2f), generated *in-situ* from α-halosulfonates **34**.[40] The absolute configurational stability of halonium ions **36**, especially in the presence of olefins, where olefin-to-olefin transfer could occur, is of great importance for catalytic transformations where unreacted alkene is in excess with respect to the halonium intermediate. The intermolecular trapping of halonium ions was studied using different nucleophiles in the presence or absence of an external olefin, using HFIP because of its ionising power and low nucleophilicity. While enantiopure chloronium ions were found to be configurationally stable, even in the presence of an external olefin, bromonium analogues undergo enantiospecific reaction in the absence of external alkene, but an erosion of enantiopurity was observed in the presence of olefins.

g) Hypervalent iodine reagents Pioneering work from Kita has shown the powerful oxidising ability of hypervalent iodine reagents (HIR) in combination with HFIP, usually described as a polar, low nucleophilic solvent, with high ability to stabilise aromatic radical cations. However, recent developments from Donohoe and Compton allowed this assumption to be re-examined, in particular with respect to the role of HFIP in activating hypervalent iodine reagents.

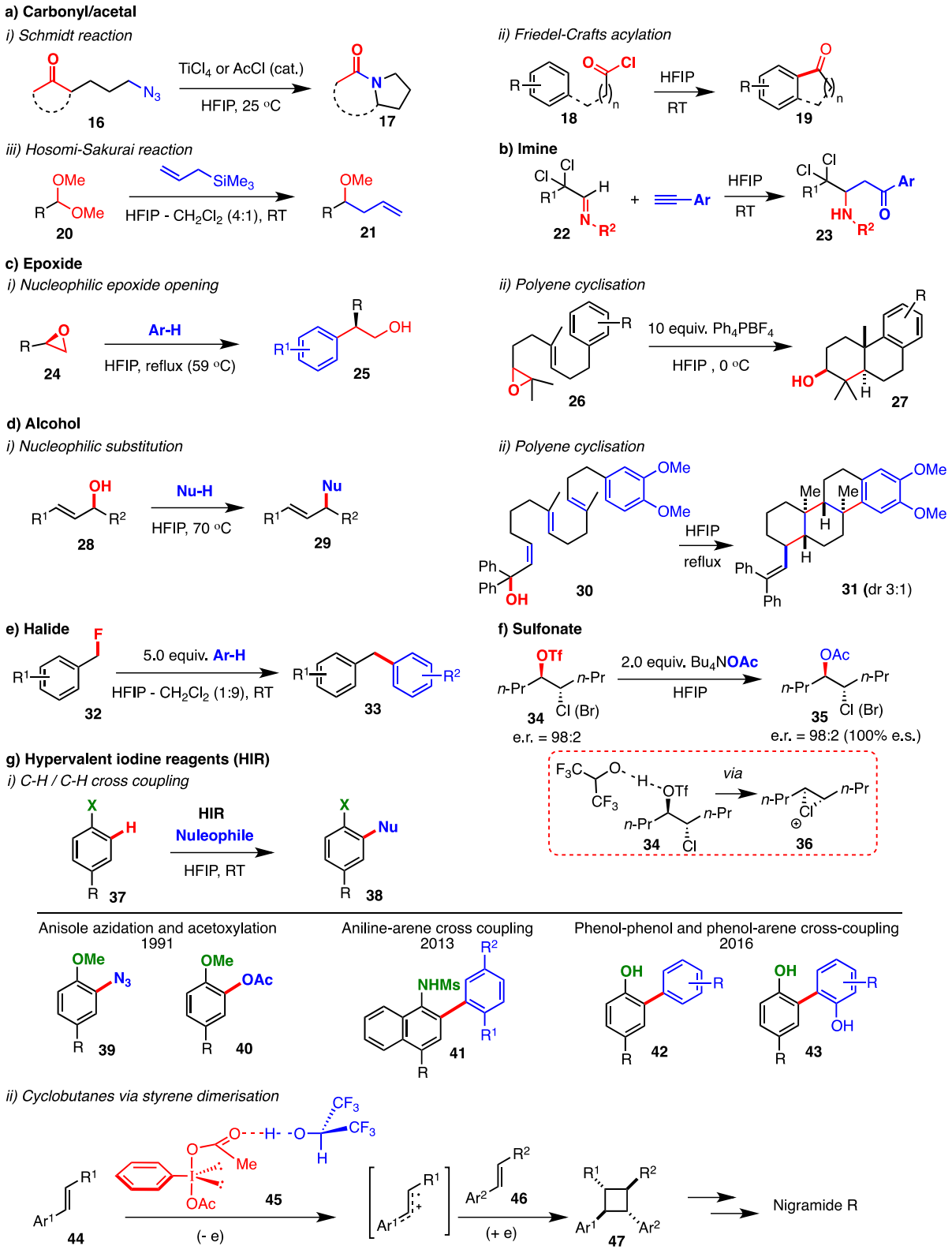


Figure 2: Selected examples for the reactivity of organic molecules, based on the functional group that HFIP can activate: a) carbonyl/acetals. b) imines. c) epoxides. d) alcohols. e) halides. f) sulfonates. g) hypervalent iodine reagents.

A seminal publication on the nucleophilic substitution of anisole derivatives using phenyliodine(III) bis(trifluoroacetate) (PIFA) in HFIP was significant in this field. Substrates bearing electron-donating groups reacted smoothly with $TMSN_3$ and TMSOAc in a net C-H oxidation process (see **39** and **40** from **37** in Figure 2g).[41] Preliminary mechanistic studies showed that the reaction proceeds via a radical cation intermediate, generated by single-electron transfer (SET). The authors invoke the formation of a charge transfer (CT) complex between the electron-rich aromatic ring and PIFA, however the reaction does not proceed in most common solvents (eg dichloromethane, *N,N*-dimethylformamide, tetrahydrofuran or methanol) and the role of HFIP as a unique solvent remained obscure.[42] This idea has been extended to oxidative C-H/C-H' cross coupling, using protected anilines (see **41** from **37** in Figure 2g)[43] and phenols (see **42** and **43** from **37** in Figure 2g)[44] in combination with electron-rich arenes, to generate functionalised biaryl compounds. The authors speculated that the coupling proceededvia a nitrenium intermediate for anilines or via phenoxyiodine(III) species in the case of phenols, although no mechanistic study was provided. Related biaryl synthesis via oxidative C-H/C-H cross coupling using electrochemical or Fe-catalysed methods in HFIP will be disclosed below. Generation of similar radical cations in HFIP using photolysis has also been reported.[45]

Finally, a highly diastereoselective synthesis of tetra-substituted cyclobutanes **47** via dimerisation of styrenes **44** and **46**, using hypervalent iodine reagents in HFIP, as a unique solvent for the reaction, has recently been reported by Donohoe (Figure 2g). The power of this methodology has been illustrated with a short synthesis of the natural product nigramide R.[46] Mechanistic studies, including electrochemical experiments in collaboration with Compton showed that the enhanced reactivity of the HIR in HFIP is due to its greater oxidising abilities in this fluorinated solvent. NMR experiments revealed the formation of a strongly H-bonded adduct **45** between the solvent and oxidising reagent, postulated as the physical origin of the altered synthetic reactivity.[47]

h) Metal-free C-H Activation: borylation and hydroxylation The diborylation of aromatic compounds commonly requires the use of expensive catalysts or ligands, rigorously inert conditions and provides only modest yields with poor regioselectivity. However, in 2016, Larionov reported a metal-free, regioselective, photoinduced dual C–H/C–X borylation approach to 1,2- and 1,3-diborylarenes (**49** and **50** respectively from **48** in Figure 3a).[48] In this work striking and complementary regioselectivities were observed upon a change of solvent from ^{i}PrOH to HFIP. Solvent effects are clearly important in this reaction, however it is noteworthy that the intrinsic bias of substituent groups can override these effects.

Very recently, Du Bois reported a new example of a catalytic C(sp^3)-H hydroxylation reaction using an oxaziridine as the active catalyst (see **52** from **51** in Figure 3b).[49] The process was shown to be highly selective for tertiary and benzylic C-H bonds, and afforded the corresponding alcohols in modest to excellent yields. The optimum solvent for this reaction was shown to be 9:1 HFIP-H_2O. The authors attributed increased active catalyst (an oxaziridine formed *in situ* from **53**) lifetime to the formation of HFIP microdroplets, protecting the catalyst from reduction in the presence of H_2O.

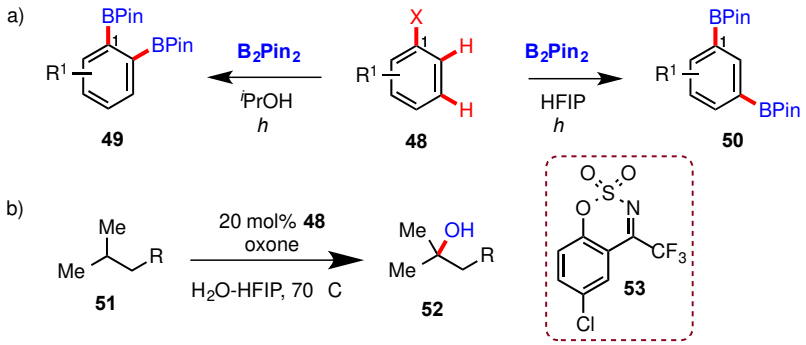


Figure 3: Selected metal-free C–H bond activation employing HFIP as a solvent. The use of fluorinated solvents in C–H bond activation processes, particularly HFIP, has become increasingly common in recent years, a) Photoinduced dual borylation of haloarenes; b) Organocatalytic C(sp^3)–H hydroxylation

4. Electrochemical methods

As mentioned above when discussing the physical and chemical properties of HFIP, the exceptional redox stability of HFIP has expanded its use in electrochemistry. Here we highlight the pioneering work by Waldvogel on C-H and N-H oxidative coupling and we predict that the union of synthetic organic electrochemistry with HFIP solvent will underpin much fruitful research in the future.

C-H and N-H electrochemical oxidative coupling

In 2009 Waldvogel reported the anodic coupling of phenols **54** using a boron doped diamond (BDD) electrode and HFIP; he faced the challenging problem of phenol self-coupling, whereby polymeric compounds are usually obtained.[50] The scope of the method was evaluated using different phenols, including sterically hindered ones or naphthols, with modest to good results (see **56** from **54** in Figure 4a). Although the specific role of HFIP is not clear, the authors speculate that its non-nucleophilic and protic nature enhances the stability of radical intermediates.

In a subsequent publication the same group extended their method to selective phenol-arene cross-coupling, establishing a new direction in this field (see **57** from **54** in Figure 4a). The main problems with the method revolved around the requirement for a large excess (10 equiv.) of arene partner, in addition to the low yields of the cross-coupling products, and the formation of arene-arene homo-coupling by-products.[51] Later on they found that the addition of substoichiometric amounts of MeOH led to an improvement of the cross-coupling isolated yield and the selectivity using a lower excess of cross-partner.[52] The addition of MeOH shifts the arene oxidation potential and also influences the HFIP clusters/solvates of the substrates involved.[53] In an effort to increase the substrate scope of the method the selective cross-coupling of two different phenols was accomplished by carefully choosing the appropriate substrates based on their redox potential (see **58** in Figure 4a).[54] Moreover two sequential C-H cross-couplings can be performed to access valuable *meta*-terphenyldiols (**59** in Figure 4a).[55]

One of the latest and most exciting contributions from the Waldvogel group relies on the electrochemical synthesis of pyrazolidin-3,5-diones **61** from protected anilines **60**, via anodic oxidation. A graphite anode in HFIP was used and an amidyl radical intermediate proposed (Figure 4b).[56]

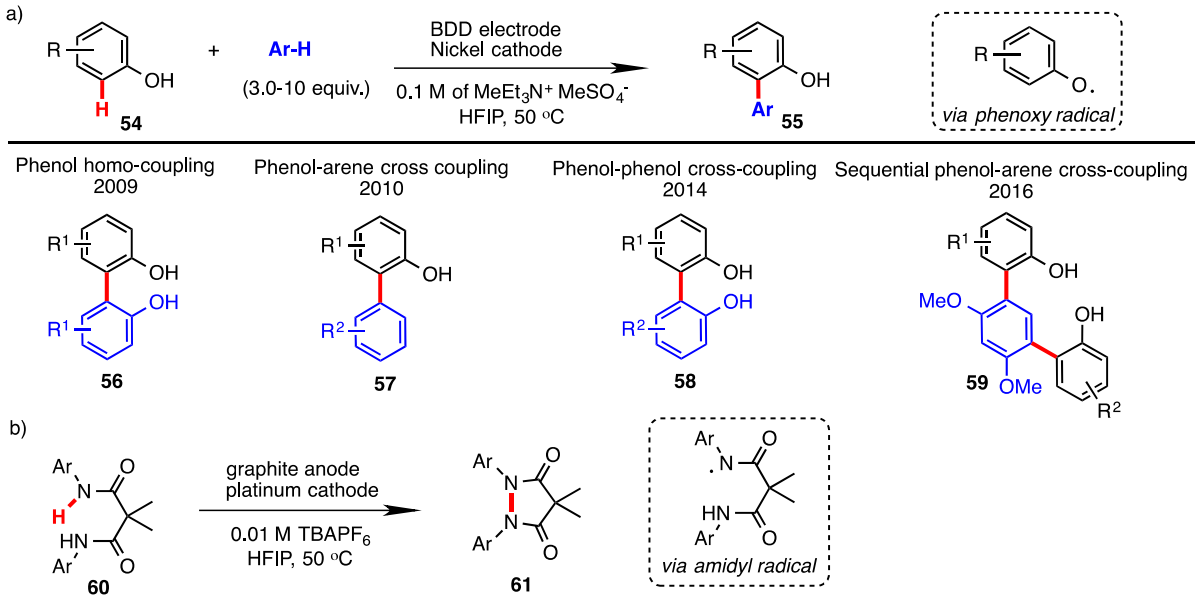


Figure 4: Selected oxidative C–H and N-H bond functionalization employing HFIP as a solvent. The use of HFIP in electrochemical processes has become increasingly common in recent years, for example in a) C–H oxidative homo- and cross-coupling of phenols; b) N-H oxidative coupling.

5. Organometallic and inorganic chemistry

As discussed above regarding the Schmidt reaction (Figure 2a), the use of HFIP in combination with metal complexes has some precedent. In this section, we will first illustrate metal-mediated C-H functionalisation, and then finish with the characterization and properties of complexes formed from organometallic species and HFIP.

a) Metal-catalysed C-H Activation The prevalence of C–H bonds in natural products and pharmaceutical compounds makes their functionalisation an attractive goal in organic synthesis. In recent years, considerable

evidence of fluorinated solvents, particularly HFIP, acting to promote C–H bond activation has been disclosed in the literature; however the origin of this effect has not been fully investigated.[57] We summarise herein some important examples.

i) Pd-mediated C-H oxidative functionalisation HFIP is commonly used as a solvent for C–H activation reactions employing weakly coordinating directing groups. For example, in seminal work by Yu, *meta*-C–H olefination was achieved using removable nitrile-containing templates in HFIP (see **64** in Figure 5a).[58] More recently, other workers in the field have used HFIP as a solvent for *para*-C–H activation reactions featuring similar directing groups (see **65** in Figure 5a).[59] Further examples of the importance of HFIP as a solvent include alkylether directed *ortho*-olefination (see **66** in Figure 5a)[60] and the *β*-arylation of thiophenes (see **67** in Figure 5a).[61] Recently, HFIP has been used as a solvent for the selective *N*-terminal C(sp^3)–H arylation of dipeptides (see **68** in Figure 5a), and it was shown that this solvent facilitated full conversion of the starting material.[62] In 2016, Yu reported the Pd(II)-catalysed *γ*-C(sp^3)–H arylation of ketones using transient amino acid-derived directing groups in HFIP/AcOH (see **69** in Figure 5a).[63] HFIP has also been found to be crucial in the enantioselective Pd(II)-catalysed arylation of aliphatic amide methylene C-H bonds, with enantiomeric ratios as high as 96:4 being reported (see **70** in Figure 5a).[64]

ii) Fe-mediated C-H oxidative functionalization In work that is related to the oxidative cross-coupling of phenols using hypervalent iodine reagents (Figure 2g) or electrochemical methods (Figure 4a), the group of Pappo has recently reported the Fe(III)-catalysed homo- and cross-coupling of phenols, in HFIP.[65] A similar pattern of reactivity is described, with HFIP modulating the oxidative potential of phenols, allowing for selective cross-coupling. Mechanistic studies were also performed,[66] focused on elucidating the origin of selectivity in the cross-coupling, and it was suggested that HFIP forms a hydrogen bonded complex with methoxy groups on one of the phenol partners (rather than the OH) so that a selective oxidation of the liberated phenol is then possible. Finally, an enantioselective version of this oxidative coupling has been reported (see **73**), using chiral BINOL-phosphates as ligands to form a chiral iron complex **74** (Figure 5a).[67]

Although commonly used as a solvent for Pd(II) and Fe(III) catalysed C–H activation reactions, HFIP has also found applications in reactions catalysed by Co(III)[68] and Rh(III).[69]

b) Non-classical hydrogen bonding between HFIP and transition metal complexes HFIP has also been found to act as a proton donor in dihydrogen bonding with a range of transition metal hydrides. Dihydrogen bonds (DHB) are medium strength, non-classical hydrogen bond between a metal hydride and a proton donor such as an –OH or –NH group, which slightly alter the electronic structure of metal complexes. This type of interaction is currently of great interest in organometallic chemistry, catalysis and biochemistry.

Extensive work from the Shubina group, in collaboration with others, has demonstrated the ability of HFIP to form DHB complexes with a number of early transition metal hydrides including niobium[70] (see **76** in Figure 5bi), iron, [71,72] ruthenium[71] and osmium[71,73] through numerous IR, NMR and computational studies. In the case of Fe, Ru and Os, it was noted that DHB strength increases down the group. Electron rich metal hydride complexes, such as those of Ru(II), Os(II) and Re(I), can form direct M-H-OR bonds to alcohols via d-electron lone pairs, although dihydrogen bonding is favoured kinetically.[72] The two bonding mode can be distinguished by IR and NMR spectroscopy. As an example of this, Shubina and Zanobini previously employed IR and NMR spectroscopy to study and characterise the strongly hydrogen bonded adduct [{(triphos)Ru(CO)(H)H}---{$HOCH(CF_3)_2$}] **78**, and found it to be in equilibrium with the non-classical η^2-H_2 complex $[(triphos)Ru(CO)H(H_2)]^+$ **79** (see Figure 5bii).[74] It is thought that M-H---HOR hydrogen bonded adducts are intermediates during proton transfer[72] in the formation of dihydrogen complexes and in the base-promoted heterolytic hydrogen splitting reaction.[75] Dihydrogen complexes have attracted some interest for hydrogen storage although the poor weight:H_2 complexation ratio and expense of many of the transition metals involved means that few applications have been realised so far.[76,77]

Boron hydrides are also capable of forming unusual hydrogen bonds with proton donors through their hydride ligands. Coordination of BH_4 to a transition metal complex gives rise to σ- complexes which are considered as intermediates in B- H bond activation, an important process in a number of reactions, for example hydroboration. The mechanism of proton transfer to transition metal η^1- BH_4 complexes depends on the ability of the metal to stabilise η^2- H_2 complexes. The interaction of [(κ^4- $P(CH_2CH_2PPh_2)_3$)RuH(η^1- BH_4)] with a range of alcohols, including HFIP, showed that the most stable DHB complex is formed by interaction with the terminal B- H however, protonation at Ru- H is favoured kinetically (**81** vs **82** in Figure 5e).[78] In the case of (triphos)Cu(η^1- BH_4), protonation is favoured at the terminal B- H over Cu- H due to the poor ability of copper to stabilize molecular hydrogen complexes. (see **80** in Figure 5biii).[79]

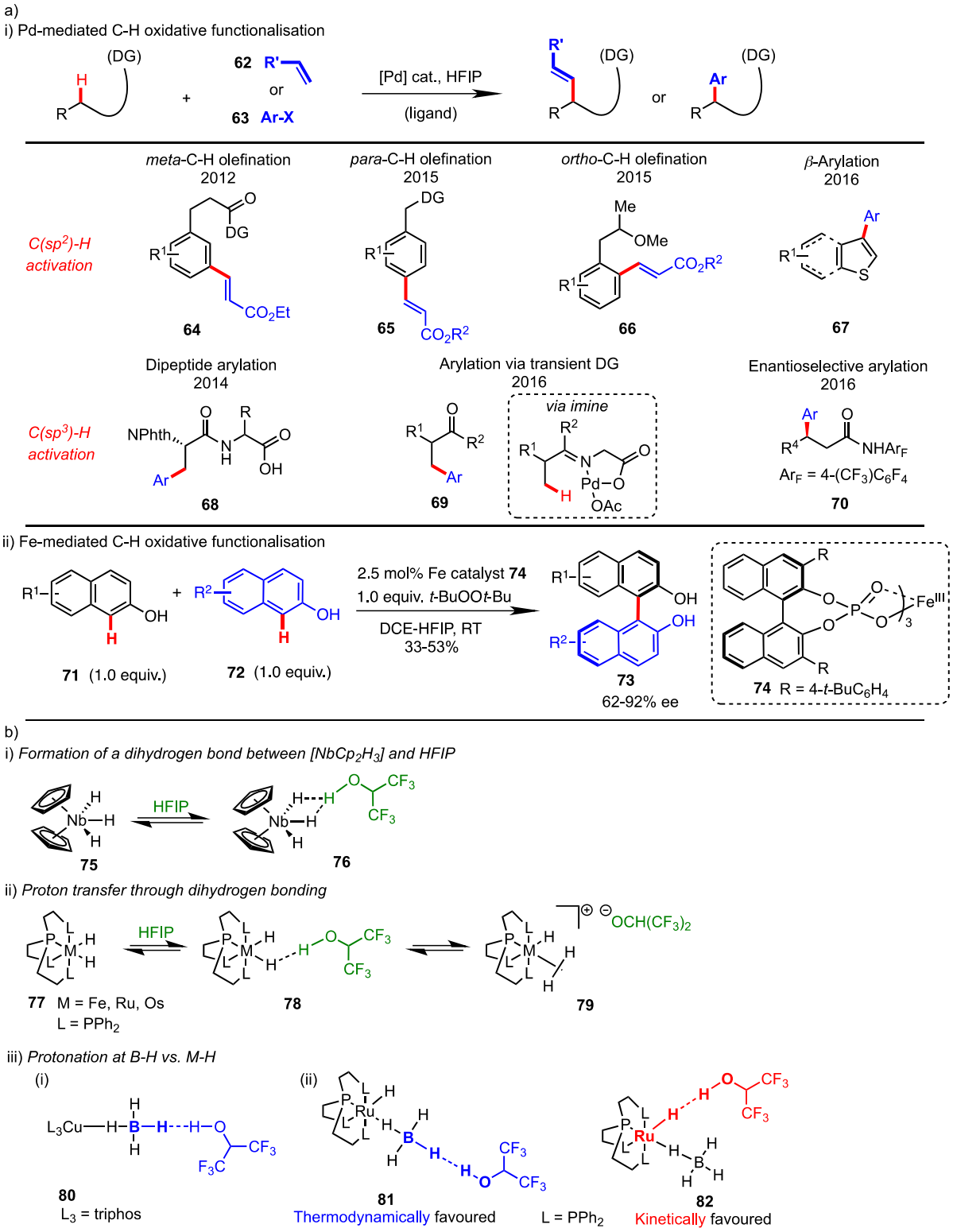
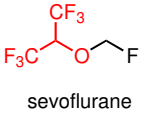


Figure 5: Selected examples of organometallic species used in combination with HFIP. a) Metal-catalysed C-H activation; b) non-classical hydrogen bonding between HFIP and transition metal complexes.

6. Chemistry and biology

a) HFIP: A primary metabolite of sevoflurane and a potential immunomodulatory drug



sevoflurane

HFIP is a primary metabolite of the widely-used inhalation anaesthetic sevoflurane.[80] Some volatile anaesthetics, such as sevoflurane, are known to provide beneficial effects in states

of hypoxia-reoxygenation and ischaemia-reperfusion associated with surgical procedures. This is thought to be due to an altered immune response which reduces the damaging inflammatory response in such situations.[81] Early work by Urner showed that the immunomodulatory effects of volatile anaesthetics are due to the presence of fluorinated carbon groups[82] and subsequently, Herrmann and coworkers postulated that HFIP could elicit a similar immunomodulatory response. Intraveneous administration of HFIP was shown to significantly improve survival rate in murine models of cecal ligation and puncture.[81] The most recent work demonstrates the effect of intraveneous HFIP administration in attenuating inflammation in rats, and found it to be equal, and in some measures superior, to inhaled sevoflurane.[82] This effect was attributed to reduced levels of proinflammatory mediators in plasma and tissue which leads to decreased white blood cell (neutrophil) invasion at the site of injury, hence attenuating apoptosis in internal organs. HFIP was also seen to help combat decreased blood pressure often associated with endotoxic shock, an effect not seen with sevoflurane treatment alone.

b) Use of HFIP in the investigation and determination of protein structure Fluorinated alcohols such as HFIP and TFE have been used in the study of protein structure and conformation for many years due to the solvent's ability to stabilise the secondary structure of peptides and also induce the formation of helices.[83,84,85,86] It is thought that clusters of HFIP molecules associate with the hydrophobic surface of an α-helix or β-strand in such a way that it mimics the interior of a lipid membrane or the interior of a folded protein.[83,87] There is also a possibility that the addition of fluoroalcohols to aqueous peptide solutions mimics hydrophobic collapse in the early stages of protein folding.[88] Chatterjee showed that the 20-residue artificial peptide Trp-cage is selectively solvated by HFIP in a HFIP/water system, and that the concentration of HFIP surrounding the protein may be 3 to 4 times higher than in the bulk solution.[89] Recent studies by Beck-Schimmer have also demonstrated that HFIP-protein interactions are short lived and diffusive, using the honey bee venom protein, melittin. **Error! Bookmark not defined.**

c) Transmembrane iron transport proteins Slc11a1 and Slc11a2 Studies of proteins in HFIP may also provide important structural insights to aid the development of new treatments. For example, the 3D structure of two key transmembrane domains of Slc11a1 have recently been elucidated using NMR and CD studies of aqueous HFIP protein solutions and it is hoped that the findings can also be applied to Slc11a2 which is highly similar.[83] Since Slc11a2 is found in the membrane of the small intestine and mediates iron absorbtion, a deficiency in this protein can lead to hypochromic microcytic anaemia.[90]

d) Membrane surfactant proteins

Membrane surfactant protein B (SP-B) is an important hydrophobic component of lung surfactant, and is essential for normal breathing. SP-B deficiency leads to conditions such as respiratory distress syndrome, which presents in premature babies and may also arise with illness or injury in adults. Artificial lung surfactants incorporating proteins such as SP-B have been shown to be a more effective treatment than protein‐free surfactant preparations. NMR and CD studies of SP‐B in both HFIP and sodium dodecyl sulfate (SDS) micelles have led to the assignment of the secondary structure of the C terminus. Whilst SDS is commonly chosen for its membrane‐mimetic properties, solutions of the peptide in HFIP may give a more accurate impression of the hydrophobic nature of the interior of a cell membrane.[91]

7. Supramolecular, materials and polymer science

a) Molecular tweezers 'Molecular tweezers' based on a bis[alkynylplatinum(II)] terpyridine have been developed by the group of Wang and utilised to develop a three-component supramolecular recognition system.[92] It was found that the addition and removal of trace amounts of HFIP to the chloroform solution of host **83**, platinum complex **84** and amide **85** caused a shift in binding preference between the two guest molecules. The ability of **83** to hydrogen bond to host **85** means that the interaction is drastically affected by solvent changes, and accordingly the binding strength of **83/85** was found to be more sensitive to HFIP than the binding of **83/84**. Addition of HFIP promotes strong hydrogen bonding to **85** and, therefore, **83** binds to **84**; removal of HFIP favours binding of **83** to **85** (Box 2a). This whole process was shown to be reversible for several cycles and may provide potential for development into a novel colourimetric and fluorescent sensor system, particularly if it can be expanded to recognition of bio- or environmental-related guests. This work is also exciting in the wider context of molecular switches, machines and devices.

b) HFIP in Radical Polymerisation Reactions Radical polymerisation is a widely used technique in the industrial production of polymeric materials[93] and in particular, controlled/'living' radical polymerisations (CRP) have received a lot of attention in the literature. Single electron transfer-living radical polymerisation (SET-LRP) was reported by Percec and co-workers[94] and has significant benefits over traditional CRP methods,

for example, only very small amounts of catalyst are required, and the polymerisation is very fast and leads to high molecular weight and low polydispersity.[95] The ability to control precisely molecular weight and tacticity is important because this greatly affects the physical properties of polymers such as toughness, thermal resistance and optical properties.[94]

HFIP has become increasingly widely used due to its ability to simultaneously improve control over the molecular weight and stereoregularity of the resultant polymers and has been studied by several groups. For example, Okamoto found that fluoroalcohol solvents, in particular HFIP, have a profound effect on the rate and tacticity in the free-radical polymerisations of a number of vinyl esters when compared to traditional solvents such as THF.[96] Xiulin Zhu's group have been at the forefront of this field, and have investigated the effects of HFIP on a number of copper(0) catalysed CRPs. Early work on the SET-LRP of methyl methacrylate (MMA) showed that HFIP gave rise to a 'living' polymerisation with enhanced control over molecular weight and tacticity when compared to common solvents such as DMSO and DMF.[97] The authors suggest that this may be due to coordination of HFIP to the catalytic copper species, creating a more effective catalyst and further decreasing the energy barrier to polymerisation. In fact, a similar complex was observed by mass spectroscopy during the study of the atom transfer radical polymerisation of MMA by Okamoto in 2006. It was also postulated that HFIP may be effective at solvating intermediate radical anions, thus further facilitating polymerisation.

Further examples from Zhu and co-workers include the polymerisation of 4-vinylpyridine (4VP),[98] and 2-vinylpyridine (2VP, Box 2b).[99] In both cases HFIP was seen to give low poly dispersity index (PDI) and good control over molecular weight, which was largely attributed to hydrogen bonding between HFIP and the monomer. In addition, enhanced syndiotactic-specificity was observed for 4VP and was thought to be due to the bulk of HFIP closely associated with the 4VP units. This gives rise to steric interactions between the growing chain and incoming monomer, thus forcing syndiotactic propagation.

The Zhu group have also applied their knowledge to the polymerisation of *N*-vinylpyrrolidine (NVP), and found that the use of HFIP greatly enhanced reactivity, again thought to be due to hydrogen bonding interactions, and led to a well-controlled RAFT polymerisation. This use of HFIP to effectively tune the properties of monomers provides exciting scope for the development of future processes and to access polymers with diverse properties, which previously may not have been possible.[100]

c) Polymerisation of pinene β-Pinene, which is readily extracted from turpentine, is the monomer of the important polymer poly-β-pinene (PBP). Smit and co-workers discovered that PBP could be furnished quickly, and in near quantitative yield, by the simple mixing of β-pinene and HFIP (Box 2c). The weight averaged molecular weight (M_w) of the resulting polymer was found to be significantly higher and also less varied than that made by traditional Lewis-acid catalysed cationic polymerisation processes. [101] However, α-pinene, also isolated in large quantities from turpentine, cannot be polymerised directly. Kamigaito and co-workers have recently developed a selective ring-opening radical polymerisation of pinocarvone, which is easily obtained from α-pinene by visible light photooxidation (Box 2d). Pinocarvone was polymerised quantitatively in HFIP, using AIBN as a radical initiator. The resulting chiral polymer features α,β-unsaturated ketones along the backbone which provide scope for further manipulation.[102]

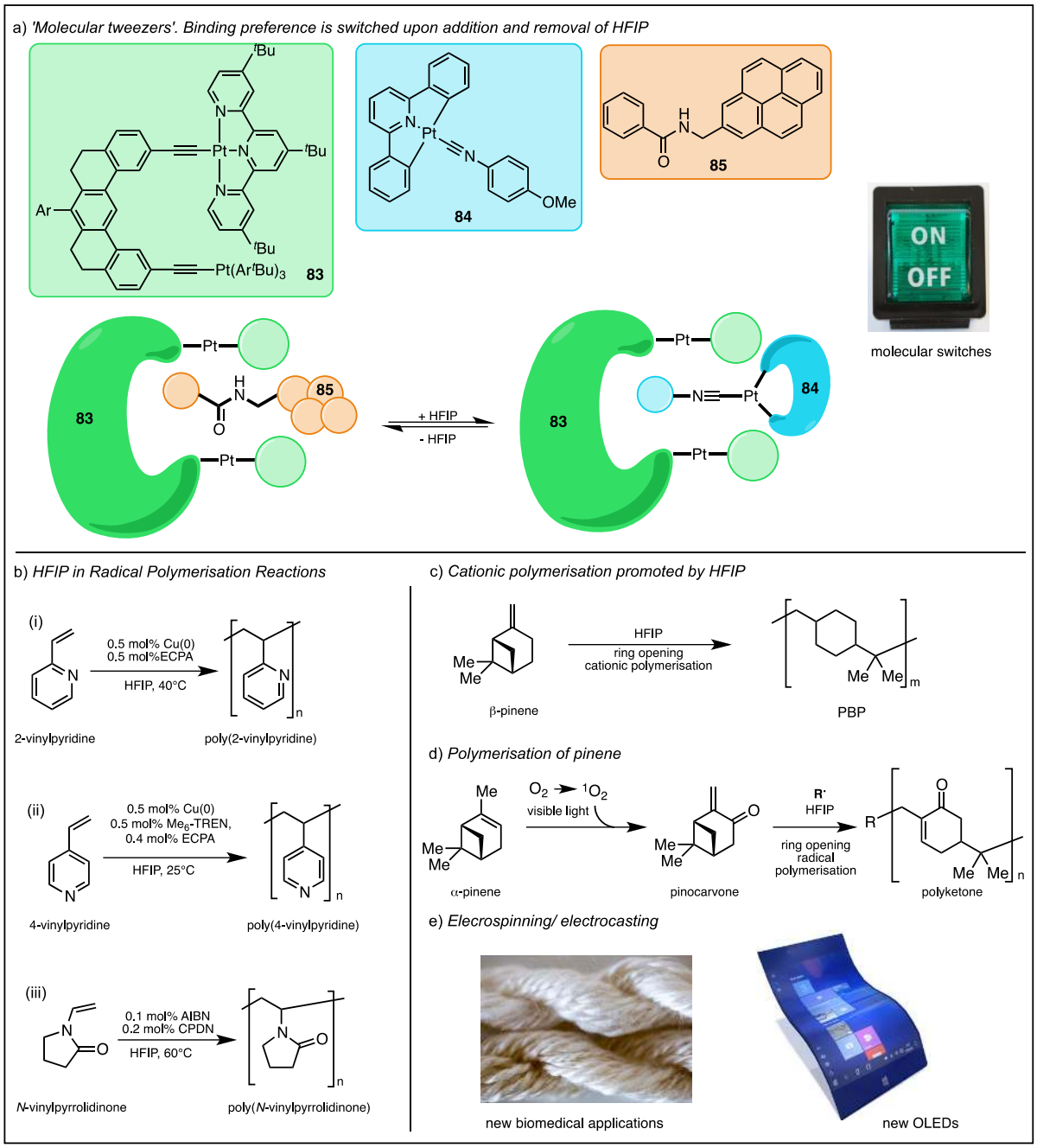
d) Cationic polymerisation promoted by HFIP Cationic polymerisation of styrene and its derivatives, using HFIP as the sole proton source and reaction solvent was also developed by Smit and coworkers.[103] To negate the poor reactivity of styrene, the addition of catalytic amounts of more easily polymerised alkenes, such as β-pinene, *p*-MeO-styrene, or *p*-Me_2N-styrene gave reasonable yields of the corresponding mixed polymers (Box 2d). Since HFIP has relatively low Bronsted acidity, the proton transfer step required to initiate polymerisation was postulated to involve a cluster of HFIP molecules. Further to this work, the authors subsequently discovered that the polymerisation of styrene and indene could also be promoted by catalytic quantities of *p*-anisaldehyde dimethyl acetal or benzaldehyde dimethyl acetal in HFIP solution.[104]

e) Electrospinning/Electrocasting A further use of HFIP lies in the polymers and materials field as a solvent for the electrospinning of nanofibres of materials such as silk fibroin [105,106,107] and poly(lactic-co-glycolic acid) (PGLA),[108] to form scaffolds and woven mats which are useful in many biomedical applications. Although the effects of using HFIP as a solvent for these applications are not well understood, it often produces materials with significantly different properties to those spun from other solvents.[107,108] For example Asukura and coworkers prepared porous scaffolds using silk fibroin derived from either sucrose/HFIP or sodium chloride/water systems, which were then used to study cartilage growth. It was found that the sucrose/HFIP system gave a smoother and thinner pore wall but with a less microporous internal architecture which proved to be beneficial for cartilage formation.[105]

DNA-surfactant complexes can also be spun or cast into fibres or films from HFIP solution. Sotzing and coworkers found that the complex of DNA with cetyltrimethylammonium (CTMA) cast from HFIP was

aligned out of the plane of the film, whilst casting from butanol resulted in the DNA-CTMA lying along the plane. These differences were attributed to stronger hydrogen bonding between DNA and HFIP than butanol, which disrupted inter-strand hydrogen bonding and led to better solvation and a more expanded structure. Additionally, the DNA-CTMA cast from HFIP was found to have significantly improved dielectric properties which may impact its applications in devices such as organic light emitting diodes (OLEDs), quantum dots and organic field-effect transistors (Box 2e).[109]

Box 2: Supramolecular, polymer and materials chemistry that is influenced by HFIP solvent.



8. Future perspectives

Understanding the unusual properties of HFIP, which are sometimes more extreme than commonly assumed will allow a rational search for new applications of this compound. Uncovering the interaction of HFIP with functional groups within organic molecules or with metal complexes may reveal new modes of activation that will lead to new modes of reactivity. In particular, taking advantage of the strong hydrogen-bonded complexes formed with certain molecules could reveal very interesting properties in the field of chemical biology and polymer science. Supramolecular chemistry will surely find use for such an interesting solvent and/or additive as HFIP, as evidenced in the section above. We predict that many exciting and wide-ranging applications of HFIP will appear in the future, providing ever more opportunities to harness the unique properties of this fluorinated alcohol.

Acknowlegements

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