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Progress in organocatalysis with hypervalent iodine catalysts

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Hypervalent iodine compounds as environmentally friendly and relatively inexpensive reagents have properties similar to transition metals. They are employed as alternatives to transition metal catalysts in organic synthesis as mild, nontoxic, selective and recyclable catalytic reagents. Formation of C–N, C–O, C–S, C–F and C–C bonds can be seamlessly accomplished by hypervalent iodine catalysed oxidative functionalisations. The aim of this review is to highlight recent developments in the utilisation of iodine(III) and iodine(V) catalysts in the synthesis of a wide range of organic compounds including chiral catalysts for stereoselective synthesis. Polymer-, magnetic nanoparticle- and metal organic framework-supported hypervalent iodine catalysts are also described.

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1. Introduction

The major challenge of synthetic organic chemistry in the 21st century is the selective synthesis of target compounds in an efficient and economical way using mild reaction conditions. The most striking approach in environmentally benign

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Fateh V. Singh

Fateh V. Singh was born in Ravani Katiry, Bulandshahr, UP, India in 1976. He completed his Masters in Chemistry at SSV College, Hapur, UP, India in 1998. He received his PhD in 2007 under the supervision of Dr Atul Goel, CSIR-CDRI, Lucknow, India. After the completion of his doctoral studies, he was in Prof. H. A. Stefani's research group at USP, São Paulo, Brazil for more than two years. In 2010, he joined as a Marie Curie postdoctoral fellow with Prof. Thomas Wirth at Cardiff University, UK and learned various new reactions regarding organoselenium and hypervalent iodine chemistry. He subsequently stayed with Prof. G. Mugesh at IISc Bangalore, India for more than one year. In 2014, he started his independent career and joined VIT Chennai as an Assistant Professor. His research group is interested in new organoselenium and hypervalent iodine catalysts for organic synthesis.

Samata E. Shetgaonkar

Samata E. Shetgaonkar was born in Morjim, Pernem, Goa, India in 1992. After completing her MSc in Chemistry at Goa University, Goa, India, in 2015, she completed her PhD at VIT Chennai under the supervision of Dr Fateh V. Singh. She has published more than 15 research papers during her doctoral research studies. Her research interest mainly involves the synthesis of novel hypervalent reagents and their application in organic synthesis.

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reactions is the development of catalytic strategies in the synthesis of organic molecules. Over the past few decades, hypervalent iodine reagents have emerged as efficient organocatalysts for the oxidative transformations of a wide range of organic substrates.[1–5] These reagents are mild, non-toxic, moisture resistant, inexpensive and often recyclable. These properties make them ideal eco-friendly reagents to be employed for various organic transformations.[6,7] Several reviews,[6,8–22] book chapters[23–27] and books[28–31] have been published in the past years emphasising the progress and development of hypervalent iodine chemistry.

Prominent features of hypervalent iodine compounds are their oxidising properties and their electrophilic nature. They are commonly used as stoichiometric oxidants which makes them attractive candidates for the replacement of toxic heavy-metal oxidants.[6] Moreover, hypervalent iodine reagents have been extensively used in the total synthesis of natural products and their intermediates.[32] Representative examples of various hypervalent iodine reagents are shown in Fig. 1. For example, (diacetoxyiodo)benzene **1** and [bis(trifluoroacetoxy)-iodo]benzene **2** are used as efficient oxidants in many organic transformations such as oxidation of alcohols, alkenes or organosulfides,[33,34] rearrangements,[35] cyclisations[36,37] and transition metal-catalysed C–H bond functionalisations[38,39] and alkene difunctionalisations.[40,41]

(Dichloroiodo)benzene **3** is a chlorinating reagent[7] while [hydroxy(tosyloxy)iodo]benzene **4** (Koser's reagent) can be used for α-oxytosylations of ketones.[42–44] Owing to the electrophilic and excellent leaving nature of diaryliodonium salts **5**, they are employed as versatile arylating agents in coupling reactions by reacting with suitable nucleophile.[45] Cyclic hypervalent iodine(III) reagents such as 2-iodosobenzoic acid **6** (IBA) is synthesised by the oxidation of 2-iodobenzoic acid and less explored due to its poor reactivity.[46] Trifluoromethyl benziodoxolone **7** was developed by Togni's research group as

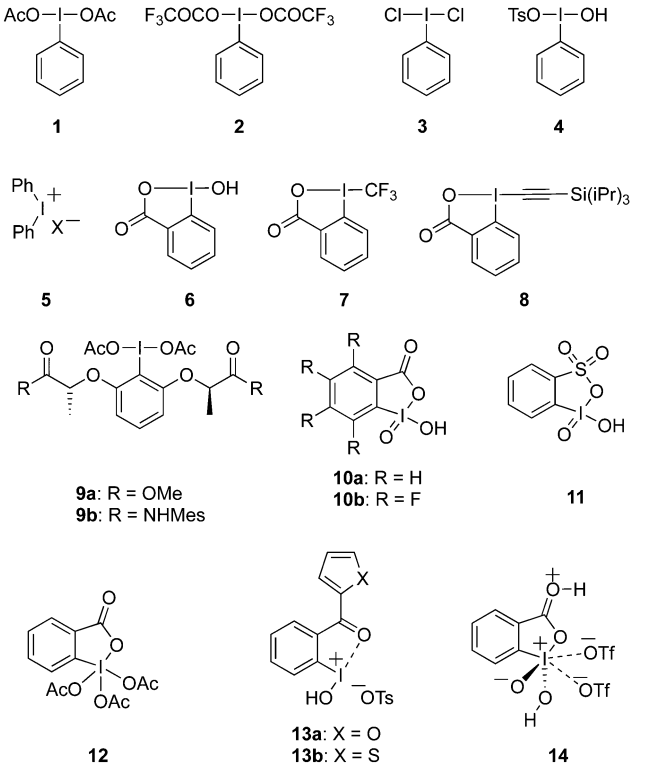

Fig. 1 Examples of hypervalent iodine(III)/(V) reagents **1–14**.

Manjula Krishnan

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Thomas Wirth

Thomas Wirth is a professor of organic chemistry at Cardiff University. He received his PhD after studying chemistry at Bonn and the Technical University of Berlin. After a postdoctoral stay at Kyoto University as a JSPS fellow, he worked independently at the University of Basel before taking up his current position at Cardiff University in 2000. He has been invited as a visiting professor to a number of places such as Toronto, Tokyo, Osaka and Kyoto. He was awarded the Werner Prize from the New Swiss Chemical Society, the Furusato award from JSPS London, the Wolfson Research Merit Award from the Royal Society and the Bader Award from the Royal Society of Chemistry and was elected as a Fellow of The Learned Society of Wales. His main interests of research concern stereoselective electrophilic reactions, oxidative transformations with hypervalent iodine reagents and flow chemistry performed in microreactors.

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trifluoromethylation reagent for the transfer of CF_3 moiety to the organic molecules.[47,48] Zhdankin and coworkers reported the synthesis of 1-[(triisopropylsilyl)ethynyl]-1λ^3,2-benziodoxol-3(1*H*) TIPS-EBX **8** as an efficient alkyne transfer reagent to various substrates.[49] Later on Waser and coworkers published a review article in which they have compiled the application of other benziodoxole-based reagents.[50]

Chiral hypervalent iodine reagents in stereoselective synthesis have made an impressive developments in recent times.[12] The first chiral reagent was prepared by Pribram[51] in 1907 followed by many more optically active iodine(III)/(V) compounds which have been employed in asymmetric transformations.[12] For example, Ishihara and his team reported the preparation of lactate-based C_2-symmetric chiral iodine(III) reagents **9a–b** and their use in enantioselective spirolactonisations of 1-naphthol derivatives with high selectivities.[52] Furthermore, pseudocyclic hypervalent iodine compounds is another interesting class containing additional non-covalent coordination at the iodine center.[53]

Iodine(V) reagents such as 2-iodoxybenzoic acid (IBX) **10a** and FIBX **10b**, 2-iodoxybenzenesulfonic acid (IBS) **11** and Dess–Martin periodinane (DMP) **12** are routinely used as oxidising agents in a variety of oxidative transformations including oxidation of alcohol moieties and other functional groups.[54,55] Recently, Wirth and his team synthesised pseudocyclic iodine(III) reagents containing furan and thiophene units **13a,b** and proved their oxidising nature in various oxidative transformations.[56] Very recently, Zhdankin and co-workers reported the synthesis of a powerful iodine(V) oxidant, 2-iodoxybenzoic acid bistriflate **14**, by reacting IBX with trifluoromethanesulfonic acid and illustrated its potential application in the direct oxidation of hydrocarbons.[57]

Hypervalent iodine reagents have properties resembling those of transition metals and can be employed as environmentally sustainable alternatives to transition metal catalysts such as mercury, lead and thallium reagents.[58,59] Within this context, copious synthetic procedures have been developed using achiral or chiral iodine(III)/(V) pre-catalysts in the presence of stoichiometric oxidants such as *m*CPBA, oxone, peracetic acid and molecular O_2, *etc.* which play a significant role in the *in situ* generation of active catalytic species such as hypoiodite, trivalent, or pentavalent hypervalent iodine species.[3] The utility of hypervalent iodine reagents as catalyst was introduced by Fuchigami and Fujita in 1994 during the electrocatalytic fluorination of dithioacetals (Fig. 2).[60] Initially, the progress of hypervalent iodine catalysis was not quite encouraging as it relied mainly on electrocatalysis that required a particular relation in the oxidation potential of catalyst and substrate to generate the active hypervalent iodine catalyst.[61] To overcome the limitation, some inorganic oxidants were tested to generate the catalytic species but success was quite limited.[62–64] Later on a remarkable success of hypervalent iodine catalysis was achieved with the use of organic oxidants to generate the catalytic species *in situ*.[3] As a sequel to the review published by our group in 2014,[3] we highlight herein the use of hypervalent iodine catalysts in synthetic transformations since 2014.

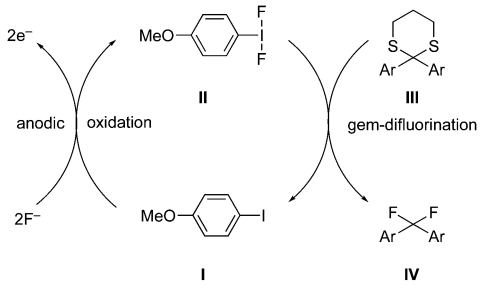


Fig. 2 Iodine(III)-catalysed *gem*-difluorination of dithioketals **III** using *in situ* generated iodine(III) catalytic species **II** by anodic oxidation of 4-methoxyiodobenzene **I**.

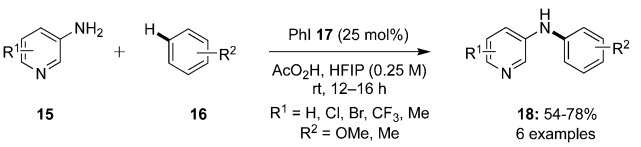
2. Aminations

Amines have widespread uses in many facets of our lives and are present not only in natural products, but also play a vital role in medicinal chemistry. Metal-free approaches for the synthesis of amines through C–H aminations using hypervalent iodine reagents as catalysts were initially developed by the research groups of Chang,[65] DeBoef[66] and Antonchick.[67]

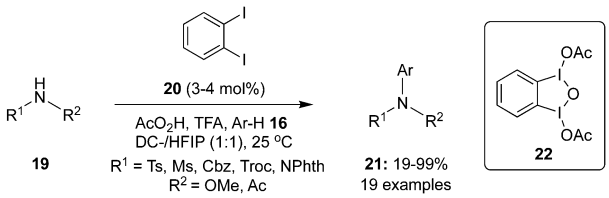
2.1. C–H amination of arenes

2.1.1. Intermolecular C–H amination of arenes. C–H Aminations of arenes is a common reaction catalysed by an active hypervalent iodine catalytic species under mild reaction conditions. A novel metal-free route for the amination of simple electron-rich arenes **16** with 3-aminopyridine derivatives **15** using iodobenzene **17** as catalyst in the presence of peracetic acid as oxidant was developed by Antonchick and co-workers (Scheme 1).[68] The desired arylated 3-aminopyridines **18** were formed in good yields. Notably, the amination of electron-deficient arenes was not observed.

Later, Muñiz and co-workers employed 1,2-diiodobenzene **20** as the pre-catalyst for an intermolecular C–H amination of substituted arenes **16** using *N*-disubstituted amines **19** as nitrogen sources and peracetic acid as oxidant (Scheme 2).[69]



Scheme 1 Iodine(III)-catalysed amination of arenes **16** with 3-aminopyridine derivatives **15** using peracetic acid as an oxidant.



Scheme 2 Iodine(III)-catalysed C–H amination of arenes **16** with **19** using **20** as precatalyst.

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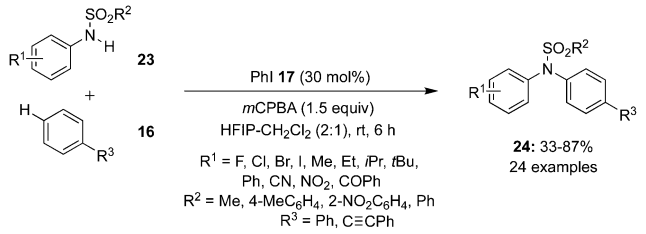


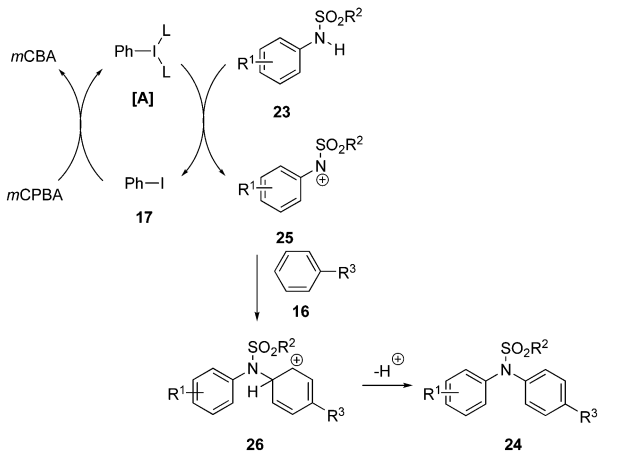
Scheme 3 Iodine(III)-catalysed *N*-arylation of **23** with **16** using iodobenzene **17** as pre-catalyst.

The reaction performed remarkably well even at reduced catalyst loadings of 3–4 mol%. The interesting feature of this catalytic approach is the successful amination of electron-deficient arenes. However, the amination products of electron-deficient arenes **16** were obtained in poor yields compared to other arenes. Mechanistic studies revealed the formation of μ-oxo-bridged bisiodine(III) derivative **22** upon oxidation of 1,2-diiodobenzene with peracetic acid.

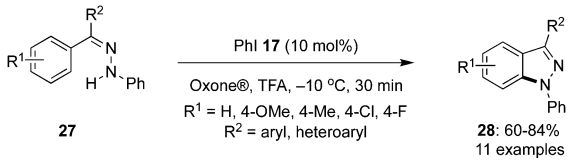
The concept of soft–hard acid–base (SHAB) theory was introduced in the N–H arylation of sulfanilides **23** by Mal and Maiti. The catalytic system comprises of iodobenzene **17** as the pre-catalyst and *m*CPBA as oxidant (Scheme 3).[70] Sulfanilides with electron donating and sulfonyl groups like $-SO_2Ph$, –Ts and –Ns were tolerated and amination products **24** were isolated in moderate to excellent yields.

The proposed catalytic cycle for the *N*-arylation of **23** with **16** is shown in Scheme 4. Nitrenium ion **25** is a soft electrophile and generated from the interaction between sulfanilide **23** and iodine(III) species [A].[71] The newly generated nitrenium ion **25** interacts with electron rich arenes and undergoes an electrophilic aromatic substitution to furnish arylated amines **24** *via* generating carbocation intermediate **26.** The regenerated iodobenzene **17** is further oxidised to the iodine(III) compound **[A]** re-entering the catalytic cycle.

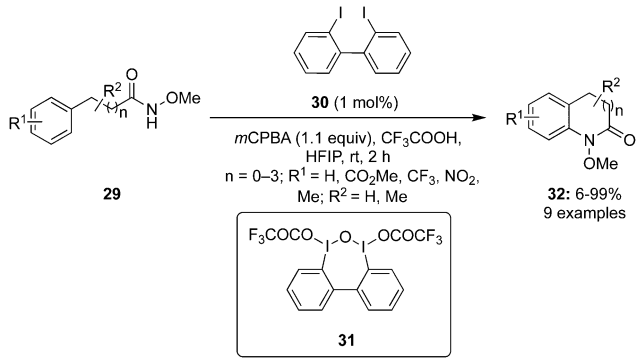
2.1.2. Intramolecular C–H amination of arenes. Tanimori's research group reported an iodine(III)-catalysed intramolecular oxidative C–H amination of aryl hydrazones **27** to provide *N*-arylsubstituted 1*H*-indazoles **28** with iodobenzene **17** as pre-catalyst in the presence of Oxone® and TFA (Scheme 5).[72] Aryl hydrazones **27** with electron-withdrawing as well electron-donating groups afforded the desired products **28** in moderate to good yields. However, hydrazones with terminal nitrogen atom without substituents or with substituents that destabilize the nitrenium ion intermediate were not tolerated. They also successfully demonstrated a one pot process for the synthesis of indazoles without isolating the intermediate hydrazone **27** using benzophenone and phenyl hydrazine as precursors in the presence of acid catalyst under the optimal conditions.



Scheme 4 Catalytic cycle for the iodine(III)-catalysed *N*-arylation of **23** with **16** to **24** using iodobenzene **17** as pre-catalyst.



Scheme 5 Iodine(III)-catalysed intramolecular oxidative C–H amination of aryl hydrazones **27** to **28**.



Scheme 6 Hypervalent iodine-catalysed C–H amination of aryl amides **29** for the synthesis of benzolactams **32**.

In 2022, Kita and co-workers designed an efficient method to synthesize benzolactams **32** *via* an intramolecular C–H amination of aryl amides **29** using biaryl-based iodoarene precatalyst **30**.[73] The reaction involves the *in situ* generation of μ-oxo hypervalent iodine compound **31** through the oxidation of iodoarene **30** using *m*CPBA as oxidant (Scheme 6). When 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was used as solvent, the desired benzolactams **32** were obtained in higher yields. Addition of CF_3COOH (2.0 eq.) significantly boosted the production of **32.** Notably, other pre-catalysts such as iodobenzene, 4-iodotoluene and 4-iodoanisole were found unsuitable to catalyse this oxidative C–H amination reaction. Aryl amides **29** substituted with nitro, trifluoromethyl or ester functionalities were tolerant to the catalytic conditions. Moreover, the synthesis of five-, seven-, and eight-membered benzolactams was achieved successfully in excellent to good yields using this protocol.

An interesting intramolecular C–H amination of aryl substituted amides **33** to functionalized lactams **35** was developed

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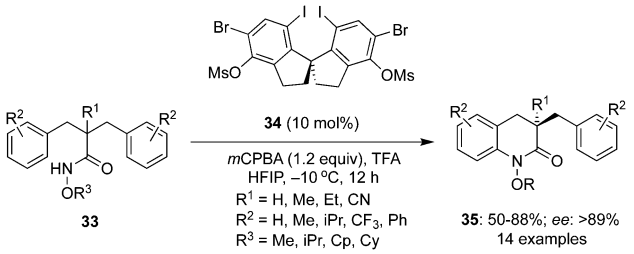


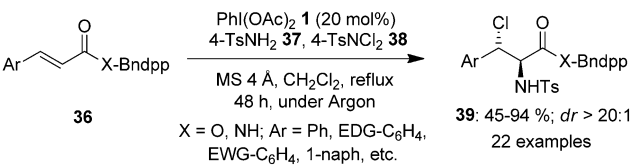
Scheme 7 Intramolecular C–H amination of aryl substituted amides **33** followed by desymmetrisation using **34** as chiral pre-catalyst.

by involving chiral diiodospirobiindane precatalyst **34** in the presence of *m*CPBA by Cai and co-workers (Scheme 7).[74] The key feature of the reaction was the amination of amides along with desymmetrisation. Amides with cyclopentoxy substituents on the nitrogen gave the desired lactams **35** with better enantioselectivities than with other alkoxy substituents. The substrate scope was further corroborated with other functional groups R^2 on the aryl moiety.

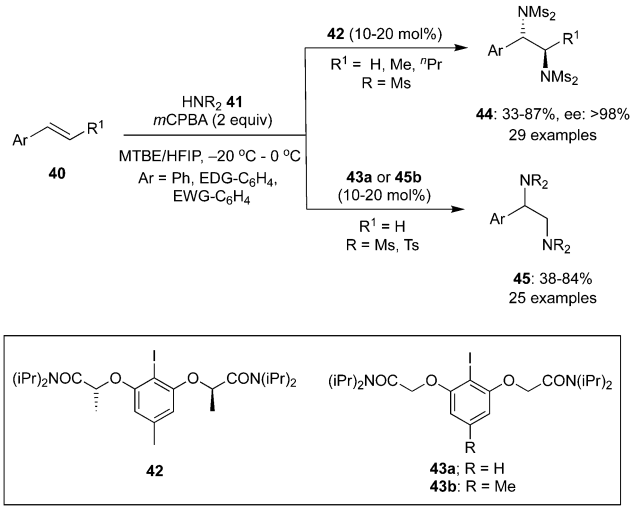
2.2. Amination of alkenes

2.2.1. Intermolecular amination of alkenes. The amination of alkenes is a useful reaction providing easy access to different aliphatic amines. In 2022, a methodology of group-assisted purification (GAP) was adopted by Ali and co-workers for the regioselective and stereoselective synthesis of vicinal chloroamines **39** from electron-deficient cinnamates and cinnamamides **36** tethered with benzyldiphenylphosphine oxide (Bndpp) group as the GAP candidate (Scheme 8).[75] The reaction was carried out by refluxing GAP anchored substrates **36** in the presence of 4 Å molecular sieves, $PhI(OAc)_2$ **1** as catalyst, 4-$TsNH_2$ **37** and 4-$TsNCl_2$ **38** as the nitrogen and chlorine source, respectively, in dichloromethane under argon atmosphere. This protocol tolerated an array of functional groups providing products **39** in good yields. The benefits of this method are the simple and cost-effective purification technique which requires only a wash of the crude mixture with inexpensive solvents such as petroleum ether, as well as the recyclability and reusability of GAP auxiliary.

Vicinal diamines are a significant class of compounds in the biopharmaceutical field. Enantioselective diaminations of alkenes is typically performed with palladium, copper and titanium catalysts,[76–78] and lately Muñiz and colleagues have established an inexpensive route for the intermolecular diamination of styrenes **40** with bissulfonimides **41** as nitrogen source utilizing achiral as well as chiral aryl iodides as catalysts



Scheme 8 Iodine(III)-catalysed stereoselective amino chlorination of GAP anchored cinnamates and cinnamamides **36**.

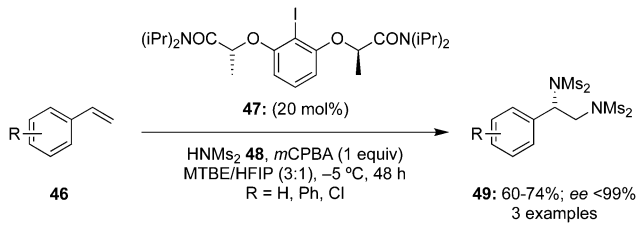


Scheme 9 Iodine(III)-catalysed vicinal diamination of styrenes **40** to **44** and **45** using pre-catalysts **42** and **43**, respectively.

(Scheme 9).[79,80] They described the first iodine(III)-catalysed enantioselective intermolecular diamination of styrenes **40** using chiral aryl iodide **42** as catalyst.[79] *anti*-Diamines **44** were obtained in moderate to good yields with high enantiomeric excess from both terminal as well as substituted styrenes. Using achiral aryliodines **43a** or **43b**, irrespective of the position of substituents, styrenes **40** with various electron donating and electron withdrawing groups afforded diamine products **45** in good yields.[80] In addition to styrenes, diamination of (*E*)-stilbene proceeded to afford diamines in moderate yield while allylbenzene produced the corresponding diamine in excellent yield.

Later, the same group developed a scale-up protocol for the synthesis of aryliodine precatalysts **47** and successfully applied it to the diamination of functionalised terminal styrenes **46** using $HNMs_2$ **48** as nucleophile and *m*CPBA as oxidant (Scheme 10).[81] Amination products **49** were obtained in moderate to good yields with high enantiomeric excess (up to 99% ee).

2.2.2. Intramolecular amination of alkenes. Wirth and co-workers employed a novel pyridine-based chiral iodine(I) catalyst **51** in the enantioselective intramolecular diamination of homoallylic guanidine and diaminosulfone derivatives **50** to bicyclic products **52** in the presence of sodium perborate and



Scheme 10 Iodine(III)-catalysed vicinal diamination of terminal styrenes **46** using C_2-symmetric chiral iodoarene **47** as pre-catalyst and $HNMs_2$ **48** as nitrogen source.

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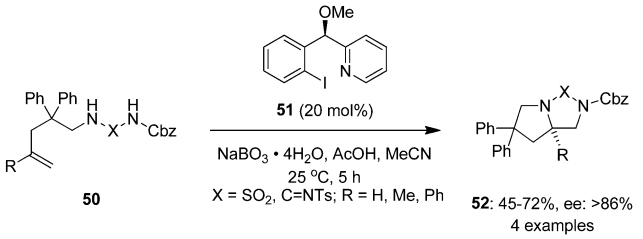
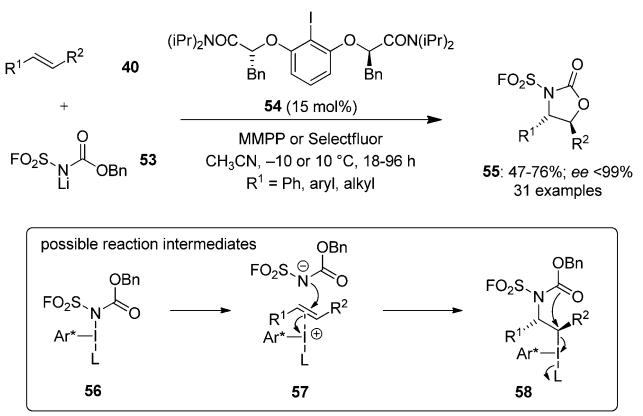


Scheme 11 Enantioselective intramolecular diamination reactions of **50** to yield **52** using chiral precatalyst **51**.

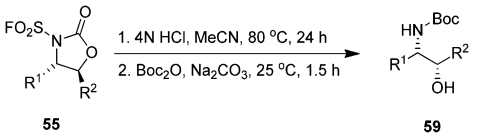
acetic acid in acetonitrile (Scheme 11).[82] Lactate-based catalysts of type **9** were found to be inefficient in this reactions. The protecting group in **52** could be removed to provide free diamines through reduction using lithium aluminium hydride.

2.3. Oxyamination of alkenes

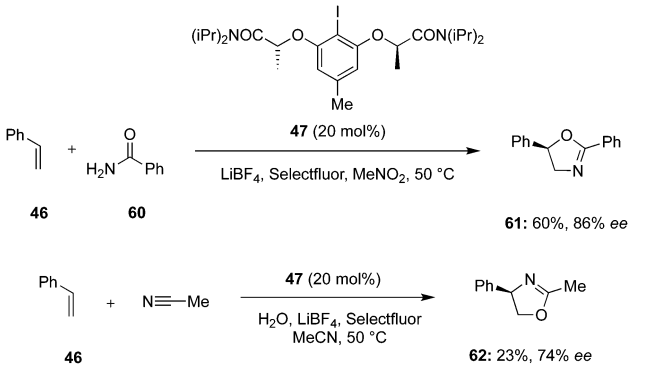
2.3.1. Intermolecular oxyamination of alkenes. During the last years, attention has been focused on the development of oxyamination reactions using hypervalent iodine catalysis. Wata and Hashimoto developed a protocol for an enantioselective oxyamination of aryl- or alkyl-substituted alkenes **40** using organoiodine(I/III) catalysis.[83] The use of *N*-(fluorosulfonyl)carbamate **53** as bifunctional *N*,*O*-nucleophile was considered as a critical element in this reaction. Chiral organoiodine catalyst **54** was found indispensable to achieve good turnover and high enantioselectivity. Notably, the use of magnesium monoperoxyphthalate hexahydrate (MMPP) as oxidant gave high product yields for electronically neutral or slightly electron-poor vinylarenes whereas Selectfluor was found optimal for electron-deficient or *ortho*-halogenated vinylarenes. The reaction proceeds *via* formation of intermediates **56–58** (Scheme 12). Carbamate **53** reacts with *in situ* generated hypervalent iodine to form intermediate **56**, which converts into intermediate **58** *via* formation of an alkene-coordinated iodonium intermediate **57**. Finally, the intermediate **58** cyclises intramolecularly to yield product **55** by the nucleophilic attack of oxygen and regenerates the chiral iodoarene **54**.



Scheme 12 Hypervalent iodine-catalysed enantioselective oxyamination of aryl- or alkyl-substituted alkenes **40**.



Scheme 13 Acid-mediated deprotection and ring opening of cyclic product **55** to amino alcohol **59**.



Scheme 14 Iodine(III)-catalysed intermolecular amination of styrene **46**.

The oxyaminated products **55** can be easily deprotected to yield free β-amino alcohols **59** in good yields without loss of enantioselectivity (Scheme 13).[83] Chiral β-amino alcohols are interesting reaction intermediates in the field of organic synthesis.

Lei and others designed a regiodivergent and regioselective intermolecular oxyamination of styrene **46** using the combination of chiral C_2-symmetric iodoarene **47** and Selectfluor as oxidant (Scheme 14).[84] Oxidation of chiral iodoarene **47** by Selectfluor and subsequent salt metathesis with $LiBF_4$ leads to the *in situ* generation of the active hypervalent iodine(III) reagent. Using amide **60** as *O*- and *N*-source and nitromethane as solvent, the desired regioisomeric oxazoline product **61** was obtained in 60% yield with 86% ee. On the other hand, the regioisomeric addition product **62** was obtained in 23% yield (74% ee) by employing acetonitrile and water as the nucleophiles.

2.3.2. Intramolecular oxyamination of alkenes. In 2021, Deng *et al.* reported an iodine(III)-catalysed intramolecular oxyamination of alkenes **63** containing an amide functionality using Ts_2NH **41** as an external nitrogen source. Optimisation results showed that 2,6-dimethoxy iodobenzene **64** provided the best catalytic activity in the presence of *m*CPBA as an oxidant (Scheme 15).[85] A variety of *N*-aryl, *N*-benzyl and *N*-methoxyl substituted pentenamides smoothly underwent this transformation, affording desired oxyamination products **65** in good yields and with high regioselectivity. Additionally, substrates with cycloalkyl rings provided spiro-tetrahydrofuranyl methanamine products in high yields.

An intramolecular oxyamination of γ,δ- and δ,ε-unsaturated esters **66** and *N*-allyl amides **70** was developed with benzyl *N*-(fluorosulfonyl)carbamate **67** as an exogenous nitrogen source using hypervalent iodine catalysis (Scheme 16).[86] Selectfluor

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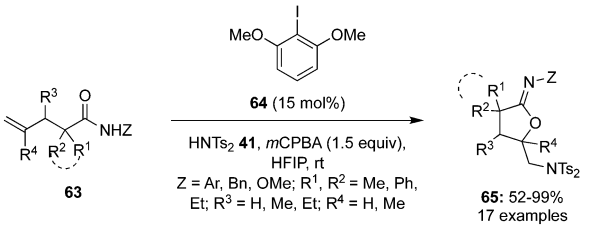
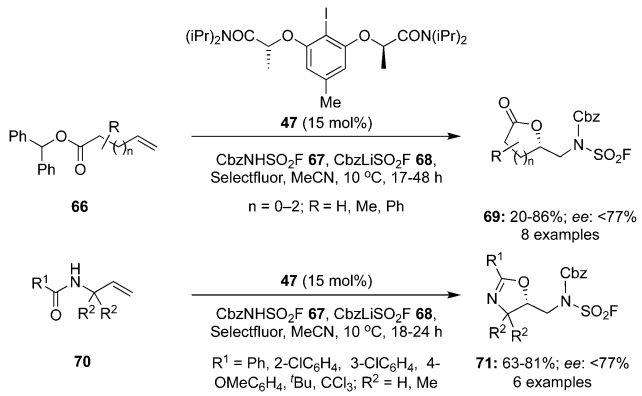


Scheme 15 Iodine(III)-catalysed intramolecular oxyamination of terminal alkenes **63** to functionalized furans **65** using $HNTs_2$ **41** as a nitrogen source in the presence of precatalyst **64**.

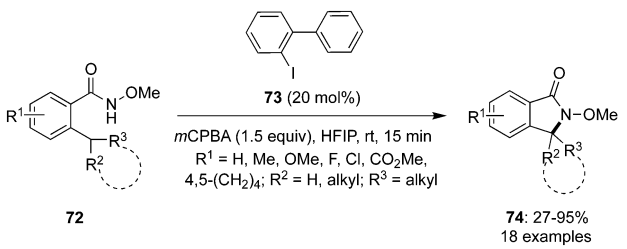


Scheme 16 Iodine(III)-catalysed intramolecular oxyamination of unsaturated esters **66** and *N*-allyl amides **70** using benzyl *N*-(fluorosulfonyl)carbamate **67** as an exogenous nitrogen source.

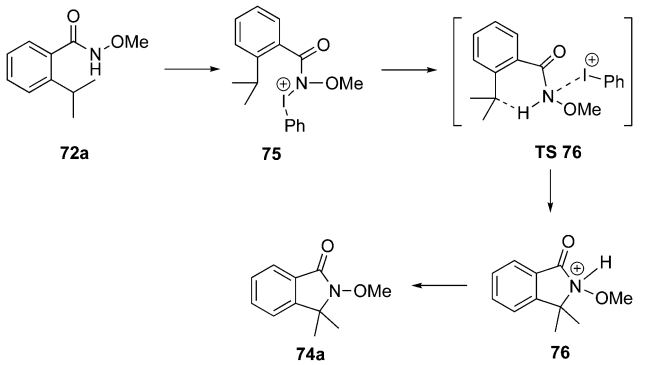
was found as the best oxidant for these aminations. Various functional groups were tolerated under the given reaction conditions and the corresponding lactones **69** and oxazolines **71** in good yields with up to 77% enantiomeric excess. Moreover, the protecting group of the aminated products was removed to make free amino compounds under acidic conditions without losing any selectivity.

2.4. C–H amination at sp^3 carbon

Shi and co-workers developed an intramolecular sp^3 C–H amination of *ortho*-substituted *N*-methoxy benzamides **72** for the synthesis of γ-lactams **74** catalysed by an iodine(III) species generated *in situ* by using catalytic amounts of iodoarene **73** in the presence of *m*CPBA (Scheme 17).[87] Among the various



Scheme 17 Iodine(III)-catalysed intramolecular sp^3 C–H amination of *N*-methoxy benzamides **72** to compounds **74**.



Scheme 18 Proposed mechanism for iodine(III)-catalysed intramolecular sp^3 C–H amination of *N*-methoxy benzamides **72** to compounds **74**.

iodoarenes investigated, 2-iodobiphenyl **73** emerged as a good pre-catalyst. The reaction proceeded smoothly with electron-neutral and electron-deficient substrates, while electron-rich substrates gave poor yield. The amination reaction worked well for cyclic as well as acyclic tertiary C–H bonds and due to the high energy barrier, a direct amination of secondary C–H bonds was not observed. Notably, the amination at chiral centres worked smoothly and it was found to be stereospecific.

The mechanism for the amination of *ortho*-substituted *N*-methoxy benzamides **72** to γ-lactams **74** is given in Scheme 18. The mechanism was proposed based on the DFT calculations for the reaction of benzamides **72a** with PIDA **1**.[87] Reaction is initiated with the formation of an iodonium intermediate **75** which converts into the protonated lactam **76** *via* the transition state **TS 76** involving a hydride shift, followed by C–N bond formation. Finally, the protonated lactam **76** undergoes deprotonation to give amination product **74a**.

2.5. Imination of benzylic C–H

In 2019, Mal and co-workers reported an intramolecular oxidative C–N bond formation *via* C–H imination reaction at sp^3 carbon centre. During these imination reactions, the synthesis of 1,2-disubstituted benzimidazoles **78** was achieved from dibenzyl amines **77** using two different catalytic systems, one with the conventional iodobenzene **17** as precatalyst[88] (Scheme 19, Method A) and the second with tetrabutylammonium iodide as precatalyst (Scheme 19, Method B).[89] The amination reaction proceeded through hydrogen elimination, two hydrogens from the highly acidic benzylic C(sp^3) and the remaining two from the aryl-N(sp^3). Symmetrical dibenzyl amines afforded a single isomer of benzimidazoles but unsymmetrical dibenzyl amines produced a mixture of isomers as major product being the imination at benzylic centre substituted with electron rich arenes.

3. Oxidation reactions

3.1. Oxidation of alcohols

3.1.1. Oxidation of primary and secondary alcohols. Oxidation of alcohols is traditionally an indispensable reaction of

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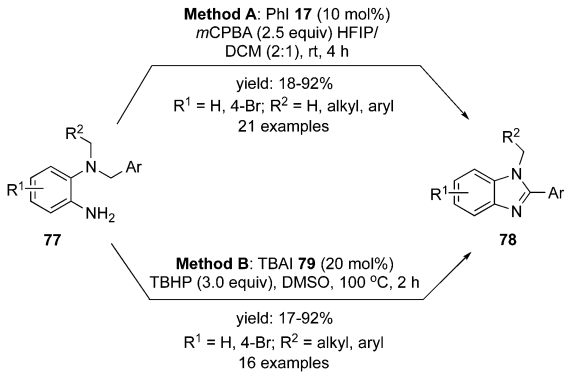
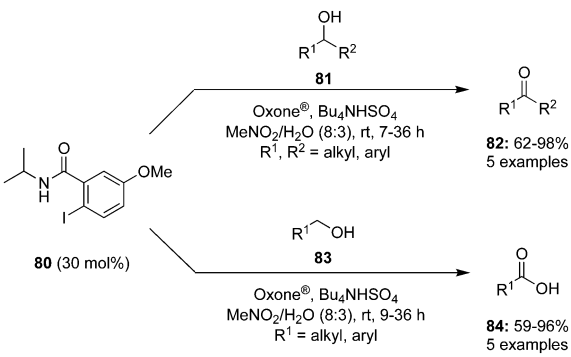


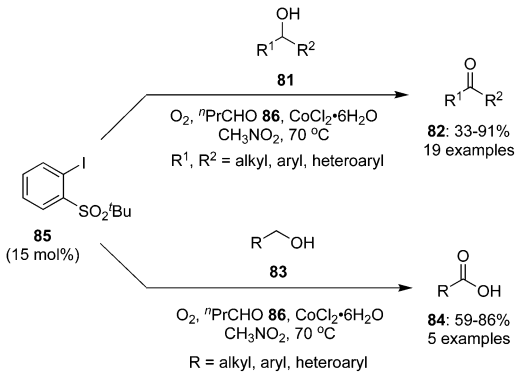
Scheme 19 Iodine(III)-catalysed C–H imination reaction of amines **77** to benzimidazoles **78**.

organic synthesis as it provides synthetically valuable carbonyl compounds. Hypervalent iodine catalysis was employed for the oxidation of alcohols for the first time in 2005.[90] Since that first report, various iodine(III) and iodine(V) catalysts have been developed for the oxidation of alcohols.[3] An eco-friendly protocol for the oxidation of primary and secondary alcohols was developed at room temperature by using 2-iodo-*N*-isopropyl-5-methoxybenzamide **80** as a catalyst with Oxone® and Bu_4NHSO_4.[91] Secondary benzylic and aliphatic alcohols **81** afforded the corresponding ketones **82** in good to excellent yields and primary alcohols **83** were converted to the corresponding carboxylic acids **84** in moderate to excellent yields (Scheme 20). During the oxidation of primary alcohols, the corresponding aldehydes were not observed probably due to the presence of water in the reaction.

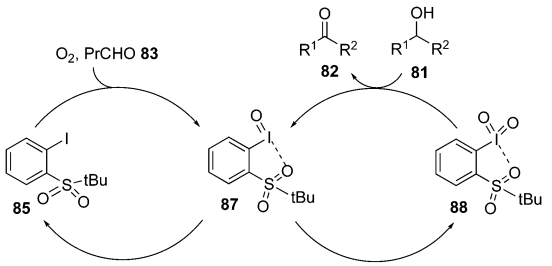
In another report, an iodine(V)-catalysed aerobic oxidation of secondary alcohols **81** to the corresponding ketones **82** was achieved in good to excellent yields catalysed by 2-*tert*-butylsulfonyl-iodobenzene **85** in the presence of *n*-butyraldehyde **86** and $CoCl_2{\cdot}6H_2O$ (Scheme 21).[92] The role of $CoCl_2{\cdot}6H_2O$ was to initiate the aldehyde-promoted aerobic oxidation of precatalyst **85** to generate the iodine(V) species *in situ*. In case of aromatic secondary alcohols, both electron rich and electron deficient derivatives were tolerated. The oxidation of primary alcohols **83** gave the carboxylic acids **84**.



Scheme 20 Oxidation of secondary **81** and primary **83** alcohols using **80** as precatalyst.



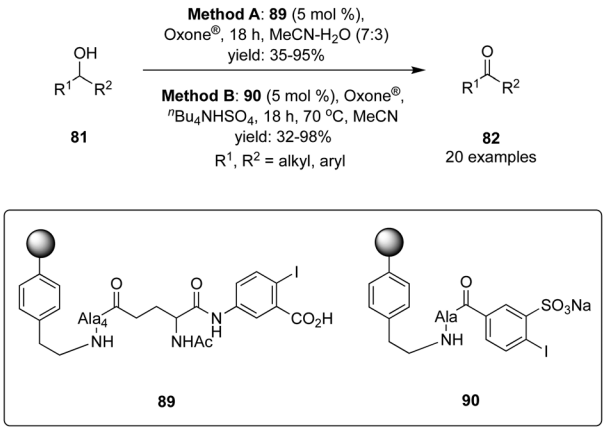
Scheme 21 Iodine(V)-catalysed oxidation of alcohols **81** and **83** to corresponding carbonyl compounds **82** and **84**, respectively using **85** as precatalyst.



Scheme 22 Catalytic cycle for the iodine(V)-catalysed aerobic oxidation of alcohols **81** to ketones **82** using **85** as precatalyst.

The proposed catalytic cycle for the above oxidation process is shown in Scheme 22. Initially, the aldehyde-promoted aerobic oxidation of precatalyst **85** occurred to form iodosylbenzene **87** followed by disproportionation to generate iodylbenzene **88**. Iodine(V) intermediate **88** then oxidises the alcohol **81** to ketone **82** and regenerates **87**, which on disproportionation forms the active catalytic iodine(V) species **88**.[91]

Polymer-supported hypervalent iodine pre-catalysts **89** and **90** were synthesised by Kirsch and Ballaschk and revealed their potential application in the oxidation of secondary alcohols **81** to corresponding ketones **82** (Scheme 23).[93] The primacy of this



Scheme 23 Iodine(V)-catalysed oxidation of alcohols **81** to corresponding ketones **82** using pre-catalyst **89** or **90**.

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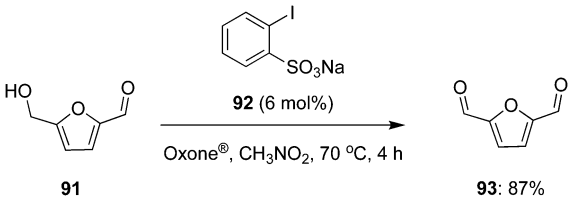


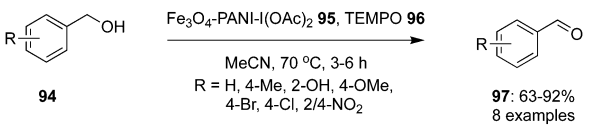
Scheme 24 Iodine(v)-catalysed selective oxidation of HMF **91** to **93** using **92** as precatalyst.

green synthesis is the multiple reusability of the catalyst without losing much catalytic activity and easy work-up. A wide range of secondary alcohols including cyclic, bicyclic and benzylic alcohols were tolerated. Phenols and amines are vulnerable to these catalytic conditions. Furthermore, the catalytic oxidation with IBS-derived catalyst **90** proceeds faster and cleaner compared to IBX-derived catalyst **89**.

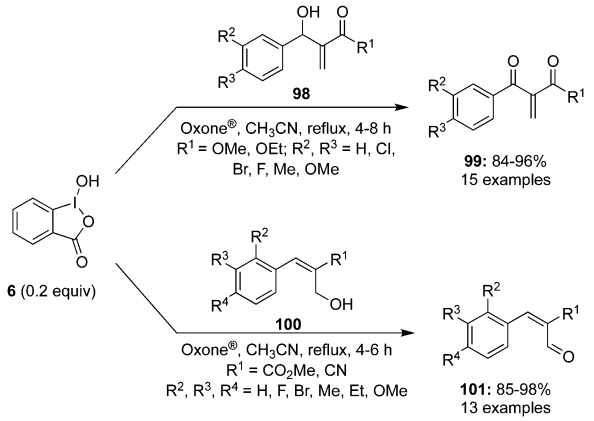
In 2020, Enderlin and co-workers demonstrated a simple and extremely efficient iodine(v)-catalysed gram scale synthesis of 2,5-diformylfuran **93** (87% yield) by the partial oxidation of 5-hydroxymethylfurfural (HMF) **91** using sodium 2-iodobenzenesulfonate **92** as precatalyst, Oxone® as oxidant and nitromethane as solvent. A notable feature of this process is its simple work-up procedure involving only filtrations and extractions to obtain **93** in high purity (Scheme 24).[94]

Nemati and co-workers designed and developed a hypervalent iodine(III) based heterogeneous nano-catalyst using magnetic polyiodoaniline nano-composite, Fe_3O_4-PANI-I(OAc)$_2$ **95** for the selective oxidation of functionalised benzyl alcohols **94** to corresponding aldehydes **97** in the presence of TEMPO **96** as oxidant and acetonitrile as solvent (Scheme 25).[95] A wide range of electron-withdrawing and donating groups were tolerated to give the corresponding benzaldehydes in desirable yields without the formation of any by-product. The key feature of this nano-composite precatalyst is its stability and reusability for five consecutive cycles.

3.1.2. Oxidation of allylic alcohols. Rao and co-workers described the catalytic use of 2-iodoxybenzoic acid (IBX) **11** generated *in situ* by the oxidation of 2-iodosobenzoic acid (IBA) **6** using Oxone® as an oxidant. During these oxidations, allylic alcohols **98** are oxidised to the corresponding ketones **99**.[96] Various electron-withdrawing and donating substituents on the aromatic moiety of the secondary alcohol were tolerated. Even the internal allylic alcohols **100** afforded the cinnamyl aldehydes **101** in excellent yields under the same reaction conditions (Scheme 26). The benchmark of this green reaction is that



Scheme 25 Iodine(III)-catalysed selective oxidation of benzylalcohols **94** to aldehydes **97** in the presence of Fe_3O_4-PANI-I(OAc)$_2$ nano-composite **95**.



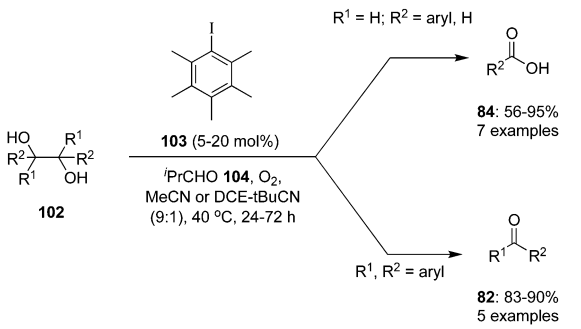
Scheme 26 Iodine(v)-catalysed oxidation of terminal allylic alcohols **98** and internal allylic alcohols **100** to corresponding carbonyl compounds **99** and **101**, respectively.

the precatalyst can be recovered by simple filtration and there was no side product observed during these oxidations.

3.1.3. Oxidation of 1,2-diols. Hypervalent iodine catalysis in the presence of molecular oxygen was used for glycol scission of 1,2 diols **102** by Uchiyama and coworkers.[97] By optimizing the reaction conditions, isobutyraldehyde **104**, pentamethyliodobenzene **103** and acetonitrile emerged as the best O_2 mediator, catalyst and solvent, for the cleavage of diols. Mono- and di-substituted diols **102** (R^1 = H; R^2 = aryl, alkyl, H) and various dihydrobenzoins were smoothly cleaved to give the corresponding carboxylic acids **84**. Notably, tri- and tetra-substituted diols **102** (R^1, R^2 = aryl, alkyl) afforded desired ketones **82** even in air or in the dark (Scheme 27). The efficiency of the reaction can be enhanced by premixing the aldehyde and O_2 before the addition of the substrate.

3.2. Oxidation of phenols

The oxidation of phenolic compounds is usually known as the dearomatisation of phenols. The oxidative dearomatisation of phenols is one of the common reaction of hypervalent iodine(III) reagents. Both internal and external nucleophiles have been employed during these oxidation reactions which



Scheme 27 Iodine(III)-catalysed oxidation of 1,2-diols **102** using pentamethyl iodobenzene **103** as precatalyst in the presence of molecular O_2 as oxidant.

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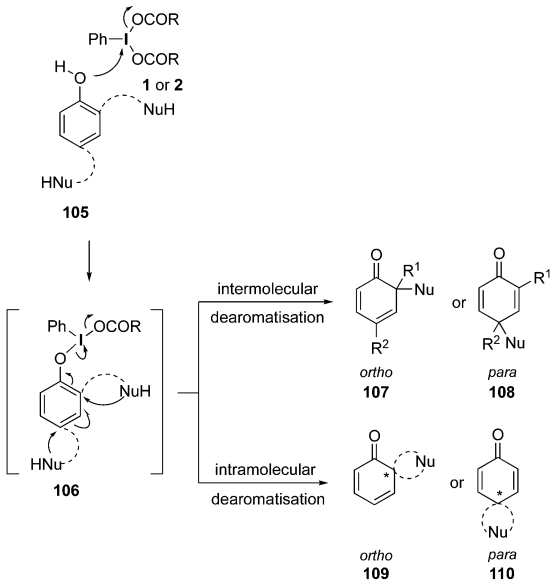
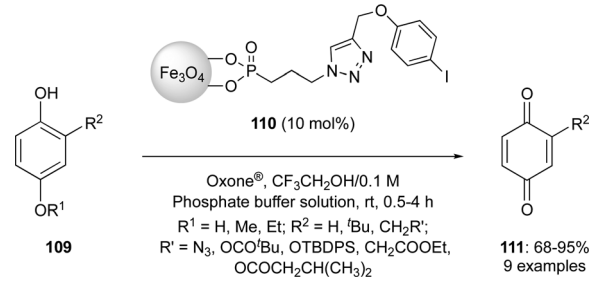
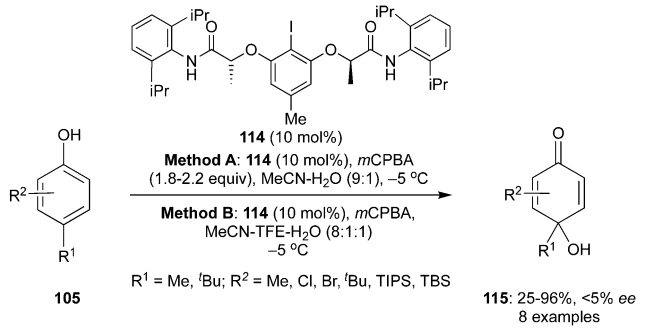


Scheme 28 Hypervalent iodine-mediated dearomatisation of phenols **105** *via* formation of intermediate **106**.



Scheme 29 Oxidation of 4-alkoxyphenols **111** to *p*-benzoquinones **113** using magnetic nanoparticle-supported iodoarene precatalyst **112**.



Scheme 30 Hydroxylative dearomatisation of phenols **105** to *p*-quinols **115** using chiral aryliodide catalyst **114**.

lead to dearomatised products such as highly functionalised quinones, quinols and spirolactones.[21,38,98]

A general reaction pathway for the hypervalent iodine mediated oxidation of phenols is shown in Scheme 28. The phenolic compound **105** reacts with the hypervalent iodine(III) compound **1** or **2** through a ligand exchange and form intermediate **106**, which then undergoes a nucleophilic attack by an external nucleophile and forms either *ortho*-cyclohexadienone **107** or *para*-cyclohexadienone **108** *via* a dearomatisation process. In case of phenols **105** having an internal nucleophile, dearomatisation to *ortho*-spirocycles **109** and *para*-spirocycles **110** are taking place.

3.2.1. Intermolecular dearomatisation of phenols. In recent years, the iodine(III)-catalysed dearomatisation of phenols has received a particular attention by various hypervalent iodine chemists around the world.[3,21] Dearomatisations of phenols have been developed using hypervalent iodine catalysis in past two decades.[3] An eco-friendly protocol was reported by Yakura and co-workers for the oxidation of 4-alkoxyphenols **111** to *p*-benzoquinones **113** in good yields using magnetic nanoparticle-supported iodoarene catalyst **112** in the presence of Oxone® (Scheme 29).[99,100] The catalyst consists of phosphonate groups connecting magnetite (Fe_3O_4) nanoparticles to the iodoarene catalyst. After the completion of reaction, the catalyst can be easily separated by applying an external magnetic field and reused several times.

Muñiz and Fra described an enantioselective hydroxylative dearomatisation of 4-substituted phenols **105** to afford the corresponding *p*-quinols **115** using the lactic amide motif-based chiral aryliodide catalyst **114** in the presence of *m*CPBA as an oxidant (Scheme 30).[101] Two different solvent mixtures (A and B) were used during these dearomatisation reactions. The dearomatised products **115** were obtained in almost similar yields in both reaction conditions. However, the chiral catalyst could not transfer the chirality successfully and products were obtained in only up to 5% enantiomeric excess.

Hypervalent iodine(V)-mediated hydroxylative dearomatisation of 2-substituted phenols **105** to their cyclodimers **117** *via* [4+2] cycloaddition was developed by Ishihara and co-workers.[102] The catalytic system comprises of precatalyst **116a** or **116b** which generates the catalytic species 2-iodoxybenzenesulfonic acid *in situ* in the presence of Oxone® as oxidant (Scheme 31). Inclusion of a trialkylsilylmethyl substituent at the *ortho*-position of phenols facilitates the reaction and use of buffered Oxone® suppresses silanol elimination. The reaction was performed with various (2-(silylmethyl)phenols) **105** (R^2 = CH_2SiMe_3) requiring the addition of K_2CO_3 (0.375 eq.). Under similar catalytic conditions, oxidation of *o*-substituted 1- or 2-naphthols **118** provided *ortho* naphthoquinols **119** in excellent yields (Scheme 31). The same catalytic approach was employed for the synthesis of the natural products biscarvacrol and lacinilene C methyl ether in high yields.

Over the past few years, metal–organic frameworks (MOFs) have emerged as a support to catalyse organic reactions by offering high reactant selectivity and reusability. Various multivariate Al and Zr-MOF supported iodine catalysts **120** and **121**, that can be recovered and recycled several times, were developed by Cozzolino and co-workers for the oxidation of hydroquinones **111** to *p*-quinones **113** in the presence of *m*CPBA and $MeNO_2$ (Scheme 32).[103] These catalysts were prepared by treating the appropriate amount of linkers with zirconium(IV)chloride or aluminiumchloride and catalysts with 25% linkers were found to be ideally suited to achieve the

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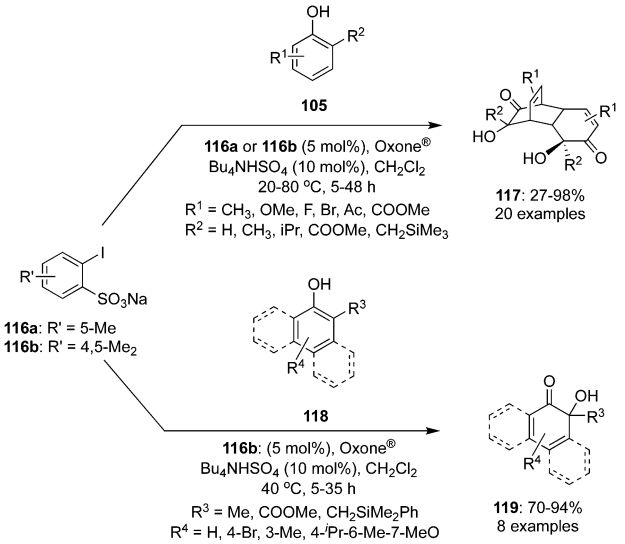
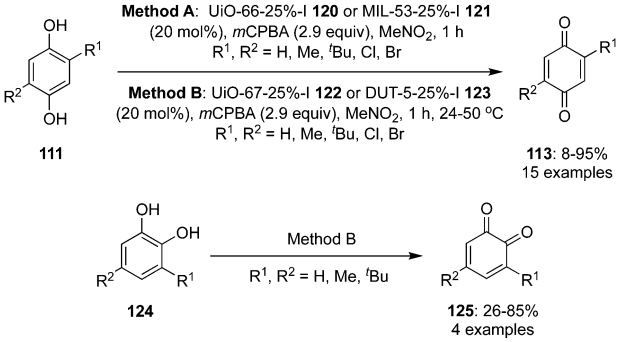


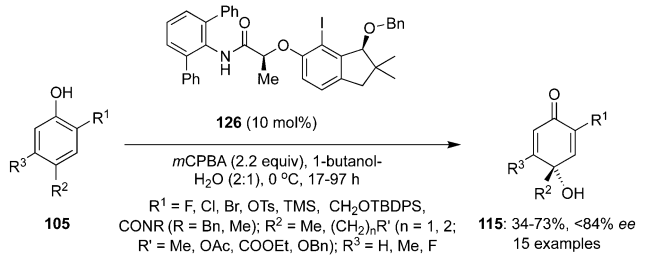
Scheme 31 Iodine(v)-catalysed dearomatisation of functionalised phenols **105** and naphthols **118**.



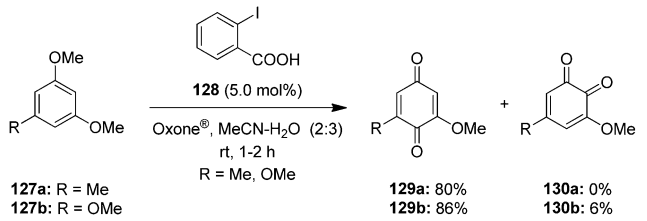
Scheme 32 Iodine(v)-catalysed oxidation of hydroquinones **111** and catechols **124** to *p*-quinones **113** and *o*-quinones **125**, respectively using Al and Zr-MOF supported iodine catalysts **120–123**.

optimal balance between catalyst loading and catalyst accessibility. 2-Iodoterephthalic acid was used as iodine linker in UiO-66 25%-I **120** and MIL-53 25%-I **121**. The same group prepared two novel expanded-pore iodine-functionalized UiO-67 (Zr) **122** and DUT-5 (Al) **123** catalysts and employed them in the oxidation of hydroquinones **111** to *p*-quinones **113** and catechol derivatives **124** to *o*-quinones **125**, respectively (Scheme 32).[104] 2-Iodo-[1,1′-biphenyl]-4,4′-dicarboxylic acid was used as linker in the UiO-67-25%-I **122** and DUT-5 25%-I **123** catalysts. Like other oxidations, *m*CPBA was used to regenerate the active iodine(v) catalytic species.

Hashimoto and co-workers introduced a coherent procedure for the asymmetric catalysis of *para*-hydrative intermolecular dearomatisation of functionalised phenols **105** to **115** through *in situ* generation of a chiral iodine(iii) catalyst by oxidation of indanol-based precatalyst **126** in the presence of *m*CPBA and butanol-H_2O as solvent mixture (Scheme 33).[105] A variety of functional groups are tolerated and *p*-quinols **115** were obtained in good yields with up to 84% ee.



Scheme 33 Iodine(iii)-catalysed enantioselective dearomatisation of functionalized phenols **105** to *p*-quinols **115** using **126** as precatalyst.



Scheme 34 Iodine(iii)-catalysed oxidation of alkoxyarenes **127** to *p*-quinones **129** using **128** as precatalyst.

An environmentally friendly hypervalent iodine-catalysed oxidation of alkoxyarenes **127a,b** to *p*-quinones **129** was developed using 2-iodobenzoic acid **128** as precatalyst and Oxone® as oxidant in acetonitrile–water (Scheme 34).[106] This approach provides *p*-quinones **129** in excellent yields in a short reaction time at room temperature. Usually, these oxidation reactions suffer from the formation of *o*-quinones as side products, but this reaction provides *p*-quinones exclusively. Earlier studies[107] using Oxone®-generated hypervalent iodine oxidants for the dearomatisation of phenols have indicated a preference for *p*-quinones **129** formation over *o*-quinones **130**, which made Oxone® as the oxidant of choice in this procedure (Scheme 34). Notably, the *in situ* generated cyclic iodine(iii) compound IBA **6** was acting as catalytic species.

3.2.2. Intramolecular dearomatisation of phenols. Intramolecular dearomatisation of phenols using hypervalent iodine reagents provides various biologically active cyclic and spirocyclic scaffolds.[38] Several hypervalent iodine-catalysed approaches are now available for the intramolecular dearomatisation of phenols.[3,21]

The first hypervalent iodine-catalysed intramolecular dearomatisation of phenols was investigated in 2005 by Kita and co-workers.[108] Kita and few other research groups employed hypervalent iodine catalysis to construct different spirocyclic scaffolds *via* intramolecular dearomatisation of phenols and naphthols.[109–116] All these reports are covered in our previous review on hypervalent iodine catalysis published in 2014.[3]

Ishihara and co-workers developed the spirolactonisation of phenols **131** with a propionic acid functionality in the *ortho*-position to enantiomerically rich *ortho*-dioxolanones **133** using a conformationally flexible chiral iodoarene **132** as precatalyst in the presence of *m*CPBA (Scheme 35).[117] Oxidation products

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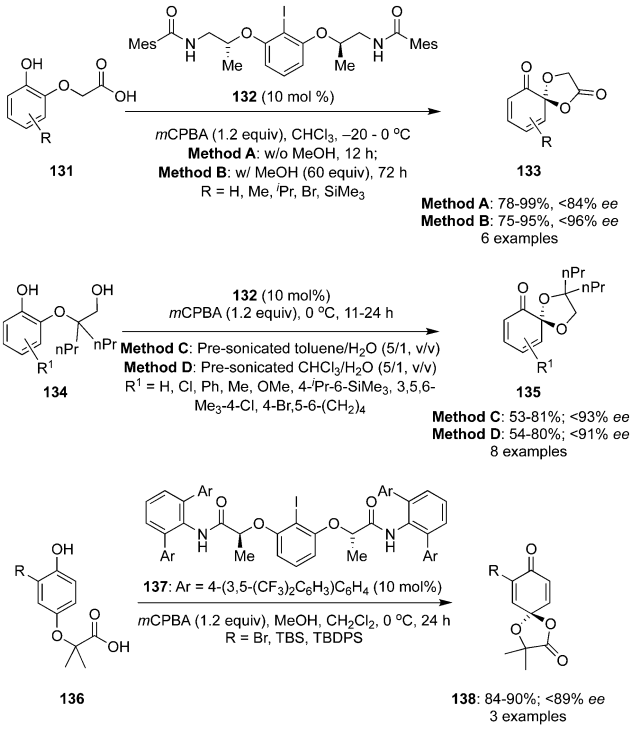
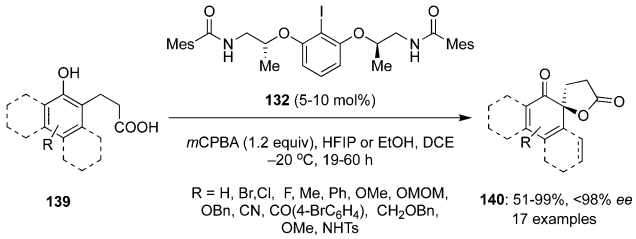


Scheme 35 Hypervalent iodine(III)-catalysed enantioselective dearomatisation of phenolic compounds **131**, **134** and **136**.

133 were obtained comparatively with low ee when 10% of methanol was used as an additive (Method A). Interestingly, the ee was improved up to 96% in case of 60 equivalents of methanol (Method B). Probably, methanol suppresses the dissociative pathway of ligand(III) and might improve the selectivity.[118,119] The reaction required longer reaction time as methanol deactivates the regeneration of iodine(I) to iodine(III). The absolute configuration of products (*S*-isomers) were assigned based on single crystal X-ray analysis.

It was observed that few of the dioxolanones were not stable at room temperature while the same catalytic system was employed for the oxidation of phenols **134** to spiroketals **135** with excellent selectivity (up to 93% ee) (Scheme 35).[117] Interestingly, same precatalyst **132** was not found suitable for the lactonisation of phenols **136** substituted with acetic acid in the *para*-position to *para*-dioxolanones **138**. Another conformationally flexible chiral iodoarene based precatalyst **137** was used for the lactonisation of phenols **136** and *para*-dioxolanones **138** were obtained with up to 89% ee (Scheme 35).[117]

The same group accomplished an enantioselective hypervalent iodine(III)-catalysed intramolecular oxidative dearomatisation of naphthols **139** by generating conformationally flexible λ^3 iodine catalysts *in situ* from 2-aminoalcohol based aryl iodide **132** in the presence of *m*CPBA as oxidant (Scheme 36).[120] Highly functionalized spirolactones **140** were obtained in moderate to high yields with up to 98% ee. Use of HFIP as an additive along with the solvent DCE facilitated the oxidation of less reactive 2-naphthols whereas ethanol was used as additive in the case of 1-naphthols. The current protocol

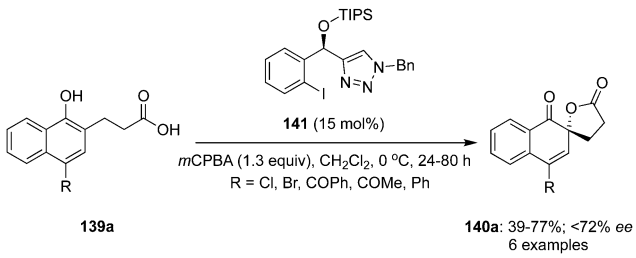


Scheme 36 Iodine(III)-catalysed enantioselective spirolactonisation of naphthols **139** to **140** using conformationally flexible chiral iodoarene **132** as precatalyst.

tolerates electron-donating as well as electron-withdrawing substituents in **139**.

Similarly, an iodine(III)-catalysed enantioselective spirolactonisation of 4-substituted 1-naphthols **139a** was developed by Nachtsheim *et al.* using a novel triazole-based chiral iodoarene precatalyst **141** in the presence of *m*CPBA (Scheme 37).[121] During these oxidations, spirolactones **140a** with electron withdrawing and donating groups were prepared in moderate to good yields. Notably, the precatalyst **141** was not found equally effective compare to the C_2-symmetric chiral precatalyst **132** for the same reaction and enantiomeric excess was reduced to <72% (Scheme 37).[121]

Atropisomers play a crucial role as catalyst in asymmetric catalysis. In 2017, Ogasawara and co-workers developed a novel C_2-symmetric conformationally rigid atropisomeric chiral diiododiene **142** from 1,2-bis(4,4-dimethyl-2-pentynyl)benzene and Cp_2ZrCl_2/Mg.[122] Design and synthesis of low-cost and reliable chiral iodoarene reagents for asymmetric catalysis is of tremendous interest nowadays, two research groups recently succeeded in constructing novel chiral organoiodanes based on carbohydrates and helicenes. Ziegler and Imrich reported D-glucose-based chiral iodoarene **143**.[123] Helicine-based chiral iodoarene catalyst **144** was designed and synthesised by Quideau and co-workers through a double Wittig olefination followed by the double photo-cyclisation from inexpensive starting materials.[124] These novel chiral aryl iodide reagents served as interesting catalysts for the spirolactonisation of naphthols **139b** to afford chiral spirolactone **140b** employing *m*CPBA as oxidant (Scheme 38). The reaction catalysed by **142** yielded **140b** as (*S*)-isomer in 73% ee whereas **143** or **144** provided **140b** as (*R*)-isomer with up to 60% ee. Notably, the



Scheme 37 Iodine(III)-catalysed enantioselective spirolactonisation of 4-substituted 1-naphthols **139a** to spirolactones **140a**.

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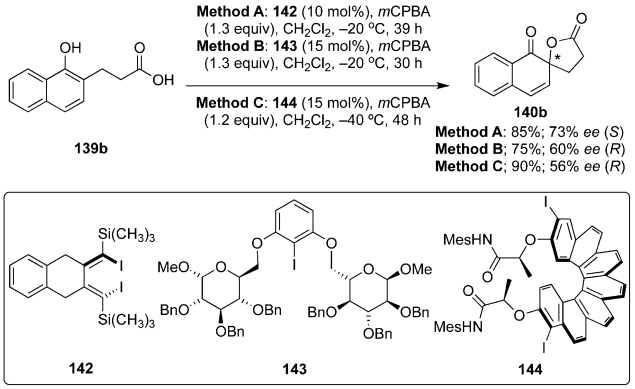
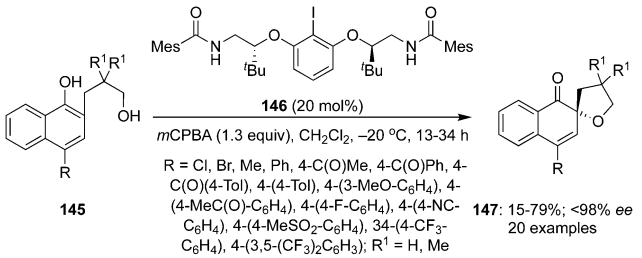


Scheme 38 Iodine(III)-catalysed enantioselective spirolactonisation of naphthols **139** to spirolactones **140** using precatalysts **142–144** in the presence of *m*CPBA.

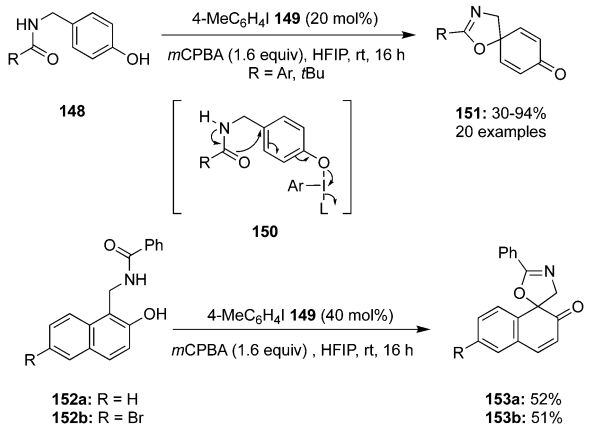


Scheme 39 Iodine(III)-catalysed enantioselective oxidative spirocyclocetherification of naphthoic alcohols **145** to **147** using **146** as precatalyst.

lower reaction temperature resulted in longer reaction times with improved yield and enantioselectivity.

In 2017, Ciufolini and co-workers described an enantioselective intramolecular oxidative spiroetherification of naphthoic alcohols **145** employing chiral aryl iodide **146** as precatalyst in the presence of *m*CPBA (Scheme 39).[125] A wide range of spirocyclic ethers **147** bearing electron donating and withdrawing substituents were synthesized in high yields with up to 93% enantiomeric excess. Like in other spirocyclisations, the active iodine(III) catalytic species was generated *in situ* by oxidation of the chiral precatalyst **146** with 3-chloroperbenzoic acid. The absolute configuration of product **147** was assigned as (*R*)-isomer by its single crystal X-ray analysis.

In 2020, Tariq and Moran performed an oxidative dearomatisation of amide-tethered phenols **148** mediated by λ^3-iodanes generated *in situ* from the 4-iodotoluene **149**/*m*-CPBA catalytic system (Scheme 40).[126] The intramolecular dearomatisation protocol furnished spirooxazolines **151** in 30–94% yields with excellent functional group compatibility. The reaction scope was investigated with a range of aryl, alkyl and heteroaryl amide-based phenols under optimised conditions. Notably, methoxy and alkyl substituted phenyl amides **148** yielded spirocycles **151** in moderate yields whereas the fluoro-substituted substrates led to the higher yields of the products. It was suggested that the activation of phenolic oxygen by λ^3-iodane and subsequent cyclisation of pendent amide on to the

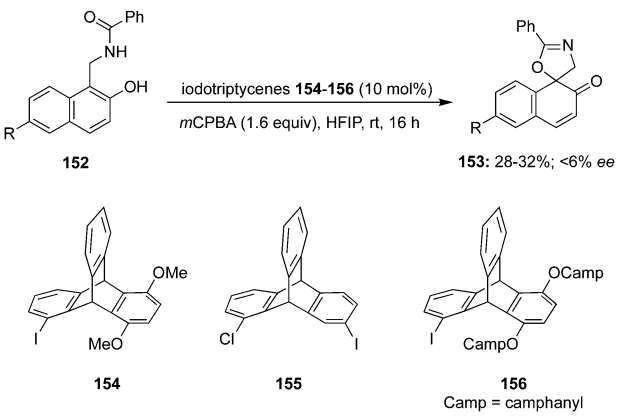


Scheme 40 Iodine(III)-catalysed synthesis of spirooxazolines **151** and **153** by dearomatisation of phenolic compounds **148** and **149**.

aromatic ring results in the formation of dearomatised product **151**. Further oxidative dearomatisation of naphthols **152** was performed with 40 mol% of 4-iodotoluene **149** to produce spirocycles **153** in moderate yields. Moreover, triptycene based pre-catalysts **154–156** were also employed in the same reaction but could achieved only very limited success.[127]

Wirth and co-workers developed the synthesis of novel iodotriptycenes **154–156** and employed them as precatalyst for the intramolecular dearomatisation of naphthols **152**. The spirocyclic product **153** was obtained in moderate yields with only up to 6% ee (Scheme 41).[127]

Gong and co-workers described an elegant method for the construction of spirooxindoles **159** by an intramolecular dearomatisation of 1-hydroxy-*N*-aryl-2-naphthamides **158** using chiral iodoarene **157** as precatalyst (Scheme 42).[128] This is the first example of an enantioselective dearomatisation of 1-hydroxy-*N*-aryl-2-naphthamides **158** providing a facile access to a library of spirooxindoles **159** in good yields with up to 92% ee. The dearomatisation involves the oxidation of chiral iodoarene **157** to generate the active chiral hypervalent λ^3-iodane *in situ*, which catalyses the oxidative of spirocyclisation.



Scheme 41 Iodine(III)-catalysed dearomatisation of phenolic compound **152** using triptycene based pre-catalysts **154–156**.

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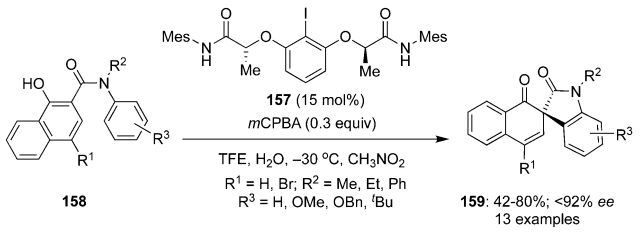
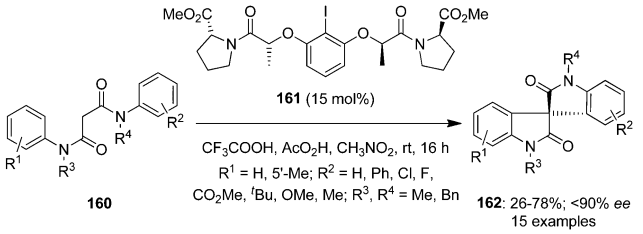


Scheme 42 Iodine(III)-catalysed intramolecular dearomatisation of 1-hydroxy-*N*-aryl-2-naphthamides **158** to spirooxindoles **159**.



Scheme 43 Iodine(III)-catalysed enantioselective synthesis of spirooxindoles **162** from N^1,N^3-diphenylmalonamides **160** using (*S*)-proline-derived chiral iodoarene **161** as precatalyst.

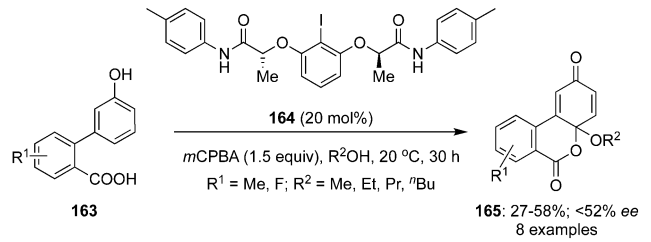
Notably, an all-carbon stereogenic centre in the products is generated during these oxidation reactions.

In another report, the same research group developed a highly enantioselective approach for the spirocarbocyclisation of N^1,N^3-diphenylmalonamides **160** using hypervalent iodine catalysis.[128] Oxidation reactions were performed by using (*S*)-proline-derived chiral iodoarene **161** as precatalyst in the presence of peracetic acid leading to the synthesis of spirooxindoles **162** in variable yields with up to 90% ee (Scheme 43).[129] Once again a quaternary carbon stereogenic centre is generated.

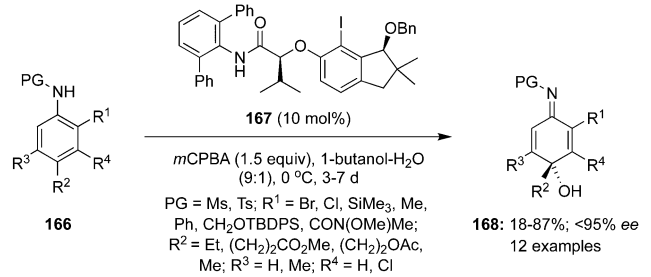
In 2020, Xiong and co-workers developed an enantioselective intramolecular alkoxy-oxylactonisation followed by dearomatisation of 3′-hydroxy-[1,1′-biphenyl]-2-carboxylic acids **163** employing chiral C_2-symmetric iodoarene **164** as precatalyst using *m*CPBA and MeOH (Scheme 44).[130] Functionalised cyclohexadienones **165** were prepared in moderate yields in up to 52% ee. The size of the alkyl group in the alcohols played a significant role as the yields of the products were decreased with an increased size while the ee was improved significantly. Moreover, the selectivity was influenced by the position of substituents. Selectivity was quite similar in case of *o*- and *m*-substituted phenols while ee was improved significantly with *p*-fluoro substituted phenols due to an increased nucleophilic character of the carboxylate. This is one of the rare reports where oxylactonisation is achieved alongside the dearomatisation.

3.3. Oxidation of aromatic amines

Hypervalent iodine reagents have been employed successfully for the dearomatisation of aromatic amines but there is paucity of the literature to achieve similar oxidations using hypervalent



Scheme 44 Iodine(III)-catalysed intramolecular dearomatising alkoxy-oxylactonisation of 3′-hydroxy-[1,1′-biphenyl]-2-carboxylic acids **163** to cyclohexadienones **165**.



Scheme 45 Iodine(III)-catalysed highly enantioselective hydrative *para*-dearomatisation of anilides **166** using indanol-based chiral organoiodine precatalyst **167**.

iodine catalysis.[23] In 2021, Shimazaki *et al.* developed a highly enantioselective hydrative *para*-dearomatisation of anilides **166** with water as nucleophile using indanol-based chiral organoiodine precatalyst **167**. This oxidation approach offers functionalised *p*-quinol imines **168** in poor to excellent yields with up to 95% enantiomeric excess (Scheme 45).[131] In general, 4-methyl sulfonanilides with different 2-substituents such as chloro, bromo, methyl, phenyl, silyl and amide groups were tolerated. Moreover, the dearomatisation of 2-bromoanilides **166** substituted with ethyl, methyl, acetoxy and methoxycarbonyl functional groups at *para* position of the phenyl ring were also accomplished successfully under these conditions.

3.4. Oxidation of sulfides and sulfenamides

Various hypervalent iodine reagents have been used as oxidants for the oxidation of organosulfur compounds under mild reaction conditions.[21] The role of hypervalent iodine catalysis in the oxidation of organosulfur compounds is very limited.[3] In 2021, Kong and co-workers reported an environmental friendly approach for the oxidation of sulfides **169** to NH-sulfoximines **174** by the use of hypervalent iodine(III) catalyst **173** generated *via* anodic oxidation of 4-iodoanisole **172** (Scheme 46).[132] During these oxidations, n-Bu_4NPF_6 was employed as a supporting electrolyte and $AcONH_4$ as an ammonium source. The combination of graphite (C) anode and Pt cathode led to the highest product yields. Methyl phenyl sulfides **169** substituted with electron-withdrawing and -donating groups gave the desired products **174** in good to excellent yields. Additionally, the synthesis of NH-sulfonimidamides **175** from variety of sulfenamides **170** was achieved under standard conditions

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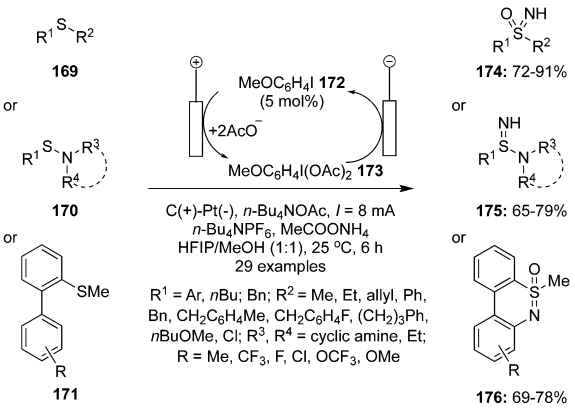


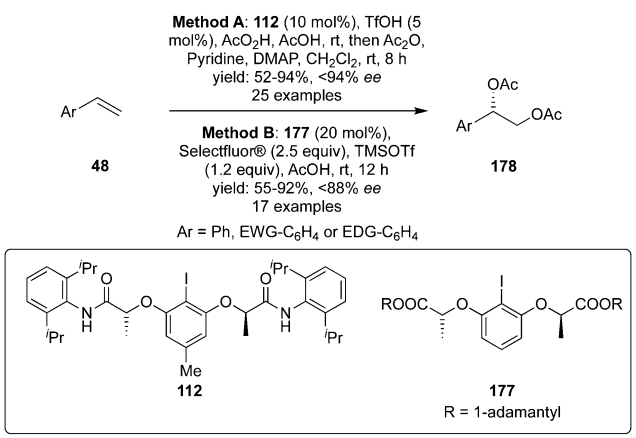
Scheme 46 Iodine(III)-catalysed electrochemical oxidation of sulfides **169**, sulfenamides **170** and [1,1′-biaryl]-2-sulfonamides **171**.

(Scheme 46).[130] Furthermore, an electrochemical oxidation of [1,1′-biaryl]-2-sulfonamides **171** provided the corresponding dibenzothiazines **176** in good yields (Scheme 46).[132]

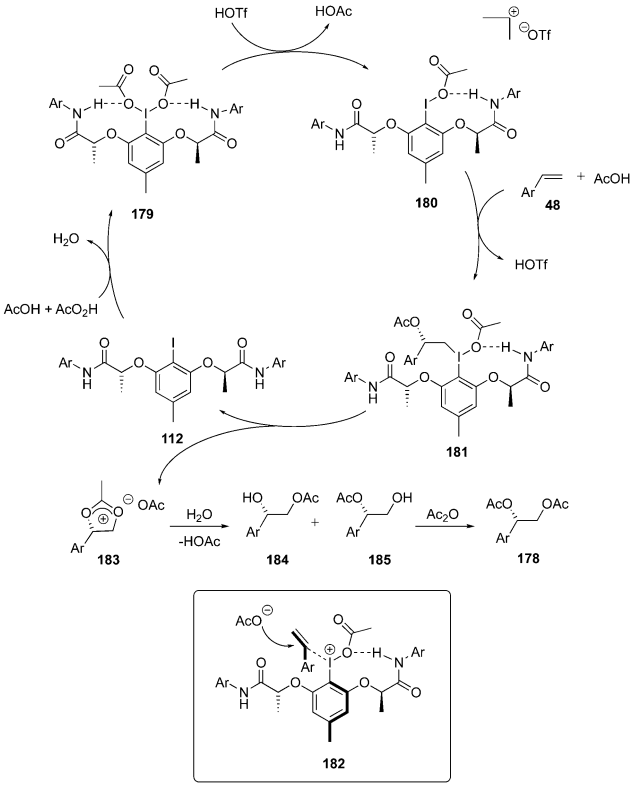
3.5. Oxidation of alkenes

Oxidation of alkenes with hypervalent iodine reagents is one of the key reaction of hypervalent iodine reagents.[21] Usually, hypervalent iodine reagents activates the olefinic double bond and lead to different oxidations such as epoxidations, hydroxylations, acetoxylations or oxidative cleavages.[23] Oxidation of alkenes achieved by involving hypervalent iodine catalysis until 2014 are compiled in our previous review article.[3]

3.5.1. Acetoxylation of alkenes. Muñiz and co-workers developed iodine(III)-catalysed enantioselective diacetoxylation of styrenes **48** to **178** using C_2-symmetric chiral iodoarene **112** as precatalyst, peracetic acid as an oxidant and acetic anhydride as the acetylating agent (Method A, Scheme 47).[133] Various substituted styrenes gave the desired diacetoxylation products **178** in good yields with high enantioselectivities (up to 94% ee). Another iodine(III)-catalysed approach was developed by using chiral precatalyst **177** in the presence of Selectfluor as a terminal oxidant and diacetoxylation of styrenes **48** was



Scheme 47 Iodine(III)-catalysed enantioselective diacetoxylation of styrenes **48** using chiral precatalyst **112** and **177**.



Scheme 48 Catalytic cycle for iodine(III)-catalysed enantioselective diacetoxylation of styrenes **48**.

achieved in high yields with up to 88% ee (Method B, Scheme 47).[134]

A proposed mechanism for the diacetoxylation of styrenes **48** using chiral iodoarene **112** is shown in Scheme 48. Peracetic acid oxidises the iodoarene **112** to the iodine(III) species **179**. One of the acetate group in **179** dissociates to create a free coordination site at iodine(III) in the presence of triflic acid while the other acetate group participates in hydrogen bonding to generate intermediate **180**. Subsequently, styrene **48** coordinates to intermediate **180** followed by nucleophilic attack of acetate to the exposed re-face of **180** to form intermediate **181**. Intramolecular nucleophilic addition of the acetyl group provides Woodward dioxolonium intermediate **183** and regenerates the iodine(I) catalyst **112**. Dioxolonium intermediate **183** gives two regioisomeric alcohols **184** and **185** on hydrolysis, which on further treatment with acetic anhydride generates the desired product **178**.[133]

Pyridine-based iodoarene **187** was developed and employed as precatalyst for the iodine(III)-catalysed vicinal diacetoxylation of trisubstituted alkenes **186** in the presence of peracetic acid (Scheme 49).[135] The acetoxylation exhibited good functional group tolerance and afforded vicinal diacetoxylation products **188** in good yields. This catalyst acts as a kinetically excellent catalyst due to the Lewis base adduct formation between the pyridine nitrogen and electrophilic iodine(III) centre.

3.5.2. Fluorination of alkenes. In recent years, several research groups have established different methodologies for

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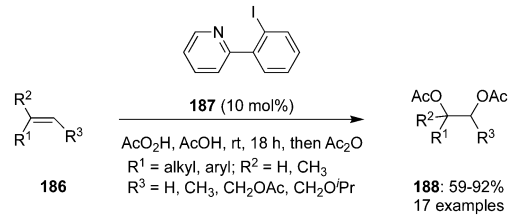
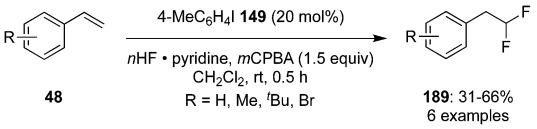


Scheme 49 Iodine(III)-catalysed vicinal diacetoxylation of trisubstituted alkenes **186** to **188** using **187** as precatalyst.

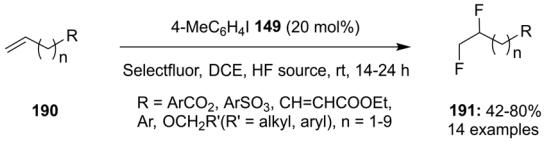


Scheme 50 Iodine(III)-catalysed difluorination of styrenes **48** to **189** using 4-iodotoluene **149** as precatalyst.

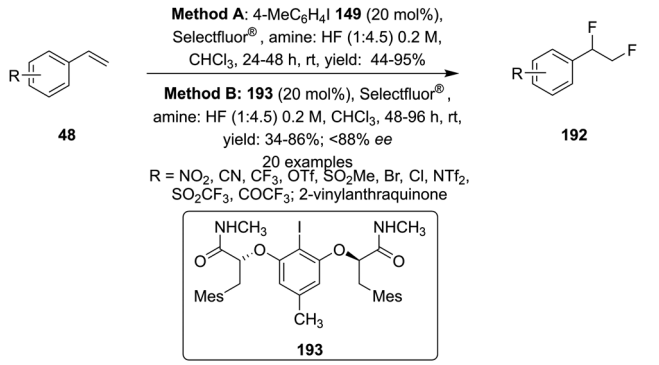
vicinal and geminal difluorinations of alkenes by involving hypervalent iodine catalysis.[64] Kitamura and co-workers developed the geminal difluorination of functionalised styrenes **48** with 4-iodotoluene **149** in the presence of *m*CPBA as oxidant and pyridine·HF as fluorine source to afford the 1,1-difluorinated compounds **189** in 31–66% yield (Scheme 50).[136] An increase in reaction time or temperature did not influence the yield of the products. The reaction was applicable for styrenes substituted with alkyl groups and halides.

4-Iodotoluene **149** was also employed for the vicinal difluorination of terminal olefins **190** using Selectfluor as an oxidant. Vicinal fluorinated products **191** can be obtained in good yields and different functional groups were successfully tolerated under the given reaction conditions (Scheme 51).[137] Notably, alcohol containing alkenes were fluorinated with the protection of alcohol functionality. The combination of amine and HF was used as source of fluorine and their ratio is playing a vital role during the progress of this reaction. Fluorination reactions were influenced significantly by the ratio of amine and HF and the best results were obtained with using amine–HF in a ratio of 1 : 4.5. Attempts were also made to develop the stereoselective version of the reaction using C_2-symmetric chiral iodoarene **136** but only low selectivities were observed. Different reaction conditions and reagents can lead to either a vicinal or geminal difluorination, details are shown below (Scheme 58).

Later on, the same research group reported vicinal difluorinations of styrenes **48** using the precatalyst **149** in the presence



Scheme 51 Iodine(III)-catalysed 1,2-difluorination of terminal olefins **190** to **191**.



Scheme 52 Iodine(III)-catalysed vicinal difluorination of alkenes **48** using achiral precatalyst **149** (Method A) and chiral precatalyst **193** (Method B).

of Selectfluor as the oxidant and in combination of an amine and HF as fluorine source (Scheme 52).[138] Fluorinations proceeded smoothly and vicinal difluorinated products **192** were obtained in good yields. The percentage of geminal fluorination was enhanced on increasing the ratio of HF/amine and the geminal fluorination was observed when amine–HF was used in a 1 : 9.2 ratio. Additionally, an enantioselective catalytic fluorination of styrenes **48** to **192** was also developed by employing the chiral iodoarene **193** (Scheme 52).[138] Similar to racemic fluorinations, enantioselective fluorinations proceeded smoothly and vicinal difluorinated products are obtained in good yields in up to 88% enantiomeric excess. The major enantiomer was assigned to have *syn* configuration based on X-ray analysis. Brønsted acidity of the HF-amine source and deactivating groups in the aromatic ring are significant factors which favours the formation of vicinal difluorination over the geminal by subduing the 1,2-aryl shift. The effect of electronic factors were further validated by computing correlations of the enantioselectivity *versus* the ^{13}C NMR shift of *ipso* carbon of the aryl ring and log(ee) *versus* the Hammett value σ.

Jacobsen's research group reported a novel method for the catalytic 1,2-difluorination of trisubstituted olefins **186** using aryl iodide catalyst **194** in the presence of HF–pyridine as the nucleophilic fluoride source and *m*CPBA as the stoichiometric oxidant (Scheme 53).[139] Terminal and internal alkenes, especially with substituents such as amino and nitrogen containing heterocycles, were tolerated under the reaction conditions. *anti*-Difluorination products **197** and **199** were observed with *o*-nitro styrenes **196** and acrylamides **198** due to the anchimeric assistance of Lewis basic groups adjacent to the reaction site (Scheme 53).[139]

A stereoselective version of this reaction was endeavoured by using the chiral precatalyst **200** with the same oxidant and fluorine source to afford vicinal *anti*-difluorination product **199** in 51% yield with 93% ee (Scheme 54).[139] The reaction using the chiral precatalyst was much slower compared to the achiral precatalyst.

The ester moiety of **200** was modified to form another precatalyst **202** for an enantioselective geminal difluorination of tetra-substituted olefins **201** to **203**.[140] Reactions were performed at relatively at low temperate (−50 °C to −20 °C) and

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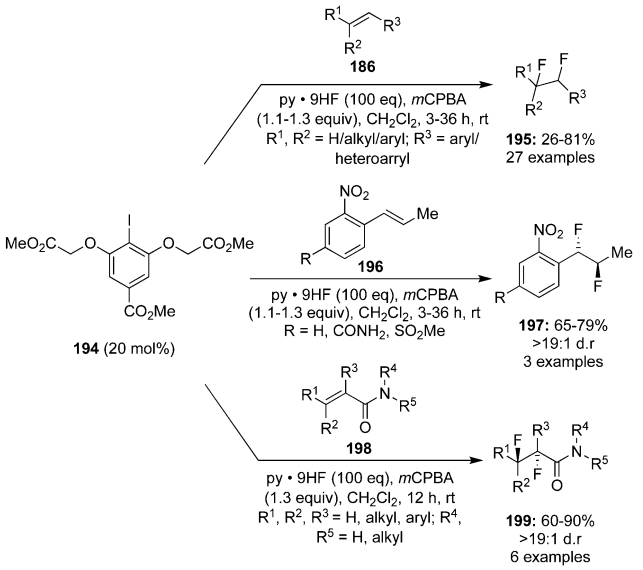
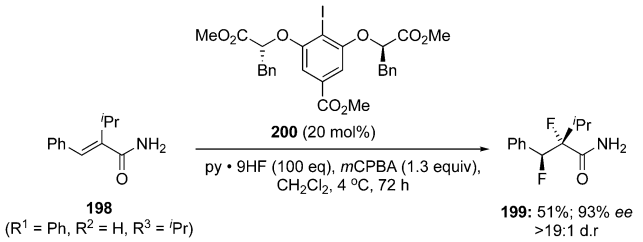
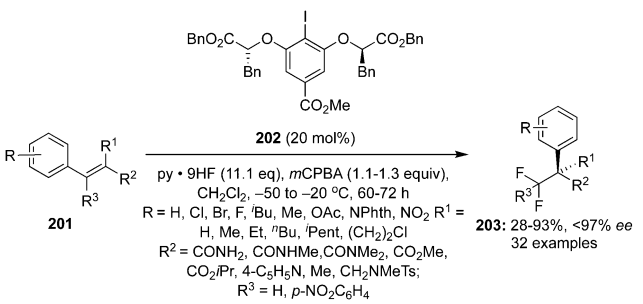


Scheme 53 Iodine(III)-catalysed 1,2-difluorination of alkenes **186**, **196** and **198** using **194** as precatalyst.

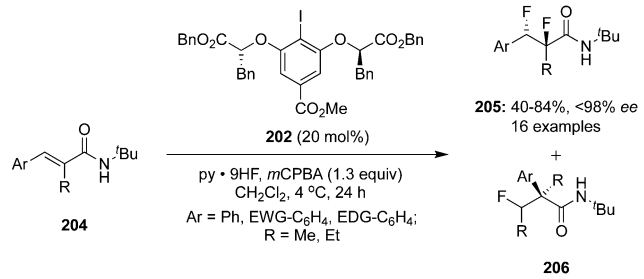


Scheme 54 Iodine(III)-catalysed enantioselective 1,2-difluorination of alkenes **198** using chiral precatalyst **200** in the presence of *m*CPBA.

fluorinated products **203** were obtained in good yields with up to 97% ee (Scheme 55).[140] Introducing a substituent at benzylic position of the styrenes provided high enantioselectivity. Notably, the cinnamamides and cinnamate esters afforded the desired products **203** in excellent yields (Scheme 55). Tertiary and quaternary stereocenters were generated during these geminal difluorination and cation···π interactions played a vital role in achieving the high selectivity. Absolute



Scheme 55 Geminal difluorination of olefins **201** to **203** using chiral iodoarene **202** as precatalyst.



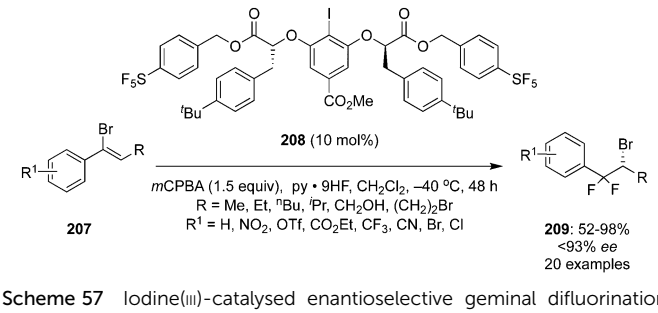
Scheme 56 Iodine(III)-catalysed enantioselective difluorination of **204** to **205** using C_2-symmetric chiral precatalyst **202**.

configuration of the product was assigned based on the single crystal X-ray analysis.

The same research group reported an enantiocontrolled synthesis of vicinal 1,2-difluorinated products **205** from secondary cinnamamides **204** using hypervalent iodine catalysis.[141] Vicinal difluorinated products were obtained in moderate to high yields with up to 98% ee (Scheme 56). Interestingly, anchimeric assistance by the neighbouring *tert*-butyl amide group suppresses the competing 1,1-difluorination reaction *via* a rearrangement pathway thereby increasing chemoselectivity towards the formation of vicinal 1,2-difluorinated products **206**. Notably, the ratio of geminal difluorination was increased in case of neighbouring Me or Et instead of ^{t}Bu in the substrates.

Another novel chiral precatalyst **208** was synthesized by Jacobsen and co-workers and employed in the iodine(III)-catalysed enantioselective geminal difluorination of α-bromostyrenes **207** to afford β,β-difluoroalkyl bromides **209** in moderate to excellent yields with up to 93% enantiomeric excess (Scheme 57).[142] Electron-deficient bromo styrenes with *meta*- and *para*-substituents were tolerated whereas *ortho*-substituted as well as electron-rich styrenes were not tolerated due to the proclivity of the substrates to engage in selective π interactions with the catalyst in the enantio-determining transition state as revealed by SAPT studies.

A general mechanism for iodine(III)-catalysed vicinal and geminal difluorination of alkenes is shown in Scheme 58.[138,143] The catalytic cycle is initiated by the iodoarene oxidation to the active catalytic species **210**. This activates the olefinic substrate **48** to afford an iodonium intermediate **211**. Iodonium intermediate **211**



Scheme 57 Iodine(III)-catalysed enantioselective geminal difluorination of **207** to β,β-difluoroalkyl bromides **209** using chiral iodoarene **208** as precatalyst.

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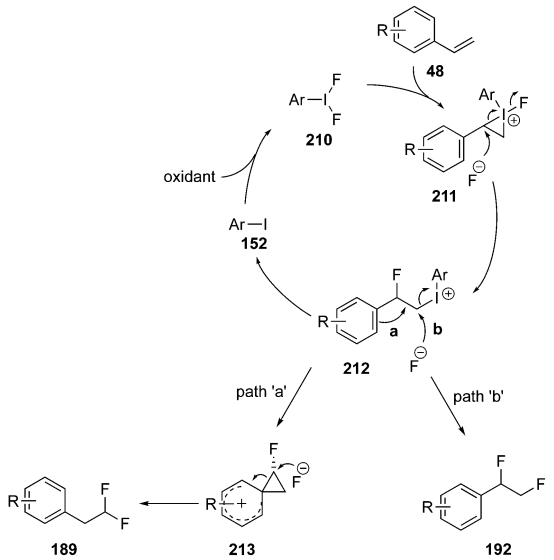
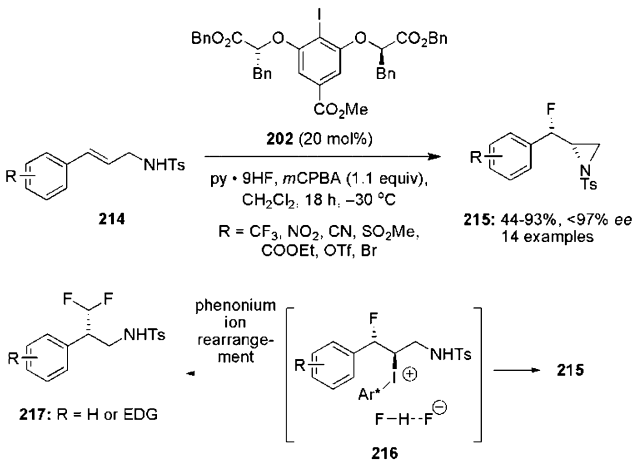


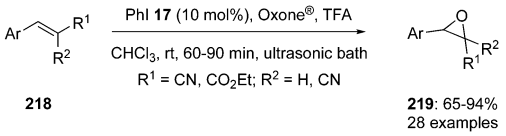
Scheme 58 General mechanism for vicinal and geminal difluorination of olefins **48** using iodine(III) catalysis.

undergoes ring opening by the nucleophilic attack of fluoride ion to form a common intermediate **212**. Intermediate **212** leads the formation of two different reaction products through path 'a' and 'b'. In path 'a', intermediate **212** undergoes a nucleophilic substitution reaction with fluoride ion to yield vicinal difluorination product **192**. In path 'b', intermediate **212** undergoes an aryl migration *via* formation of phenonium intermediate **213** to provide the geminal fluorination product **189**. The mechanism is well supported by theoretical studies.[143]

3.5.3. Fluoroaziridination of alkenes. Hypervalent iodine catalysis can also be efficiently used for the development of aziridinations of electron deficient alkenes.[144] Previously, chiral aryl iodide **202** was employed for the iodine(III)-catalysed fluoroaziridination of cinnamyl amines **214** to enantiomerically enriched fluoroaziridines **215** in moderate to good yields (Scheme 59).[143]



Scheme 59 Iodine(III)-catalysed *anti*-β-fluoroaziridination of cinnamyl amines **214** to fluoroaziridines **215** using precatalyst **202**.

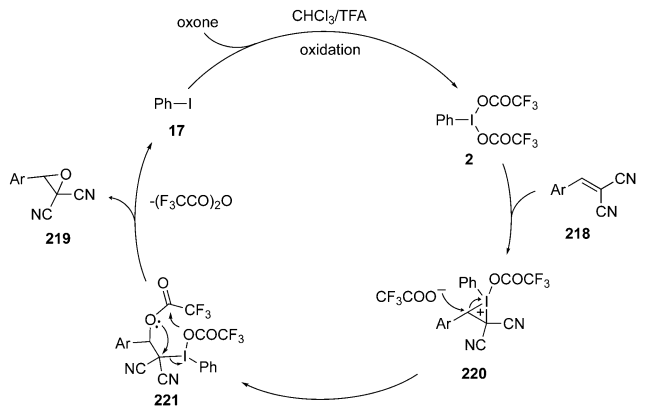


Scheme 60 Iodine(III)-catalysed epoxidation of β-cyanostyrenes **218** to **219**.

The absolute configuration of the fluoroaziridines **215** was assigned as *anti*-isomer based on single crystal X-ray analysis. Cinnamyl amines with electron-withdrawing substituents were tolerated well, but electron-rich substrates afforded 1,1-difluoromethylated products **217** instead of the desired fluoroaziridines **215** *via* a phenonium ion rearrangement pathway.[138] Moreover, the aziridine ring of *anti*-fluoroaziridines **215** was opened by using different nucleophiles to obtain enantiomerically enriched *anti*-fluoroamines.

3.5.4. Epoxidation of alkenes. Hypervalent iodine catalysis was employed for the epoxidation of electron deficient alkenes **218** using iodobenzene **17** in the presence of terminal oxidant Oxone® using TFA as an additive. Reactions were completed in a short reaction time by using ultrasound as energy source and afforded the epoxides **219** in good yields (Scheme 60).[145] Oxone® was particularly selected as oxidant to generate the hypervalent iodine catalytic species in this reaction because of its inertness towards the alkene epoxidation. Substrates with electron-donating substituents gave excellent yields compared to hindered substrates and arenes with electron-withdrawing groups. The scope of the reaction was also extended to styrenes with ester functionality.

A possible catalytic cycle for the epoxidation of alkenes **218** to epoxides **219** is given in Scheme 61.[145] The catalytic cycle is initiated with the formation of an iodine(III) species **2** by *in situ* oxidation of iodobenzene **17**. The iodine(III) species **2** activates the olefinic double bond and forms an iodonium intermediate **220** which converts to intermediate **221** on the ring opening by the nucleophilic attack by trifluoroacetoxy anion. Finally, intermediate **221** cyclizes intramolecularly to epoxides **219** along with the formation of precatalyst **17**. The active catalytic



Scheme 61 Possible catalytic cycle for iodine(III)-catalysed epoxidation of electron deficient alkenes **218** to epoxides **219**.

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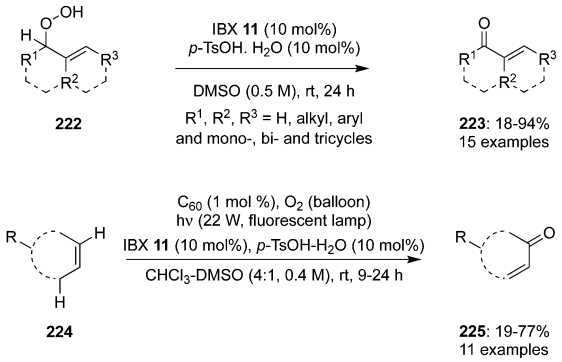


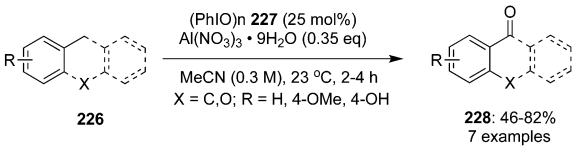
Scheme 62 Iodine(v)-catalysed oxidation of allylic hydroperoxides **222** and alkenes **224** to enones **223** and **225**.

hypervalent iodine species **2** is regenerated by the oxidation of precatalyst **17** to continue the catalytic cycle.

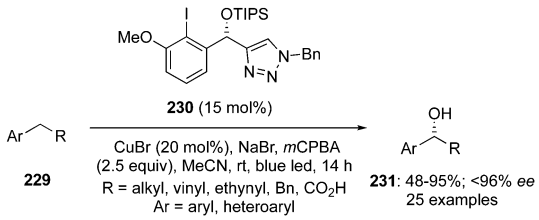
3.5.5. Epoxidation of hydroperoxides. Hypervalent iodine catalysis was used for the dehydration of hydroperoxides.[146] Hydroperoxides are useful substrates and provide the corresponding carbonyl compounds through oxidation. Hydroperoxides **222** were oxidized to α,β-unsaturated carbonyl compounds **223** when treated with 10 mol% of IBX **11** as dehydration catalyst in the presence of *p*-TsOH hydrate in DMSO at room temperature (Scheme 62).[147] The iodine(v)-catalysed dehydration of hydroperoxides worked well and both acyclic and cyclic allylic hydroperoxides are successfully converted during these catalytic reactions. In most of the oxidation reactions, enones were obtained in good yields except with acetal based hydroperoxides, which decomposed and formed the products in low yields. It is quite challenging to use allylic hydroperoxides due to their explosive nature.[147] To overcome this issue, a promising one pot methodology was developed for the direct conversion of alkenes **224** into enones **225** using C_{60} as a photosensitizer in an O_2 atmosphere using a fluorescent lamp in the presence of IBX **11** (Scheme 62).[147] Enones were obtained in good yields except the amino based cyclic olefins. Acyclic enones were obtained in only moderate yields probably due to the low selectivity of singlet oxygen in ene reactions of acyclic alkenes. Low concentration of hydroperoxides in ^{1}H NMR studies clearly supports the better safety profile of this one pot oxidation compared to the direct oxidation of hydroperoxides generated by singlet oxygen.[147]

3.6. Oxidation of benzylic C–H bonds

Oxidation of benzylic C–H bonds is an important reaction in organic synthesis and a number of hypervalent iodine mediated approaches have been used to achieve these oxidation reactions.[148,149] In 2020, Maruoka and co-workers reported the application of a hypervalent iodine(III) reagent as redox-neutral catalyst for the selective benzylic C–H oxidation of various arenes **226** to the corresponding carbonyl derivatives **228** at room temperature by employing polymeric iodosylbenzene $(PhIO)_n$ **86** as catalyst and $AlNO_3$ as oxidant.[150] Monomeric PhIO, the active iodine(III) species, is generated *in situ* by



Scheme 63 Benzylic oxidation of arenes **226** using hypervalent iodine catalysis.



Scheme 64 Iodine(III)-catalysed enantioselective benzylic hydroxylation of **229** to **231** using chiral precatalyst **230**.

the depolymerisation of $(PhIO)_n$ **228** using aluminium nitrate as reagent (Scheme 63). Interestingly, only arenes that are moderately activated by electron-donating groups were reactive in these oxidations. The current protocol is inefficient for arenes which are strongly activated with electron-rich groups and N-heterocycles, the former leads the over-oxidation products (benzoic acids) and the latter was unreactive due to the Lewis basicity of nitrogen.

Another catalytic approach for benzylic C–H oxidation was developed by Nachtsheim and co-workers.[151] An enantioselective hydroxylation of alkyl arenes **229** to **331** with a newly designed triazole substituted chiral precatalyst **230** was communicated, which acts not only as a halogen donor for the non-stereoselective radical halogenation but also as a chiral ligand during these enantioselective oxidations. This methodology involved irradiation of alkyl arenes **229** with blue LED's in the presence of chiral aryl iodide **230** (15 mol%), *m*CPBA (2.5 eq.), CuBr (20 mol%) in combination with NaBr (1.5 eq.) in acetonitrile at room temperature (Scheme 64).[151] Various substrates were found to be compatible with this current protocol to afford the corresponding benzylic alcohols in moderate to good yields with excellent enantioselectivities.

4. α-Functionalisations of ketones

Functionalisation of carbonyl compounds in the α-position employing hypervalent iodine reagents is another key reactions of organic synthesis.[21] Additionally, hypervalent iodine catalysis has been proved a quite useful approach for the developing these reactions.[3] In this section, various α-functionalisations of carbonyl compounds will be discussed.

4.1. α-Oxytosylation of ketones

Basdevant and Legault achieved the α-oxytosylation of acetyl enol ether **232** using hypervalent iodine catalysis in the presence of PhI **17**, *m*CPBA and *p*-TsOH·H_2O. It was required

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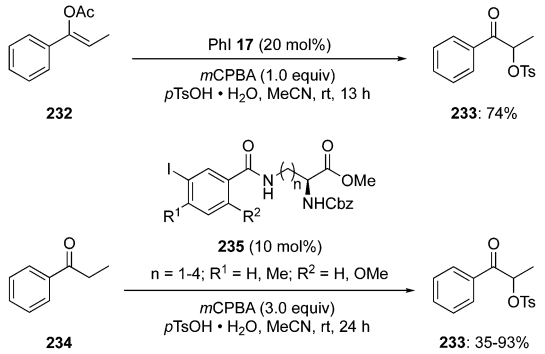


Scheme 65 Iodine(III)-catalysed α-oxytosylation of acetyl enol ether **232** and propiophenone **234** to α-tosyloxy ketone **233**.

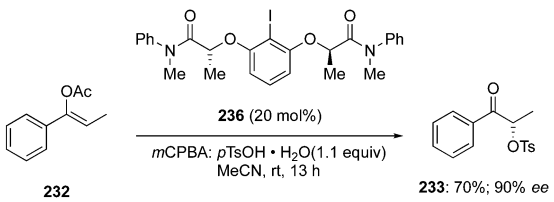
to add the precursor **232** in portions and only then α-tosyloxy ketone **233** was obtained in 74% yield (Scheme 65).[152] It was observed that the catalytic reaction was quite slow compared to the stoichiometric reaction. Under catalytic reaction conditions, acetyl enol ethers **232** served as suitable substrates due to their low nucleophilicity and easy availability.[151]

Furthermore, Whitehead and coworkers designed and synthesised a series of iodoarenes **235** coupled with diamino acids and the reactivity of these catalysts was assessed for α-oxytosylation of propiophenone **234** (Scheme 65). These pre-catalysts **235** allow the α-oxytosylation of propiophenone **234** in 35–93% yield. Notably, there was no asymmetric induction observed during these reactions.[153]

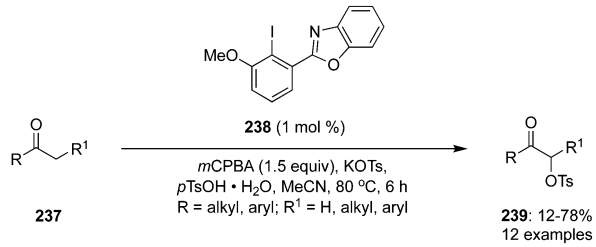
In the continuation of searching for high selectivities during these reactions, a novel C_2-symmetric chiral iodoarene **236** was synthesised and used as precatalyst to transfer the chirality in the presence of terminal oxidant during the α-oxytosylation of acetyl enol ether **232**.[154] Once again, the catalytic reaction was found slower than the stoichiometric reaction, but the α-oxytosylated product **233** was obtained as (*S*)-isomer in 90% ee (Scheme 66). Notably, the same precatalyst **236** showed moderate selectivity in the direct oxytosylation of propiophenone **234**.[154]

Recently, the concept of ''hypervalent twist'' was effectively used to develop more reactive hypervalent iodine reagents.[155–159] In case of twisted hypervalent iodine reagents, the presence of *ortho*-substituents leads to an out-of-plane distortion that destabilises the hypervalent iodine reagents.[160]

The same concept was used to design and synthesis of N-heterocyclic substituted iodoarene precatalyst (NHIA) **238** which was used for α-oxytosylation of ketones **237** in the



Scheme 66 Iodine(III)-catalysed α-oxytosylation of acetyl enol ether **232** to enantiomerically enriched α-tosyloxy ketone **233**.



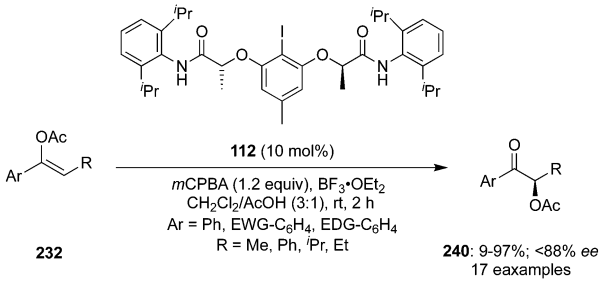
Scheme 67 Iodine(III)-catalysed α-oxytosylation of ketones **237** by using N-heterocyclic substituted iodoarene precatalyst (NHIA) **238**.

presence of *m*CPBA (Scheme 67).[161] Notably, very low catalytic loadings (1 mol%) were efficient the catalyse these reactions successfully and in good yields. The reaction showed tolerance for both aromatic and aliphatic ketones but α-oxytosylation of aromatic ketones provided better yields. Aromatic ketones bearing electron donating functionalities exhibited lower yields during these transformations. Moreover, the same reaction condition was applied for the α-oxytosylation of cyclic ketones.

4.2. α-Acetoxylation of ketones

In 2020, Wirth and Hokamp reported an iodine(III)-catalysed enantioselective α-acetoxylation of acetyl enol ethers **232** with high enantioselectivities (up to 88% ee) using hypervalent iodine catalysis (Scheme 68).[162] This methodology required resorcinol/lactamide-based chiral aryl iodide **112** as precatalyst in the presence of *m*CPBA and the additive $BF_3{\cdot}OEt_2$. Aromatic moieties with substituents such as halogens, nitro, alkyl and methoxy groups were well tolerated but substrates having electron withdrawing groups at the aromatic ring gave higher yields. The enantioselectivity was influenced by the nature and position of the functional group present in the aromatic ring. High selectivities were observed in case of substrates with electron withdrawing groups while enantiomeric excess was reduced drastically when the substitution was present at the sterically more demanding *ortho*-position.

A plausible mechanism for the iodine(III)-catalysed α-acetoxylation of acetyl enol ethers **232** is shown in Scheme 69. The catalytic cycle is initiated by the formation of an active iodine(III) catalytic species **241** through oxidation of the chiral aryl iodide catalyst **112** with the terminal oxidant. The catalytic species **241** is further activated by boron trifluoride etherate and undergoes a ligand exchange with the substrate **232** to



Scheme 68 Enantioselective α-acetoxylation of acetyl enol ethers **232** to α-acetoxylated ketones **240** using iodine(III) catalysis.

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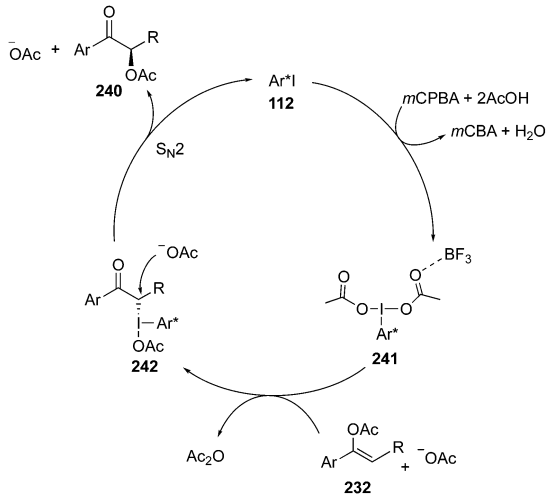


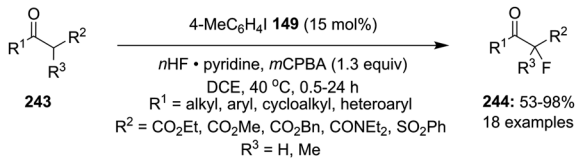
Scheme 69 Catalytic cycle for an iodine(III)-catalysed α-acetoxylation of acetyl enol ethers **232** using precatalyst **112**.

form another intermediate **242.** The subsequent S_N2 displacement provides α-acetoxylated ketones **240** with regeneration of precatalyst **112.**[162]

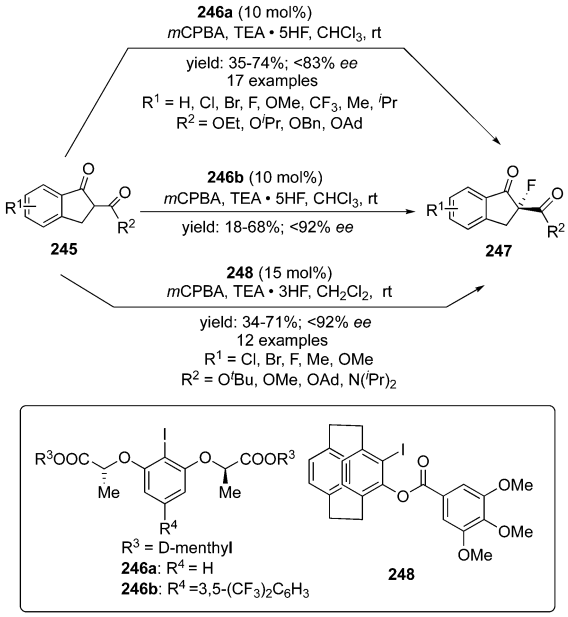
4.3. α-Fluorination of ketones

Fluorination of carbonyl compounds is an interesting reaction for the formation of C–F bonds.[43] Shibata and co-workers reported the α-fluorination of 1,3-dicarbonyl compounds **243** catalysed by 4-iodotoluene **149** using *m*CPBA as oxidant and HF/pyridine as fluorine source (Scheme 70).[163] The targeted tertiary α-fluorinated compounds **244** were obtained in moderate to excellent yields. In the case of α-fluorination, aromatic compounds with electron-withdrawing as well as electron-donating substituents, aliphatic and heteroaromatics substrates were tolerated. In addition, the reaction of cyclic/acyclic tertiary β-ketoesters provided α-fluorinated-β-ketoesters with a quaternary stereogenic centre in good yields.

A versatile asymmetric α-fluorination of cyclic β-keto esters **245** using the C_2-symmetric aryl iodide catalyst **246a** or **246b** in the presence of *m*CPBA and triethylamine pentafluoride as fluoride source was developed by Rueping and co-workers.[164] Enantiomerically enriched α-fluorinated carbonyl compounds **247** bearing quaternary stereocenter were obtained in good yields with up to 83% ee (Scheme 71). It was observed that precatalyst **246b** exhibited better selectivities compare to **246a,** probably due to the presence of the electron-withdrawing functionality at C3 position. Interestingly, the precatalysts can be recovered and reused without loss of selectivity and catalytic



Scheme 70 Iodine(III)-catalysed fluorination of β-ketocarbonyl compounds **243** using **149** as precatalyst.



Scheme 71 Iodine(III)-catalysed enantioselective fluorination of β-keto esters **245** to the corresponding α-fluorinated chiral compounds **247** using chiral precatalysts **246** and **248**.

potential. The reaction mechanism includes *in situ* formation of chiral hypervalent iodine difluoride source which is supported by the computational studies. Different cyclic esters with electron-withdrawing and electron-donating substituents, irrespective of their position in the aromatic ring, were tolerated. Furthermore, a similar approach was developed by Zheng and co-workers using a novel planar chiral iodoarene **248** with a [2.2]paracyclophane motif for the enantioselective α-fluorination of β-ketoesters and β-ketoamides **245**, affording the enantiomerically enriched α-fluorinated carbonyl compounds **247** (Scheme 71).[165] It was observed that the enantioselectivity increases with the size of the ester group of the β-ketoesters.

5. Cyclisation reactions

In past decades, a number of cyclisation reactions have been developed using hypervalent iodine reagents.[23] These reactions constitute an integral part of organic synthesis as they lead to the formation of several biologically important heterocycles.[15] More importantly, hypervalent iodine catalysis has played a significant role in the progress of these reactions.[3] In this section, both intramolecular cyclisations and intermolecular annulations with hypervalent iodine catalysis are highlighted.

5.1. Intramolecular cyclisations

Intramolecular cyclisation reactions have been extensively used to achieve different oxygen- and nitrogen-containing heterocyclic scaffolds. Synthesis of three-membered N- and O-heterocycles[144,145] was already discussed in the oxidation of alkenes (Section 3.5). Herein, the application of hypervalent

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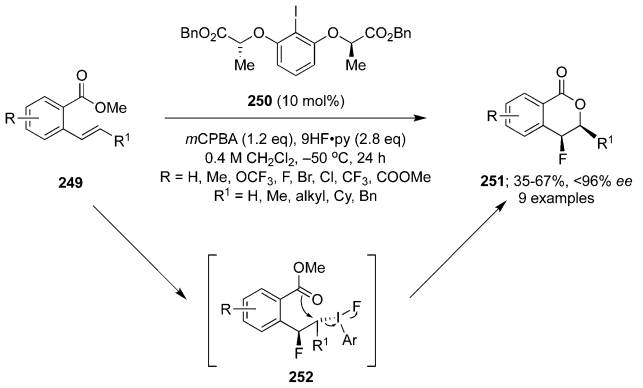


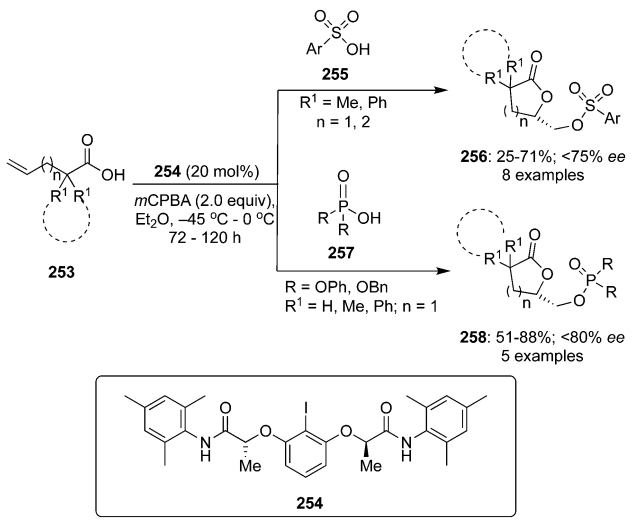
Scheme 72 Iodine(III)-catalysed fluorolactonisation of vinyl benzoates **249** to **251**.

iodine catalysis for the construction of five- and six-membered heterocycles will be discussed.

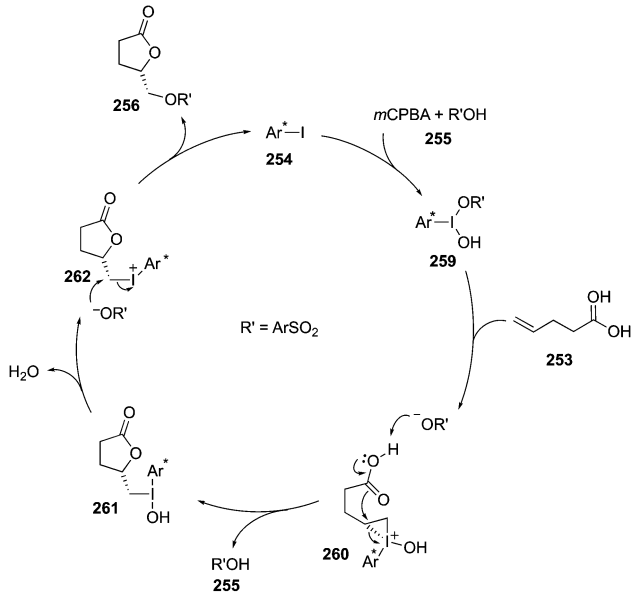
5.1.1. Synthesis of O-heterocycles

5.1.1.1. Synthesis of lactones. The synthesis of chiral 4-fluoroisochromanones **251** was achieved by Jacobsen and co-workers with excellent enantio- and diastereoselectivities.[166] The reaction involves catalytic fluorolactonisation of vinyl benzoates **249** with the aid of chiral aryl iodide **250** in the presence of *m*CPBA by taking HF·py in the ratio 1 : 9 as the fluoride source (Scheme 72). A *syn* diastereoisomer with 35–86% yield and up to 96% ee is formed in this reaction by the nucleophilic displacement of the aryliodonium group in the intermediate **252** with the aid of anchimeric assistance of the carboxylate functionality. Various electron-withdrawing and electron-donating groups at the aryl moiety are tolerated.

Furthermore, an enantioselective sulfonyloxylactonisation and phosphoryloxylactonatisation of 4-pentenoic acid derivatives **253** was reported by Masson and co-workers using C_2-symmetric chiral iodoarene **254** as precatalyst in the presence



Scheme 73 Iodine(III)-catalysed sulfonyloxylactonisation and phosphoryloxylactonisation of **253** using **254** as precatalyst in the presence of *m*CPBA.



Scheme 74 Catalytic cycle for the hypervalent iodine(III)-catalysed sulfonyloxylactonisation of 4-pentenoic acid derivatives **253** using C_2-symmetric chiral iodoarene **254** as precatalyst.

of *m*CPBA as oxidant (Scheme 73).[167] This method enabled a straightforward synthesis of sulfonyloxy- and phosphoryloxy-γ-butyrolactones **256** and **258** in good yields with moderate to high enantioselectivities. Both, 4-pentenoic acids and 1-allylcycloalkane carboxylic acids afforded γ-lactones and spirolactones, respectively, in good yields.

A possible catalytic cycle for the sulfonyloxylactonisation of iodine(III) catalysis is shown in Scheme 74. The catalytic cycle is initiated with the oxidation of chiral aryl iodide **254** to iodine(III) species **259** by *m*CPBA in the presence of sulfonic acid **255**. The iodine(III) intermediate **259** activates the double bond of olefinic acid **253** to form the chiral iodonium intermediate **260**. Iodonium intermediate **260** undergoes an intramolecular cyclisation to form the lactone intermediate **261**. Finally, lactone intermediate **261** provides sulfonylated lactones **256** and regenerates the catalyst to continue the catalytic cycle.[167]

Later, Hilt and co-workers developed an electrochemical approach for the lactonisation of vinyl benzoates **249** mediated by hypervalent iodine(III) catalysis using PhI **17** as precatalyst in the presence of lithium perchlorate as electrolyte and trifluoroacetic acid to form trifluoroethoxy-substituted isochromanones **263** in moderate to good yields (Scheme 75).[168] The scope of the reaction was expanded by changing the steric and electronic components of the substrates; only functional groups labile to oxidative conditions show low yields. Moreover, N-heterocyclic substituted iodoarene precatalyst (NHIA) **238** was also employed to achieve similar lactonisations.[161]

5.1.1.2. Synthesis of cyclic ethers. He and co-workers employed hypervalent iodine catalysis to develop the synthesis of various benzoiminolactones **265** through iodine(III)-catalysed intramolecular oxy-cyclisation of 2-vinylbenzamides **265**.[169] All

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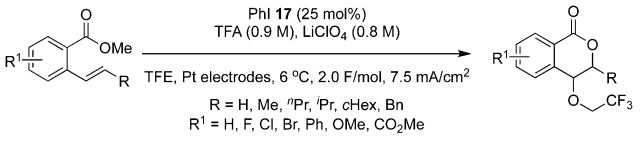
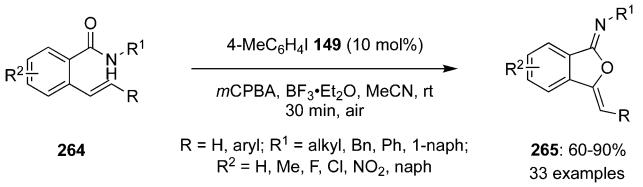


Scheme 75 Iodine(III)-catalysed lactonisation of vinyl benzoates **249** using iodobenzene **17** as precatalyst.

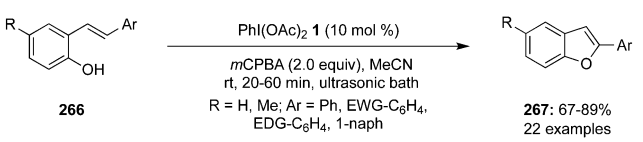


Scheme 76 Iodine(III)-catalysed intramolecular oxy-cyclisation of 2-vinylbenzamides **264** to benzoiminolactones **265** using **149** as precatalyst.

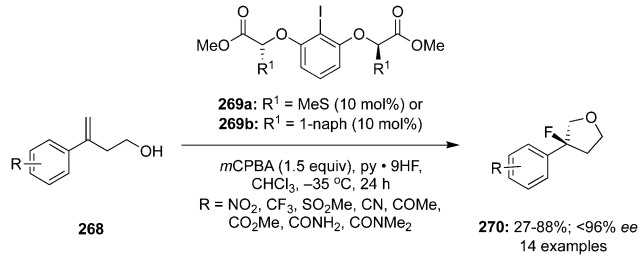
cyclisations were completed in a short reaction time and the cyclised products **265** were obtained in good to excellent yields (Scheme 76). The catalytic system comprised of 4-iodotoluene **149** (10 mol%), *m*CPBA (1.5 eq.) and Lewis acid, $BF_3{\cdot}Et_2O$ (1.5 eq.) to accelerate the oxidation process. Various 2-alkenylbenzamides with *N*-aryl as well as alkyl groups were found to be compatible with the current transformation. Moreover, iodine(III) catalysis has been used to synthesise fluorinated isochromans.[170]

An environmental friendly synthesis of 2-arylbenzofurans **267** was developed by indine(III)-catalysed intramolecular cyclisation of *o*-hydroxystilbenes **266** with the help of PIDA **1** as catalyst (Scheme 77).[171] The reaction is performed at room temperature and required a longer time to complete as unwanted side products were formed at higher temperatures. These challenges were overcome by performing the reaction using ultrasound and within a short reaction time, the desired products were obtained in good to excellent yields. The same cyclisations were developed by *in situ* generated active catalysts.[172]

In 2020, Wang *et al.* developed an oxidative fluorocyclisation of 1,1-disubstituted styrenes **268** with an internal oxygen nucleophile using *in situ* generated chiral iodine(III)-catalysts. The reaction employed C_2-symmetric aryl iodides **269** as catalyst with HF–pyridine as fluorine source and *m*CPBA as oxidant. The fluorinated cyclised products **270** were obtained in good yields with up to 96% ee (Scheme 78).[173]



Scheme 77 Iodine(III)-catalysed intramolecular cyclisation of *o*-hydroxystilbenes **266** to 2-arylbenzofurans **267** using $PhI(OAc)_2$ **1** as catalyst in the presence of *m*CPBA.



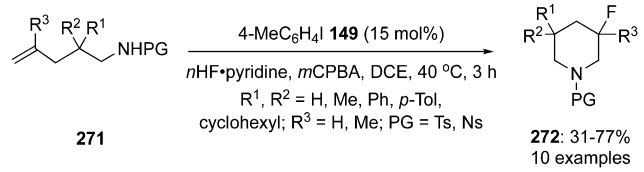
Scheme 78 Iodine(III)-catalysed enantioselective fluorocyclisation 1,1-disubstituted styrenes **268** to fluorinated cyclised products **270** using precatalysts **269**.

The fluorocyclisation of *para*-substituted styrenes **269** proceeded with high selectivity compared to *meta*-substituted derivatives, whereas low selectivities and a decreased reactivity was observed in *ortho* substituted styrenes. Optimisation of various chiral catalysts revealed that increasing the steric demand of the α-substituent R^1 in **269** improved the stereoselectivity of the fluorocyclisation. Both catalysts **269** were able to induce high enantioselectivities, particularly the newly developed 1-naphthyllactate catalyst (*R*,*R*)-**269b** yielded higher ee values than the mesityl analogue (*R*,*R*)-**269a**. Additionally, the synthesis of fluorinated pyrrolidines *via* an aminofluorination of styrenes was achieved under similar conditions.

5.1.2. Synthesis of N-heterocycles

5.1.2.1. Synthesis of piperidines. Hypervalent iodine catalysis has been successfully used to synthesise fluorinated piperidines **272** by involving an intramolecular aminofluorination of ω-aminoalkenes **271** using 4-MeC_6H_4I **149**/*n*HF·pyridine/*m*CPBA catalytic system (Scheme 79).[163] Cyclisations proceeded smoothly and various fluorinated piperidines **272** with alkyl, aryl and cyclic substituents were obtained in 31–77% yield. Notably, efforts were made to develop an asymmetric variant of this reaction, but only moderate enantiomeric excesses were obtained (not shown).

The proposed catalytic cycle for the hypervalent iodine-catalysed cyclisation of alkenes **271** to fluorinated piperidines **272** is shown in Scheme 80. The oxidant oxidises the precatalyst **149** to ArIO **273** which, in turn, reacts with HF to form the electrophilic hypervalent iodine species $ArIF_2$ **274**. $ArIF_2$ **274** reacts with alkenes **271** to form intermediate **275** with the liberation of HF. Furthermore, the intermediate **275** converts into aziridinium intermediate **277** *via* formation of intermediate **276**. Final nucleophilic attack of fluoride ion to aziridinium intermediate **277** affords the fluoropiperidine **272** along with the regeneration of precatalyst **149** to continue the catalytic



Scheme 79 Iodine(III)-catalysed synthesis of fluorinated piperidines **272** by involving an intramolecular aminofluorination of alkenes **271**.

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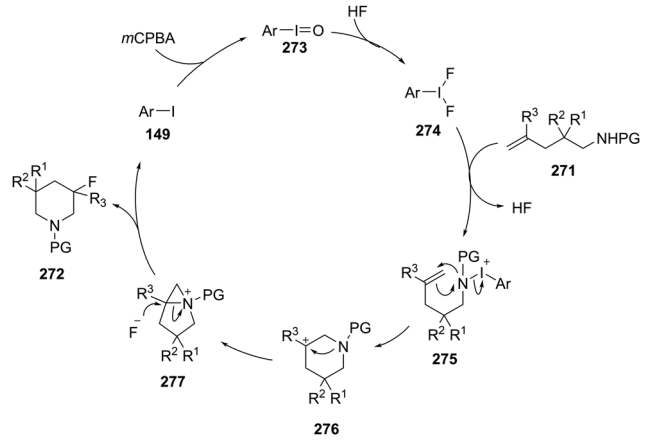


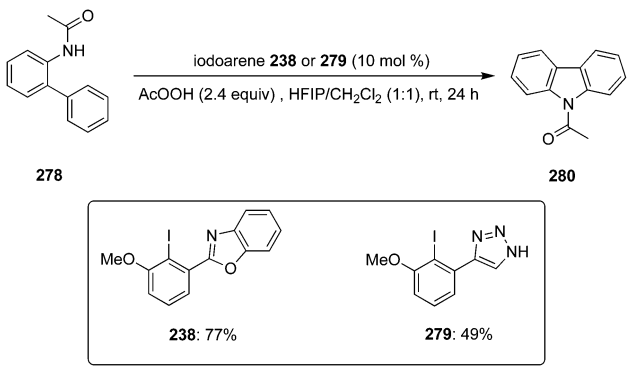
Scheme 80 Catalytic cycle for the hypervalent iodine-catalysed cyclisation of alkenes **271** to piperidines **272** using **149** as precatalyst.

cycle. To improve the yield, HF has to be used in excess because of the reversible nature of the reaction from $ArIF_2$ **274** to ArIO **273** and then due to a competitive hydroxylation reaction.[163]

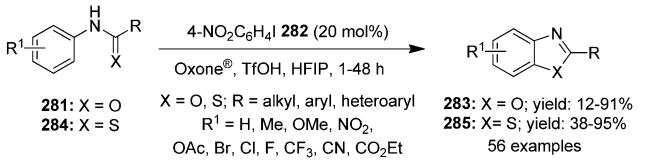
Furthermore, N-heterocyclic substituted iodoarene precatalyst (NHIA) **238** was employed for the hypervalent iodine-catalysed cyclisation of *ortho*-phenyl acetanilide **278** to *N*-acyl carbazole **280** (Scheme 81).[161] Notably, the 'twisted' hypervalent iodine species was generated during the progress of this reaction and *N*-acyl carbazole **280** was obtained in 77% yield. Moreover, another precatalyst **279** of the same series was also used and gave carbazole **280** in 49% yield (Scheme 81).[161] Peracetic was used as terminal oxidant to generate active catalytic species.

5.1.3. Synthesis of O,N-heterocycles

5.1.3.1. Synthesis of oxazoles. Punniyamurthy and co-workers developed a simple and efficient catalytic procedure for the synthesis of benzoxazoles **283** and benzothiazoles **285** by intramolecular cyclisation of arylanilides **281** and arylthioanilides **284**, respectively (Scheme 82).[174] This transformation employed 1-iodo-4-nitrobenzene **282** as precatalyst, Oxone® as oxidant in the presence of HFIP at room temperature. Anilides with halogen substituents afforded the desired



Scheme 81 Iodine(III)-catalyzed cyclisation of *ortho*-phenyl acetanilide **278** to *N*-acyl carbazole **280** using *N*-heterocyclic substituted iodoarene precatalyst (NHIA) **238** and **279**.

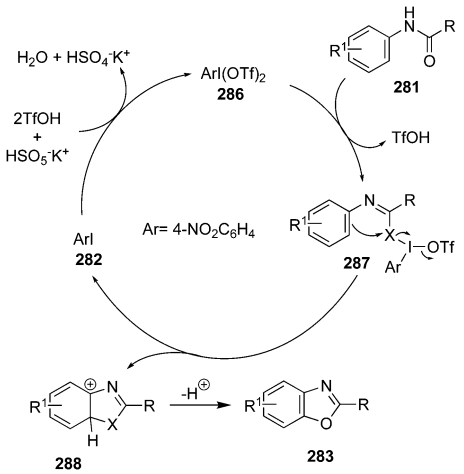


Scheme 82 Iodine(III)-catalysed synthesis of benzoxazoles **283** and benzothiazoles **285**.

products in good to excellent yields whereas nitro substituents were not compatible with the reaction. Amide groups with aryl, heteroaryl and alkyl substituents were tolerated. This protocol was successfully extended to gram scale.

The proposed catalytic cycle for the iodine(III)-catalysed cyclisation of arylanilides **281** to benzoxazoles **284** is shown in Scheme 83. As usual, the active hypervalent iodine species **286** is generated by the oxidation of aryl iodide **282** which reacts with substrate **281** to form new hypervalent iodine species **287**. Furthermore, species **287** undergo an intramolecular cyclisation to form a cationic intermediate **288**. Finally, the cationic intermediate **288** gave benzoxazoles **283** through deprotonation and releases aryl iodide **282** to re-enter into the catalytic cycle.[174]

In 2015, Moran and co-workers developed an intramolecular cyclisation of *N*-alkenylamides **289** for the synthesis of five to seven membered ring systems **291** containing both nitrogen and oxygen atoms (Scheme 84).[175] The catalytic system employed 2-iodoanisole **290** as precatalyst, Selectfluor as oxidant and TFA as additive. The cyclisation was not effective when *m*CPBA or Oxone® were used as oxidants. An array of electron rich and electron poor aryl amides were cyclised to obtain the corresponding products in good yields. Moreover, an enantioselective synthesis of isoxazoline **291a** from **289a** (R^1 = Ph; R^2 = H and n = 1) was accomplished by the use of **47** as chiral iodine precatalyst, but the product was obtained in low yield with 69% ee (Scheme 84).[175]



Scheme 83 The proposed catalytic cycle for iodine(III)-catalysed intramolecular cyclisation of arylanilides **281** to benzoxazoles **283**.

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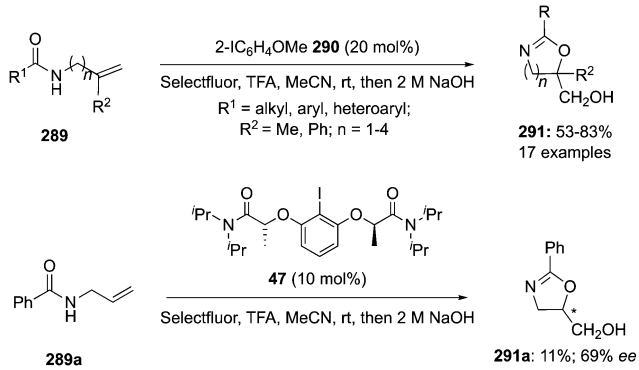
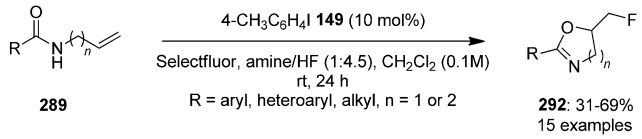


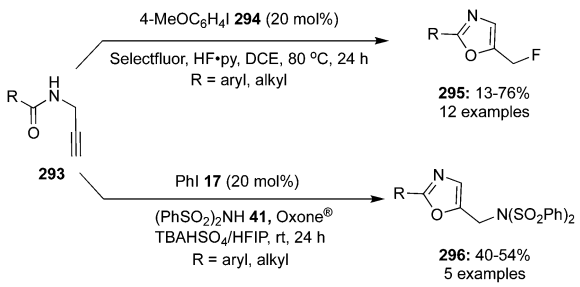
Scheme 84 Iodine(III)-catalysed intramolecular cyclisation of *N*-alkenylamides **289** to heterocycles **291** using achiral **290** and chiral **47** precatalyst.



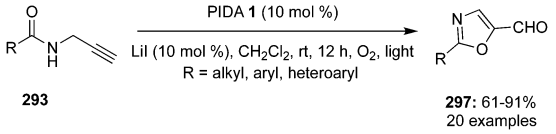
Scheme 85 Iodine(I)/iodine(III) catalysis for the cyclisation of **289** to 2-oxazolines **292**.

Similar substrates **289** were cyclised to 2-oxazolines **292** with an exocyclic fluoromethyl group in the presence of *p*-methyliodobenzene **149** as precatalyst, Selectfluor and a mixture of triethylamine tris(hydrogenfluoride) ($Et_3N{\cdot}3HF$) and Olah's reagent (Py·HF) as fluoride source (Scheme 85).[176] This cyclisation reaction was compatible with several functional groups and extended to prepare six-membered rings.

N-Propargyl amides **293** were cyclised to oxazoles **295** in good yields by iodine(III) species $ArIF_2$, generated *in situ* from 4-iodoanisole **294** in the presence of Selectfluor and HF–pyridine as the fluoride source (Scheme 86).[177] Aromatic as well as aliphatic amides were tolerated. Internal alkynes and amides containing haloarenes were found futile as substrates. Later, similar cyclisations were achieved in moderate yields by treating *N*-propargyl amides **293** with bisulfonyl(imides) **41** using PhI **17** as the precatalyst, Oxone® as oxidant and $TBAHSO_4$ (TBA: *tetra-n*-butylammonium) as a phase transfer reagent[178] or by using precatalyst (2-IC_6H_4OMe) **290** in combination with *m*CPBA.[179]



Scheme 86 Iodine(III)-catalysed cyclisation of *N*-propargyl amides **293** to oxazoles **295** and **296** using **294** and **17** as precatalyst.

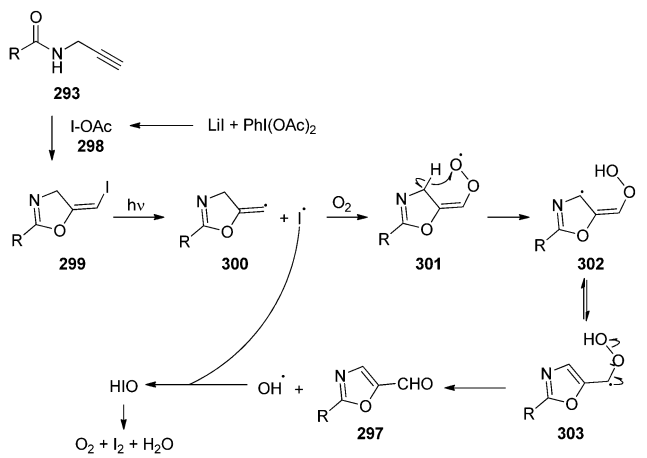


Scheme 87 PIDA-catalysed cyclisation of *N*-propargylamides **290** to oxazole-5-carbaldehydes **294**.

An one-pot protocol for the synthesis of oxazole-5-carbaldehydes **297** was developed by the cyclisation of *N*-propargylamides **293** using the PIDA/LiI catalytic system in the presence of oxygen under irradiation with visible light. This process involves an iodocyclisation followed by oxidative deiodination and cyclised products **297** were isolated in good to excellent yields (Scheme 87).[180]

The mechanism for PIDA-catalysed cyclisation of *N*-propargylamides **293** to oxazole-5-carbaldehydes **297** is given in Scheme 88. The reaction is initiated by the PIDA mediated oxidation of iodide to iodine monoacetate which induced the cyclisation of substrate **293** to cyclic intermediate **299**. Under the visible light, C–I cleaves homolytically and forms radical **300** along with an iodine radical. The radical **300** reacts with oxygen to form peroxy radical intermediate **301** which is subsequently converted to another radical intermediate **302**. Intermediate **302** rearranges to radical species **303** that gave the final aldehyde product **297** along with a hydroxyl radical. The hydroxyl radical reacts with iodine radical to form HIO that produced iodine on decomposition to continue the catalytic cycle.[180] Moreover, the tetrabutylammonium iodide (TBAI) has been also employed as precatalyst in the presence of terminal oxidant to develop the synthesis of similar oxazole scaffolds.[181]

5.1.4. Synthesis of carbocycles. Polycyclic aromatic hydrocarbons **305** were easily prepared by Murphy and others *via* oxidative intramolecular C–H coupling of styrenes **304** containing arene and alkene functionalities. These cyclisations were achieved using 4-iodotoluene **149** as precatalyst, *m*CPBA as oxidant, $BF_3{\cdot}OEt_2$ as additive and chlorobenzene as solvent (Scheme 89).[182] Polysubstituted phenanthrene derivatives were



Scheme 88 Mechanism for PIDA-catalysed cyclisation of *N*-propargylamides **293** to oxazole-5-carbaldehydes **297**.

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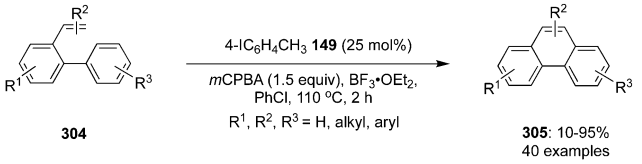


Scheme 89 Iodine(III)-catalysed oxidative intramolecular C–H coupling of styrenes **304** to polycyclic aromatic hydrocarbons **305**.

successfully prepared in moderate to high yields. Among the various functional groups, only very strong electron-withdrawing substituents such as NO_2, Ac, COOMe and CF_3 on the vinyl as well as arene moiety were not found suitable during these cyclisations. The scope of the reaction was also expanded for the formation of tetra and pentacyclic aromatics.

5.2. Intermolecular annulations

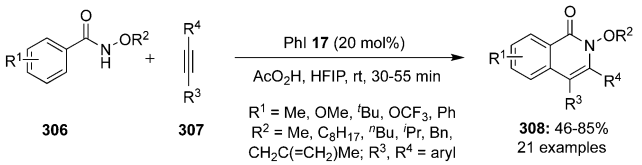
Like intramolecular cyclisations, intermolecular reactions have been extensively used for developing the synthesis of various heterocycles under metal-free reaction conditions. Applications of hypervalent iodine catalysis to achieve intermolecular annulations until 2013 are reviewed in our previous article.[3]

5.2.1. Synthesis of N-heterocycles. Various hypervalent iodine-catalysed intermolecular annulations have been used to construct nitrogen-containing heterocycles. Isoquinolones **308** were synthesised by the cycloaddition of alkynes **307** and benzamides **306** using catalytic amounts of iodobenzene **17** in HFIP in the presence of peracetic acid (Scheme 90).[183] Notably, a significant increase in the yield was observed by the portion-wise addition of the oxidant. Electron-withdrawing and electron-donating groups in alkynes were tolerated and some regioselectivity was witnessed in the case of unsymmetrically substituted diarylacetylenes. Irrespective of the position of electron-donating and electron neutral substituents on the aryl ring, various *N*-alkoxy benzamides gave the isoquinolones **308** in 46–85% yield.[183]

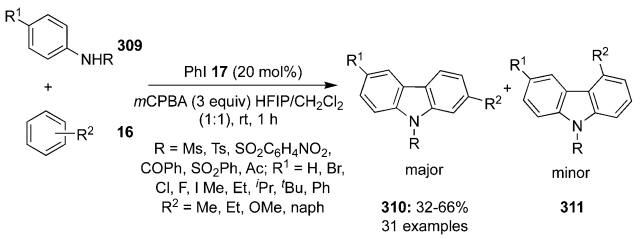
In 2017, Mal and co-workers reported the synthesis of multi-substituted carbazoles **310** in moderate to good yields *via* an intermolecular dehydrogenative annulation reaction of anilides **309** and arenes **16** (Scheme 91).[184] A trace amount of minor isomer **311** was also observed. Both, a stoichiometric and an organocatalytic version of this reaction were developed. The catalytic condition involved the use of iodobenzene **17** as the precatalyst, *m*CPBA as the oxidant and HFIP/dichloromethane as solvent at room temperature. Various anilides with electron-withdrawing and electron-donating substituents at *para*-position and arenes with alkyl/aryl/alkoxy groups provided the desired products and sulfonyl or carbonyl groups on nitrogen atoms of the anilides were also tolerated. The catalytic pathway was found to be less effective compared to the stoichiometric one.

The synthesis of benzimidazoles **313** and quinoxalines **315** was developed by Kamal and co-workers using hypervalent iodine catalysis.[185] The condensation of *o*-phenyldiamines **312** with various aryl or heteroaryl aldehydes **97** afforded the corresponding benzimidazoles **313** in good to excellent yields (Scheme 92). Moreover, the condensation of *o*-phenyldiamines **312** with benzil **314** provides quinoxalines **315** in excellent yields (Scheme 92). During these annulations, very low catalytic loading of Koser's reagent **4** (1 mol%) was sufficient to achieve the products in high yields.

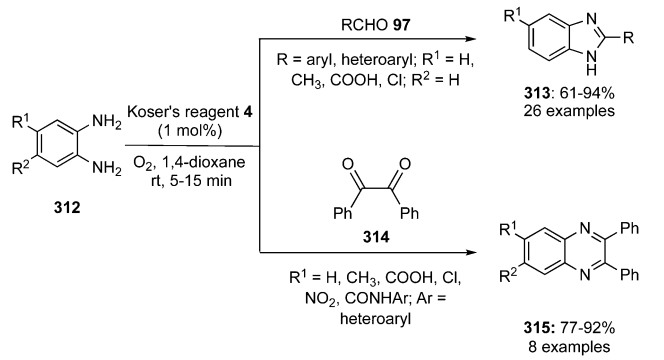
5.2.2. Synthesis of N,O-heterocycles. In the past years, organocatalysis involving hypervalent iodine catalysts has been used to construct various N,O-heterocycles.[3] Zhdankin and co-workers developed a catalytic system using hypervalent iodine(III) reagents for the synthesis of pyrrolo isoxazolines **320** *via* the oxidative cycloaddition of aldoximes **316** with maleimide **319** (Scheme 93).[186] This catalytic protocol involves an *in situ* generation of the cyclic iodine(III) species **318** (IBA-OTf) by oxidation of 2-iodobenzoic acid **317** with *m*CPBA in the presence of trifluoromethanesulfonic acid. Various substituted aromatic aldoximes **316** with electron-rich and electron-poor aryl rings were tolerated. The same research group reported also a similar catalytic protocol for the oxidative cycloaddition



Scheme 90 Iodine(III)-catalysed cycloaddition of benzamides **306** with alkynes **307** to isoquinolones **308** using PhI **17** as precatalyst.



Scheme 91 Iodine(III)-catalysed intermolecular dehydrogenative annulation reaction of anilides **309** and arenes **16**.



Scheme 92 Iodine(III)-catalysed synthesis of benzimidazoles **313** and quinoxalines **315** using Koser's reagent **4** as catalyst.

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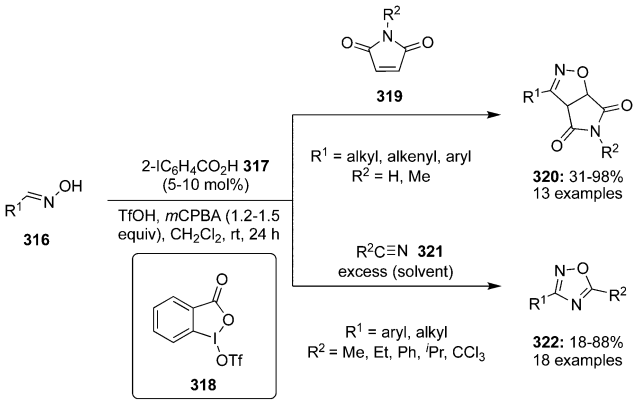
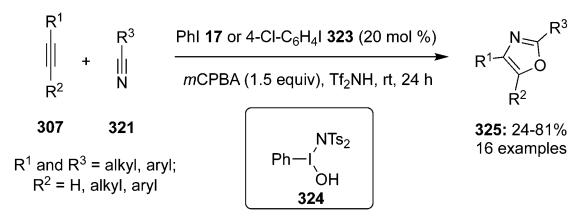


Scheme 93 Iodine(III)-catalysed oxidative cyclisation of aldoximes **316** with maleimide **319** and organonitriles **321** to N,O-heterocycles **320** and **322**.

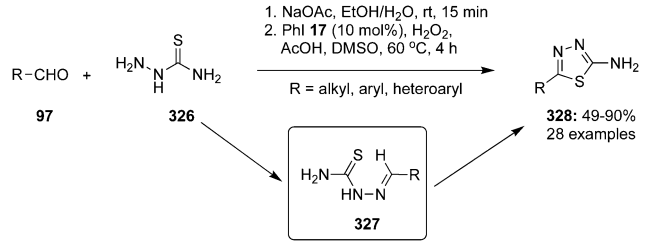
of aldoximes **316** with organonitriles **321** to prepare 1,2,4-oxadiazoles **322** (Scheme 93).[187] Moreover, similar substrates were employed in the annulations using modified reaction conditions.[188]

2,4-Disubstituted and 2,4,5-trisubstituted oxazoles **325** were synthesised regioselectively through a [2+2+1] addition of internal as well as terminal alkynes **307**, nitriles **321** and oxygen atoms employing iodine(III) catalysis. The scope of the reaction was examined by using two different precatalyst PhI **17** and 4-ClC_6H_4I **323** in the presence of *m*CPBA and Tf_2NH. All the cyclisation reactions were performed at room temperature and cyclised products were obtained in moderate to good yields (Scheme 94).[189] Mechanistic studies showed the involvement of iodine(III) species in the catalytic cycle and the active catalytic iodine(III) intermediate $PhI(OH)NTf_2$ **324** was isolated. The hypervalent iodine catalysis was also employed for the construction of isoxazole systems.[190] Moreover, a few other catalytic systems have been used to build similar scaffolds.[191]

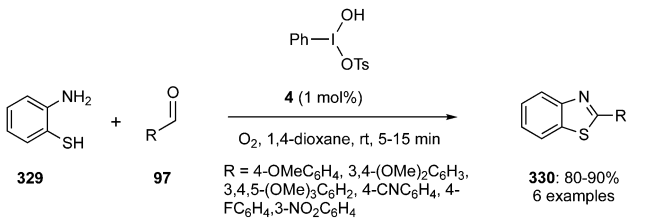
5.2.3. Synthesis of N,S-heterocycles. Wang and co-workers established a catalytic protocol for the preparation of various thiadiazole scaffolds **328** through an intermolecular oxidative annulation *via* the formation of an intermediate **327** formed from aldehydes **97** and thiosemicarbazide **326** employing a catalytic method consisting of iodobenzene **17**, H_2O_2 and AcOH (Scheme 95).[192] Mono- and di-substituted aryl aldehydes irrespective of the position of functional groups gave moderate to excellent yields. Naphthyl, heteroaryl and alkyl aldehydes were also tolerated.



Scheme 94 Iodine(III)-catalysed cycloaddition of alkynes **307** with nitriles **321** to trisubstituted oxazoles **325**.



Scheme 95 Iodine(III)-catalysed oxidative cyclisation of thiosemicarbazides **326** with aldehydes **97** to thiadiazoles **328** using iodobenzene **17** as precatalyst.



Scheme 96 Iodine(III)-catalysed synthesis of benzothiazoles **330** using Koser's reagent **4** as catalyst in the presence of molecular oxygen.

Kamal and co-workers described the synthesis of benzothiazoles **330** by the condensation of 2-aminothiophenol **329** with aromatic aldehydes **97** using Koser's reagents as catalyst in the presence of molecular oxygen. Reactions were completed in short reaction time and afforded the benzothiazoles **330** in excellent yields (Scheme 96).[185] During these cyclisations, a very low catalytic loading (1 mol%) was sufficient for catalysis to the cyclised products in high yields. Notably, aromatic aldehydes bearing electron donating groups showed slightly better yields compare to substrates with electron withdrawing groups.

6. Oxidative rearrangements

Hypervalent iodine reagents are known for activating the olefinic double bonds and later they behave as good leaving groups.[23] Additionally, they can participate in the formation of cationic intermediates that lead to variety of rearrangement reactions.[35] Initially, the focus of hypervalent iodine chemists was on the developments of oxidative rearrangements using hypervalent iodine reagents in stoichiometric amounts but later rearrangements have been developed using hypervalent iodine catalysis.[3] Some rearrangements have already been described in Section 3.5.2 discussing the geminal difluorination of alkenes.[136,142]

6.1. 1,2-Aryl/alkyl migration reactions

In 2018, Mal and co-workers developed an iodine(III)-catalysed C–H functionalisation of *N*-(5-bromo-2′,4′,6′-triethyl-[1,1′-biphenyl]-2-yl)methanesulfonamide **331** to carbazole **332** along with an 1,2-migration of an ethyl group.[193] The reaction was carried out by using 20 mol% of iodobenzene **17** in the presence of *m*CPBA in trifluoroethanol and the rearranged

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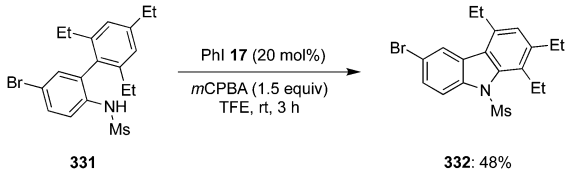
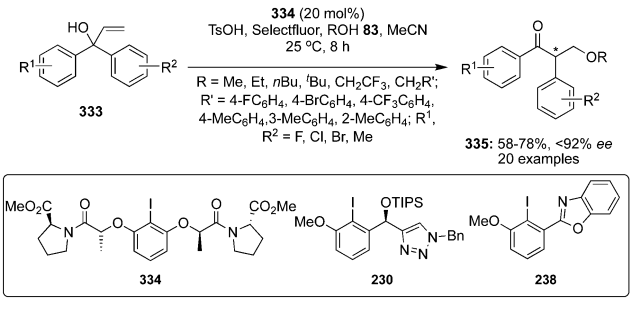


Scheme 97 Iodine(III)-catalysed C–H functionalisation of biphenylsulfonamide **331** to carbazole **332** along with 1,2-ethyl group migration.

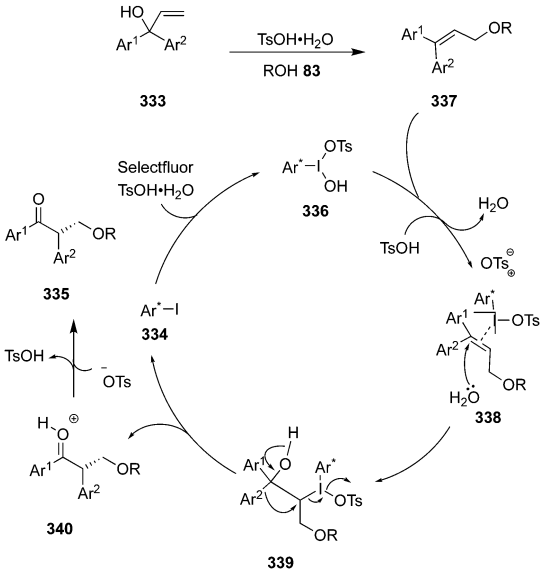
product **332** was obtained in 48% yield (Scheme 97). Notably, the stoichiometric version of the same reaction was also developed and rearranged products were obtained in better yields compare to the catalytic reaction.

An enantioselective rearrangement of allylic alcohols **333** using (*S*)-proline-derived chiral iodoarene **334** as precatalyst assisted by the Brønsted acid *p*-TsOH was described by Gong and co-workers.[194] Brønsted acids promote the formation of ethers from allylic alcohols whereas the chiral aryl iodide catalyses the 1,2-aryl migration to afford chiral α-arylated-β-alkoxylated ketones **335** in good yields and with excellent enantiomeric excess (Scheme 98).[194] The presence of electron withdrawing and electron donating groups at *para*- or *meta*-position of the phenyl rings of allylic alcohols are well tolerated. Moreover, N-heterocyclic substituted chiral iodoarene precatalyst (NHIA) **230** was also employed to perform these rearrangements under almost similar catalytic reaction conditions and the selectivity was increased to up to 98% ee.[195] The same rearrangement was also achieved by using another N-heterocyclic substituted achiral precatalyst **238** in moderate yields.[160]

A plausible mechanistic pathway for the enantioselective 1,2-aryl migration in allylic alcohols **333** catalysed by *in situ* generated chiral iodine(III) reagent is shown in Scheme 99.[193] Initially, the allylic alcohol **333** reacts with ROH **83** to form an alkoxylated product **337**. Simultaneously, aryl iodide **334** is oxidized to iodine(III) **336** which activates the double bond of diarylalkene **337** in presence of *p*-TsOH to give complex **338**. Nucleophilic attack on **338** by H_2O generates the intermediate **339** which undergoes a semipinacol-type rearrangement to furnish intermediate **340** along with regeneration of the



Scheme 98 Iodine(III)-catalysed enantioselective 1,2-aryl migration of allylic alcohols **333** to ketones **335** using C_2-symmetric iodoarene **334** and N-heterocyclic substituted chiral iodoarene **230** and achiral iodoarene **238** as precatalysts.

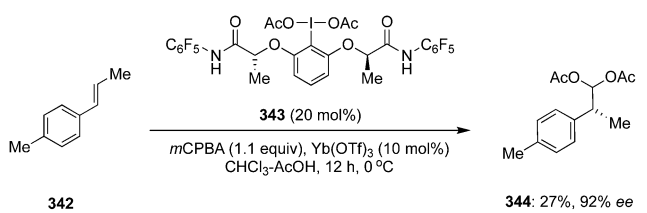


Scheme 99 Plausible catalytic cycle for the (*S*)-proline-derived chiral iodoarene-catalysed 1,2-aryl migration in allylic alcohols **333**.

precatalyst **334**. Finally, deprotonation of intermediate **340** gives the product **335**.

In 2020, Tiwari and co-workers reported an iodine(III)-catalysed enantioselective 1,2-tolyl group migration with geminal diacetoxylation of aromatic alkene **342**.[196] The reaction was performed at low temperature with the rearranged product **344** obtained in 27% yield with up to 92% ee (Scheme 100). The catalytic system involved 20 mol% chiral iodine(III) catalyst **343** and *m*CPBA in $CHCl_3$: AcOH (1 : 1). Some research groups have achieved a similar 1,2-aryl migration reactions by using ammonium iodide[197] and molecular iodine[198] as catalysts. Hypervalent iodine catalytic species are not generated during these two rearrangements but these transformations may be quite useful for the readers who are working in hypervalent iodine catalysis.

In 2015, Gulder and co-workers reported a novel rearrangement of imides **345** using catalytic amounts of iodobenzamide **346** in the presence of *N*-bromosuccinimide (NBS) **347** as oxidant in hexafluoro-2-propanol (HFIP) at room temperature.[199] This metal-free route lead to the facile preparation of valuable α,α-disubstituted-α-hydroxycarboxylamides **349** in good to excellent yields (Scheme 101).[199] The reaction involved the formation of cyclic hypervalent iodine(III) species (bromo benziodoxole) **348** by oxidation of iodobenzamide **346** with NBS **347**. Notably, none of these reactions exhibited aryl bromination and longer reaction



Scheme 100 Iodine(III)-catalysed 1,2-tolyl group migration with geminal diacetoxylation of alkene **342** using chiral iodine(III) catalyst **343**.

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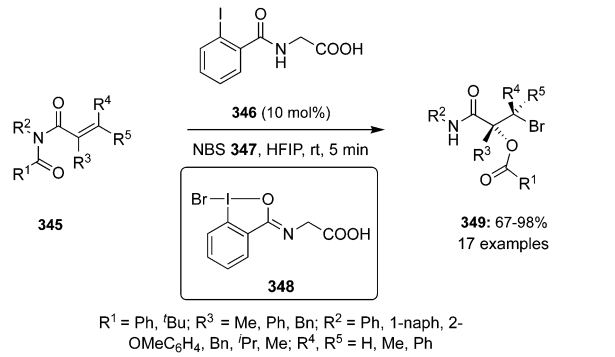
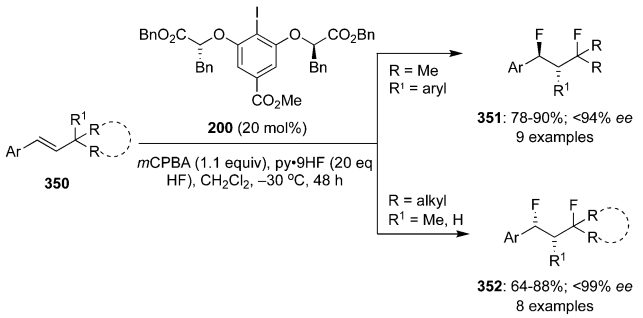


Scheme 101 Hypervalent iodine-catalysed rearrangement of imides **345** to **349** by involving cyclic iodine(III) reagent **348** as catalyst.



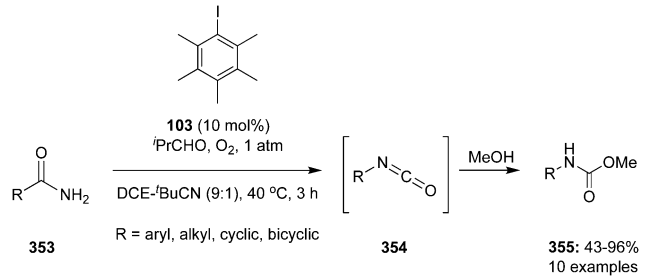
Scheme 102 Iodine(III)-catalysed Wagner–Meerwein rearrangements of β-substituted styrenes **350** to 1,3-difluorinated products **351** and **352** using C_2-symmetric chiral iodoarene **200** as precatalyst.

times were observed with reduced catalyst loading and when bromo benziodoxole **348** was used instead of NBS **347**.

In 2020, an iodine(III)-catalysed enantioselective Wagner–Meerwein rearrangement of β-substituted styrenes **350** involving aryl, alkyl and hydride migrations was published affording 1,3-difluorinated products **351** and **352** in good to excellent yields with an excellent enantiomeric excess (Scheme 102).[200] The catalytic system comprises of chiral aryl iodide **200** as precatalyst, *m*CPBA as the oxidant and py·9HF as the fluoride source. Notably, the 1,2-*anti*-diastereomers **351** were obtained when aryl is the migrating group and 1,2-*syn* diastereomers **352** were obtained when methyl is the migrating group (Scheme 102).

6.2. Hofmann rearrangements

Also Hofmann rearrangements have been developed by using hypervalent iodine reagents in stoichiometric amounts.[36,37] The first report on the Hofmann rearrangement appeared in 2012 by Ochiai and his research group.[201] Later in the same year, the application of hypervalent iodine catalysis in Hofmann rearrangements was extended by Zhdankin and co-workers.[202] In 2017, Hofmann rearrangements of primary amides **353** to carbamates **355** was successfully achieved by Miyamoto and co-workers using precatalyst **103**,



Scheme 103 Iodine(III)-catalysed Hofmann rearrangement of primary amides **353** to carbamates **355** *via* the formation of isocyanate intermediate **354**.

molecular oxygen as an oxidant and isobutyraldehyde as the O_2 mediator.[97]

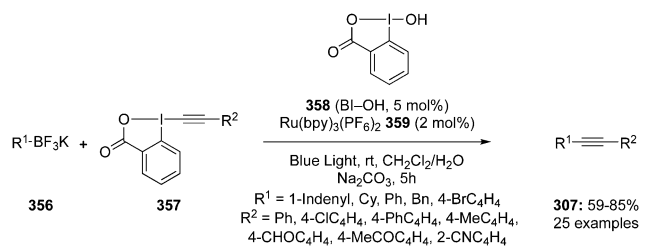
The rearranged products were obtained in moderate to excellent yields (Scheme 103). A variety of aliphatic as well as aryl amides were tolerated.

7. Photoredox catalysis

Hypervalent iodine reagents have a unique property of producing free radicals that makes these reagents suitable for photochemical reactions.[203] In past decade, a number of hypervalent iodine reagents have been successfully employed in photoredox catalysis.[19] In the majority of these hypervalent iodine induced photoredox reactions, the iodine reagents have been used in stoichiometric amounts, but there are few photoredox reactions where these reagents play a role of co-catalysts in combination with photoredox catalysts. In this section, the photoredox reactions catalysed by both hypervalent iodine and photoredox catalysts are highlighted.

7.1. Alkynylations

In 2014, Chen and others reported the deboronative alkynylation of potassium alkyl trifluoroborates **356** with EBX (ethynyl-benziodoxole) **357** as alkynyl source under visible-light catalysis conditions (Scheme 104).[204] The ruthenium complex [Ru(bpy)$_3$](PF$_6$)$_2$ **359** (2 mol%) was employed as photoredox catalyst in the presence of a catalytic amount of hydroxybenziodoxole (BI–OH) **358** as radical initiator. Blue light irradiation was critical to drive the photoredox reaction and the anticipated 1,3-disubstituted alkynes **307** were obtained in good yields.



Scheme 104 Iodine(III)-catalysed deboronative alkynylation of potassium alkyl trifluoroborates **356** with alkynyl benziodoxole **357** to alkynes **307** using photoredox catalysis in the presence of catalyst BI–OH **358**.

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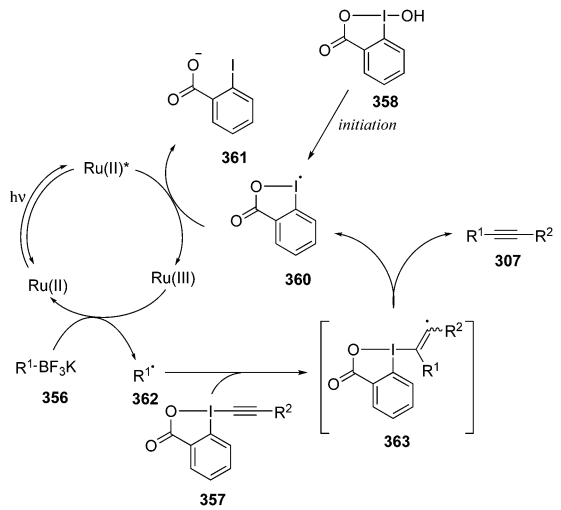
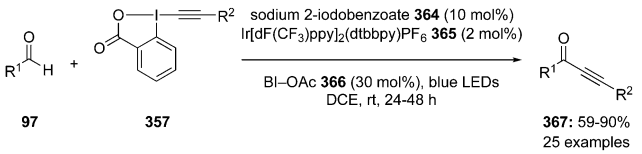


Scheme 105 Proposed catalytic cycle for iodine(III)-catalysed alkynylation of potassium alkyl trifluoroborates **356** to alkynes **307** using photoredox catalysis.

This reaction was highly chemoselective and tolerated a wide range of functional groups.

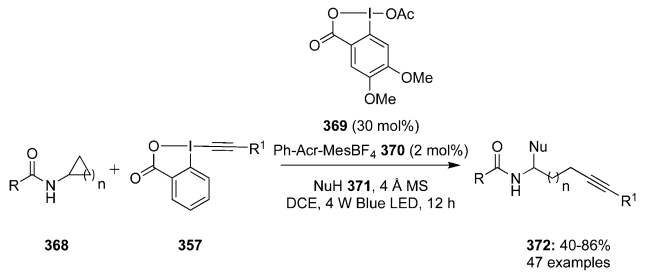
Scheme 105 depicts the proposed catalytic cycle for the photoredox-catalysed deboronative alkynylation of potassium alkyl trifluoroborates **356** with EBX **357**. Initially, photoexcitation of $Ru(bpy)_3^{2+}$ takes place to give $Ru(bpy)_3^{2+*}$, which is further oxidized to $Ru(bpy)_3^{3+}$ either by the benziodoxole radical **360** or its precursor BI–OH **358**. Eventually, $Ru(bpy)_3^{3+}$ oxidises alkyl trifluoroborate **356** to an alkyl R^1 radical **362** and regenerates $Ru(bpy)_3^{2+}$. Finally, α-addition of alkyl R^1 radical **362** to EBX **357** provides the desired alkynes **307** *via* formation of intermediate **363** and eliminates benziodoxole radical **360** which later oxidizes $Ru(bpy)_3^{2+*}$ to $Ru(bpy)_3^{3+}$ and forms *ortho*-iodobenzoic acid.

Glorius and co-workers developed a hydrogen atom transfer (HAT) method for the selective alkynylation of sp^2 C(O)–H bond of aldehydes **97** *via* photoredox catalysis (Scheme 106).[205] This process delineates effective synthesis of ynones **367** by treating aldehydes **97** with ethynylbenziodoxole (EBX) **357** using catalytic amounts of sodium 2-iodobenzoate **364** and BI–OAc **366** in the presence of photocatalyst **365**. Notably, sodium benzoate as HAT catalyst reductively quench the excited Ir(III)* to Ir(II) and generates a 2-iodobenzoyloxyl radical, which selectively



R^1 = ^{i}Pr, Bn, cyclopropyl, admentyl, $BnCH_2$, $iPrCH_2$, pentyl, 2-thienyl, Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$CF_3C_6H_4$, PhO, piperidine, $(^n Bu)_2N$ etc; R^2 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 3-$OMeC_6H_4$, TIPS

Scheme 106 Photoredox-catalysed alkynylation of aldehydes **97** with alkynyl benziodoxole **357** to ynones **367** using a catalytic amount of BI–OAc **366**.



n = 1, 2; NuH = nBuOH, MeOH, H_2O, 1-naphthol, MeC_6H_4S, indole, *N*-Me-indole, TMSCN; R = Ar, 2-naph, 2-thienyl, Bn, ^{t}Bu, O^{t}Bu, OPh; R^1 = Ar, Si^{i}Pr$_3$, TBS, TMS, ^{t}Bu

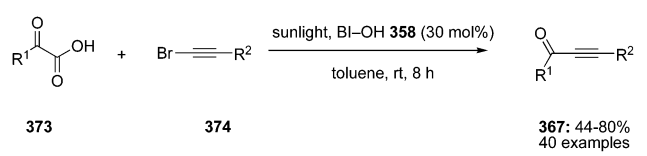
Scheme 107 Photoredox-catalysed synthesis of aminoalkynes **372** from cycloalkylamides **368** *via* a selective $C(sp^3)$–$C(sp^3)$ cleavage/alkynylation strategy.

abstracts a hydrogen and forms the carbonyl radical of the substrates. The scope of the reaction was widely explored with different aliphatic and aromatic aldehydes and the corresponding alkynylation products were obtained in decent yields.

In 2021, Chen and others reported the synthesis of aminoalkynes **372** from cycloalkylamides **368** *via* a selective $C(sp^3)$–$C(sp^3)$ cleavage/alkynylation strategy using photoredox catalysis.[206] The reaction employed Ph-Acr-MesBF_4 **370** as photocatalyst and catalytic amounts of cyclic iodine(III) reagent 3,4-OMe-BI-OAc **369** (Scheme 107). The photoredox catalyst **370** was quite effective at low catalyst loading. Notably, **369** noncovalently activates cycloalkylamide **368** thereby facilitating the single-electron oxidation and ring-opening alkynylation as governed by various mechanistic probing experiments. A variety of nucleophiles **371** such as *n*-butanol, methanol, water, *p*-toluenethiol, 1-naphthol, TMSCN, indole and *N*-Me-indole were used to trap the iminium intermediate to give the desired aminoalkyne products in decent yields. Additionally, the bifunctional aminoalkynes were used to prepare indolizidine-fused azacycles *via* metal-catalysed cyclisations.

7.2. Decarboxylative coupling of α-ketoacids

Wang and co-workers described the decarboxylative alkynylation of α-ketoacids **373** with functionalised bromoacetylenes **374** using BI–OH **358** as catalyst under sunlight irradiation. This method tolerated a wide range of functional groups and led to the energy-efficient synthesis of ynones **367** in good yields (Scheme 108).[207] The substrate scope showed that bromoacetylenes functionalised with electron-withdrawing groups



R^1 = Ph, 4-BrC_4H_4, 4-ClC_4H_4, 4-FC_4H_4, 4-MeC_4H_4, 4-$OMeC_4H_4$, 2-BrC_4H_4, 2-ClC_4H_4, 2-FC_4H_4, 2-MeC_4H_4, 2-$OMeC_4H_4$, 2,4-$Me_2C_4H_3$, 2,5-$Me_2C_4H_3$, 3,4-$(OMe)_2C_4H_3$
R^2 = Ph, 4-ClC_4H_4, 4-BrC_4H_4, 4-FC_4H_4, 4-$OMeC_4H_4$, 3-MeC_4H_4, 2-BrC_4H_4

Scheme 108 Photoredox catalysed decarboxylative coupling of α-ketoacids **373** with bromoacetylenes **374** to ynones **367** using BI–OH **358** as catalyst in the presence of sunlight.

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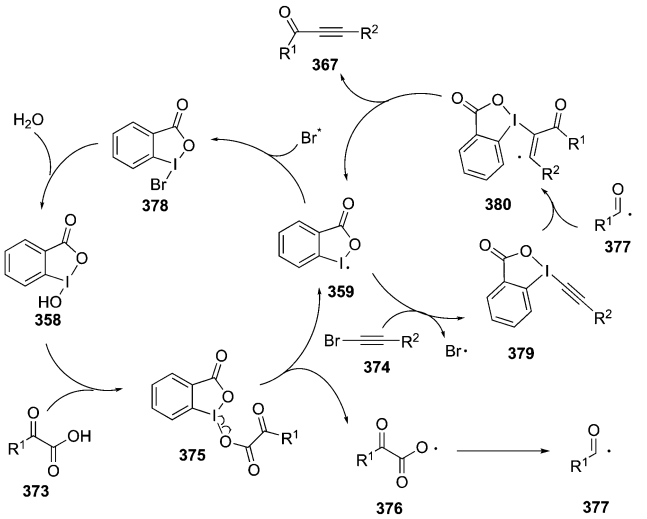


Scheme 109 Proposed catalytic cycle for the sunlight-driven decarboxylative coupling of α-ketoacids **373** with bromoacetylenes **374** to ynones **367**.

provided higher product yields while those with electron-donating groups showed inferior yields. Notably, the results of sunlight-driven reaction were comparable to those obtained by using blue light (λ = 450–455 nm).

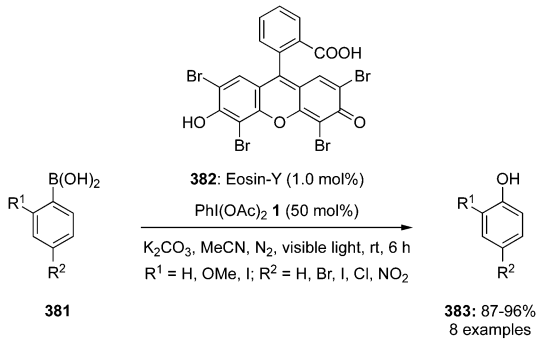
The possible catalytic cycle for the decarboxylative coupling reaction is summarized in Scheme 109. Initially, BI–OH **358** reacts with α-ketoacid **373** to form the intermediate **375**, which upon sunlight irradiation generates iodanyl radical **359** and acyl radical **376**. The iodanyl radical **359** reacts with bromoacetylene **374** to give BI–alkyne intermediate **379** along with the formation of a Br radical. Subsequently, the addition of acyl radical **377** to the intermediate **379** forms intermediate **380**, which eventually releases the coupling product **367** and regenerates intermediate **359**. Finally, coupling of iodanyl radical **359** with bromine radical produces bromobenziodoxole **378**, which undergoes hydrolysis to regenerate BI–OH **358**.

7.3. Synthesis of phenols

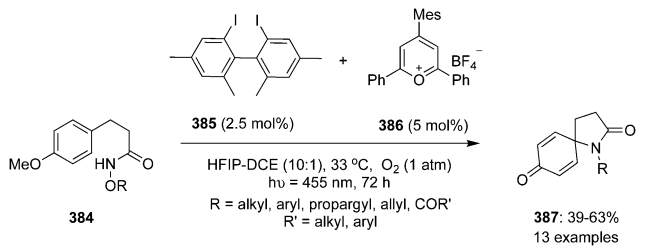
In 2015, an organo-photoredox catalysed activation of $PhI(OAc)_2$ **1** was reported by Yadav and co-workers for the conversion of arylboronic acids **381** to phenols **383**.[208] This transformation was performed with 1.0 mol% of Eosin Y **382** as photoredox catalyst and K_2CO_3 as base in acetonitrile under visible light irradiation (Scheme 110). The reaction proceeded smoothly with substrates bearing electron-donating or electron-withdrawing substituents and the corresponding phenols **383** were isolated in excellent yields. Notably, the photo-chemically excited Eosin Y activates $PhI(OAc)_2$ **1** to form a methyl radical, which plays a key role for conversion of arylboronic acids to phenols.

7.4. Dearomatisation

Furthermore, photoredox catalysis was employed for the dearomatisation of *p*-substituted anisole derivatives **384** to spirolactams **387** under blue light irradiation.[209] Photoredox catalyst



Scheme 110 Photoredox-catalysed synthesis of phenols **383** from arylboronic acids **381**.



Scheme 111 Photoredox catalysed dearomatisation of *p*-substituted anisole derivatives **384** to spirolactams **387** using Kita's catalyst **385** under blue light irradiation.

386 and iodoarene **385** used were mesityl-2,6-diphenylpyrylium tetrafluoroborate (MDPT) and Kita's catalyst, respectively. The substrates with electron-withdrawing groups and those groups capable of stabilising a putative radical intermediate on nitrogen were found ineffective while electron-rich groups were tolerated successfully. All dearomatisation reactions required longer reaction time and the products were isolated in reasonable yields (Scheme 111).

8. Photochemical reactions

There are several hypervalent iodine mediated reactions driven by light.[19] Moreover, there are hypervalent iodine catalysed organic reactions that require light to proceed. The visible-light driven decarboxylative acylarylation of acrylamides **388** with α-ketoacids **373** was developed using hypervalent iodine(III)-catalysis. This method led to the energy-efficient synthesis of 3,3-disubstituted 2-oxindoles **389** in good yields without using any photoredox catalyst (Scheme 112).[210] Hypervalent iodine reagent BI–OAc **366** was employed as catalyst, which generates the radical species by cleavage of oxygen–iodine bond in the presence of blue LED (450–455 nm). The course of the reaction was examined with a diverse array of *N*-methyl-*N*-arylmethacrylamides **388**, functionalised with electron-donating or withdrawing groups at the benzene ring and produced 2-oxindoles **389** in good yields. Notably, ketoacids **373** with electron-donating substituents in the aryl ring provided slightly higher yields.

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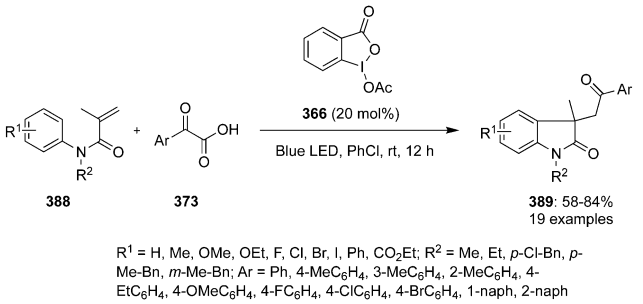
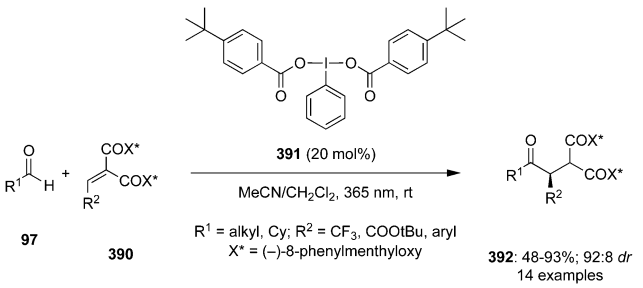


Scheme 112 Visible-light driven decarboxylative acylarylation of acrylamides **388** with α-ketoacids **373** using hypervalent iodine(III)-catalysis.

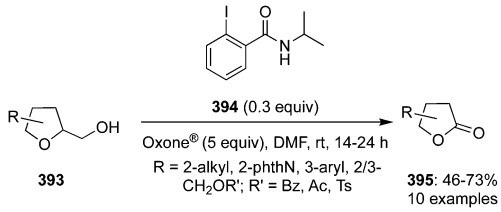


Scheme 113 Iodine(III)-catalysed diastereoselective hydroacylation of alkylidenemalonates **390** with aldehydes **97** under UV irradiation using iodine(III) catalyst **391**.

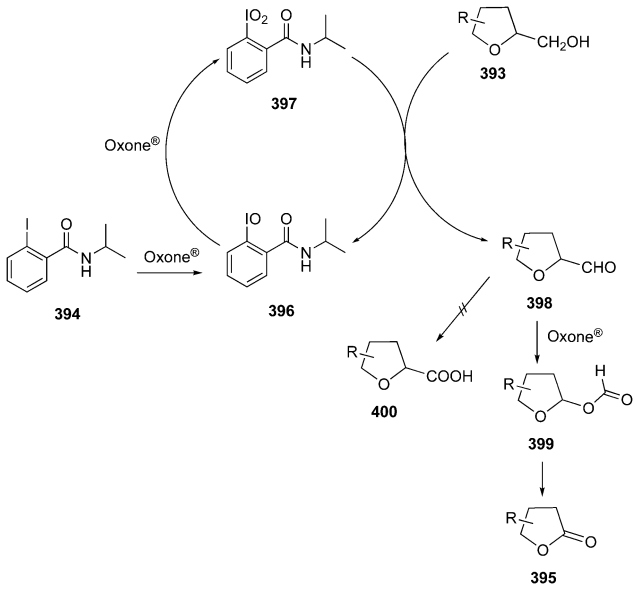
A photocatalytic approach towards the synthesis of chiral ketones **392** was introduced by Maruoka and co-workers using hypervalent iodine catalysis.[211,212] In this study, the diastereoselective radical hydroacylation of alkylidenemalonates **390** was developed with various linear and branched chain aldehydes **97** under UV light irradiation using hypervalent iodine **391** as catalyst. Chiral ketones **392** were obtained in good yields with high diastereoselectivity accomplished by employing (−)-8-phenylmenthol as chiral auxiliary (Scheme 113). Acyl radical addition preferably takes place at the less sterically hindered face of the alkenes and thereby (*S*)-isomers forms predominantly because of the effective shielding of Re face by the phenyl group of the chiral auxiliary.[211] Moreover, the same approach was successfully applied for the synthesis of (−)-methyleneolactocin.[212]

9. Miscellaneous reactions

Hypervalent iodine catalysis is used to achieve many different organic transformation and it is not possible to categorise all of the published reactions. Yakura *et al.* developed a mild, efficient and eco-friendly iodine(v)-catalysed oxidative cleavage of tetrahydrofuran-2-methanols **393** to form γ-lactones **395** using 2-iodobenzamide **394** as precatalyst and Oxone® as co-oxidant (Scheme 114).[213] The corresponding γ-lactones **395** were obtained in moderate to good yields. This protocol provides an alternate route to access functionalized γ-lactones **395** at room temperature under metal-free conditions.



Scheme 114 Iodine(v)-catalysed oxidative cleavage of tetrahydrofuran-2-methanols **393** to γ-lactones **395**.



Scheme 115 Catalytic cycle for an iodine(v)-catalysed oxidative cleavage of tetrahydrofuran-2-methanols **393** to γ-lactones **395**.

The catalytic cycle for an iodine(v)-catalysed oxidative cleavage of tetrahydrofuran-2-methanols **393** to γ-lactones **395** is explained in Scheme 115. The reaction begins with the oxidation of iodobenzamide **394** by Oxone® to give iodine(v) species **397** *via* formation of iodine(III) intermediate **396**. Iodine(v) species **397** oxidises the alcohol **393** to generate key aldehyde intermediate **398** along with the regeneration of iodine(III) species for the next cycle. Eventually, the aldehyde **398** reacts with Oxone® to form formate **399** *via* a Baeyer–Villiger type rearrangement which is oxidised to the desired lactone **395**. Notably, the aldehyde **398** did not oxidise to the corresponding carboxylic acid **400**.

Hu and colleagues developed an iodine(III)-catalysed Balz–Schiemann fluorination of aromatic diazonium salts **401** under mild reaction conditions where the iodine(III) species lowered the energy activation barrier of the reaction.[214] A wide range of aromatic fluorides **405** were prepared in good yields in the presence of **402–404** as iodine(III) catalysts and $BF_3{\cdot}Et_2O$ as additive (Scheme 116).

Cyclopropanes behave often similar to olefins and can be activated by hypervalent iodine compounds.[21] In 2017, hypervalent iodine catalysis has been used for the oxidative ring opening of substituted cyclopropanes **407** to obtain 1,3-difluorinated

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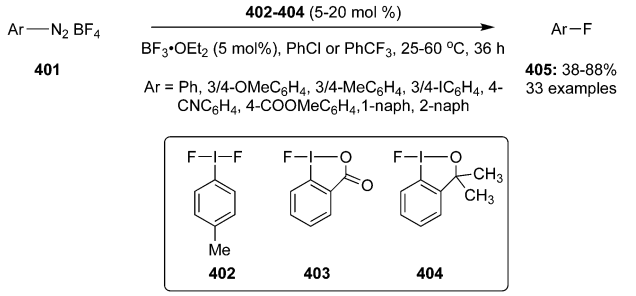
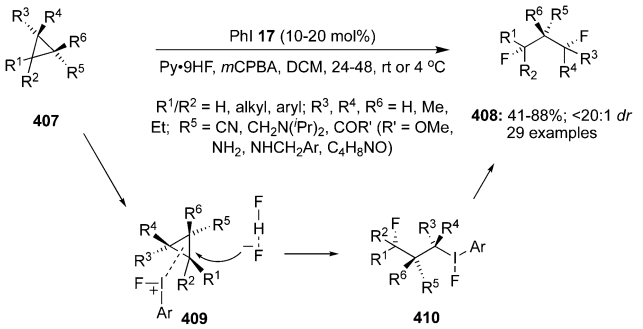


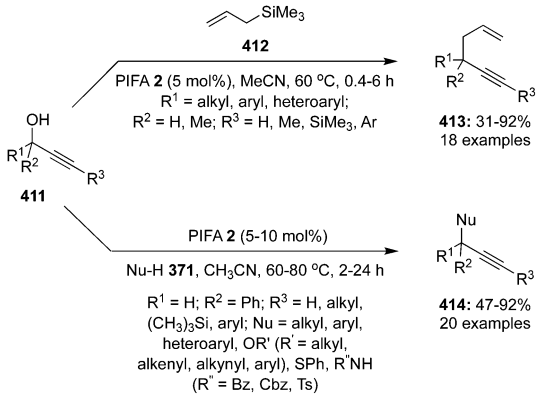
Scheme 116 Iodine(III)-catalysed Balz–Schiemann fluorination of aromatic diazonium salts **401** to aryl fluorides **405** using iodine(III) catalysts **402–404**.



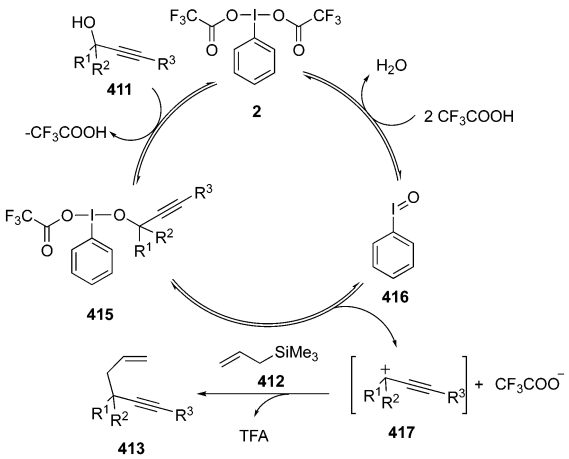
Scheme 117 Iodine(III)-catalysed ring opening of cyclopropanes **407** to 1,3-difluorinated compounds **408**.

compounds **408** using PhI **17** as precatalyst and Py·9HF as source of fluoride in the presence of *m*CPBA (Scheme 117).[215] Arylcyclopropanes **407** with electron-withdrawing substituents were tolerated while those with electron-donating substituents were not. With increased catalytic loadings (20 mol%), non-conjugated mono-substituted cyclopropanes **407** bearing ether and amine functionalities afforded difluorinated products **408** in good to excellent yields. The reaction involves the formation of key intermediate **409** that converts into a fluoroiodine(III) species **410**. Eventually, iodine(III) intermediate **410** gave the final product **408** either through a S_N1 route involving the formation of a tertiary carbocation or through a concerted backside fluoride substitution, the latter affords diastereomerically enriched products.

The acidic PIFA **2** was explored as catalyst for nucleophilic substitutions of internal and terminal propargylic alcohols **411**.[216] Aromatic and heteroaromatic propargyl alcohols **411** with electron-donating substituents reacted faster with allyl silyl ethers **412** to afford 1,5-enynes **413** in good yields using PIFA **2** as catalyst in the absence of any oxidant (Scheme 118). Various acid and transition metal sensitive groups such as halogens, methoxy, silyl and heterocyclic rings, and cyano groups were tolerated. Additionally, Friedel–Crafts type propargylation went smoothly with aromatic compounds, O, S and N nucleophiles **371** to afford propargylic arenes/ethers/sulfides/amides **414** in moderate to excellent yields (Scheme 118).



Scheme 118 Iodine(III)-catalysed nucleophilic substitution of propargyl alcohols **411** using PIFA **2** as catalyst without using any terminal oxidant.



Scheme 119 Mechanism for the PIFA-mediated nucleophilic substitution of propargyl alcohols **411** using PIFA **2** as catalyst.

The intermediate propargylic cation was generated by the reversible equilibrium between propargyl alcohol **417** and the PIFA **2** catalyst. Scheme 119 shows the proposed mechanism for the formation of an adduct **415** from the ligand exchange of PIFA **2** with propargyl alcohol **411**, which decomposes into iodosobenzene **416** and progarylic carbocation **417**. Propargylic carbocation **417** undergoes a nucleophilic substitution with allyl silyl ethers **412** to form substituted product **413**. Iodosobenzene **416** binds with the eliminated TFA to regenerate the catalyst **2**. The use of a stronger nucleophile would decrease the product yield due to the competition at the active site of PIFA **2** catalyst by the nucleophile and propargyl alcohol and anilines cannot be used as nucleophiles due to their Lewis basicity.[215]

Synthetically important *E*-vinyl boronates **420** were prepared by Wei and co-workers by the hydroboration of terminal alkynes **418** with bis(pinacolato)diboron (B_2pin_2) **419** using catalytic amounts of $PhI(OAc)_2$ **1** in the presence of ^tBuONa and EtOH as the hydrogen donor in air (Scheme 120).[217] Aromatic as well as aliphatic terminal alkynes **418** gave moderate to good yields with good regio- and stereoselectivity.

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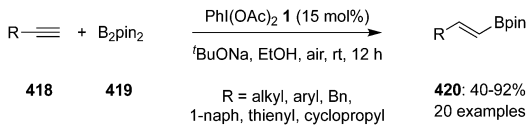
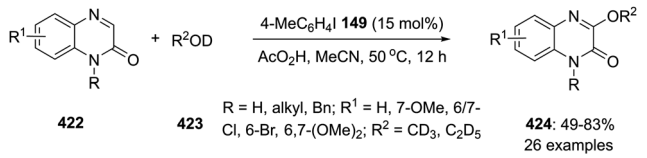


Scheme 120 Iodine(III)-catalysed hydroboration of alkynes **418** with **419** to **420** using $PhI(OAc)_2$ **1** as catalyst.



Scheme 121 Iodine(III)-catalysed synthesis of trideutero alkoxylated quinoxalinones **424** using **149** as catalyst.

A facile and effective iodine(III)-catalysed synthesis of pharmacologically important trideuteroalkoxylated quinoxalinones **424** was established by Shen and co-workers using a cross-dehydrogenative coupling of quinoxalinones **422** with deuterated alcohols **423** and 4-iodotoluene **149** as precatalyst in the presence of peracetic acid (Scheme 121).[218] Irrespective of the nature and position of different substituents on the quinoxaline rings, several *N*-substituted quinoxalin-2(1*H*)-ones gave the corresponding products in good yields.

10. Conclusions

In this review article, we highlight recent applications of organocatalysis involving hypervalent iodine catalysts in organic synthesis. Hypervalent iodine catalysis has been used for the preparation of various synthetic intermediates such as amines, carbonyl compounds, alcohols, acetals and organofluorine derivatives. Some of these catalytic approaches have been used to construct biologically active heterocyclic and spirocyclic scaffolds. Additionally, hypervalent iodine catalysis has been used significantly in asymmetric synthesis with high stereoselectivity. Mainly, hypervalent iodine catalytic species were generated *in situ* by the oxidation of iodoarene precatalysts using stoichiometric oxidants such as Oxone® and peroxyacids like *m*CPBA. In a few catalytic reactions, the catalysts were reused several times without losing their catalytic potential. In this era of ever growing interest in green chemistry, the readily available environmentally benign hypervalent iodine compounds with their ease of handling are in increasing demand as green and environmentally sustainable alternatives to heavy metals in synthetic organic chemistry. Improving the catalytic attributes of hypervalent iodine is continuing to be a challenging goal. In addition, the improvements on the stoichiometric oxidant needed for all the transformations has to be considered in the future. Recent developments such as the use of oxygen (air) or electricity seem to be highly promising in advancing this area. The often delicate balance between substrate and iodine reactivity has to be further understood and investigated as there is the need of more general applicable catalysts, especially when considering stereoselective reactions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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