N-Heterocyclic Iodanes and Iodonium Salts
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Synthesis, Characterization and Applications

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“It doesn’t stop being magic

just because you know how it works.”

-Terry Pratchett-

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Abbreviations

Ac	acetyl
$[BAr^F{}_{24}]^-$	tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BX	benziodoxolone
BZ	benziodazolone
DDQ	4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile
DMP	*Dess-Martin-Periodinane*
DSC	differential scanning calorimetry
EBX	ethynylbenziodoxolone
EBZ	ethynylbenziodazolone
ee	enantiomeric excess
ENHI	ethynyl-*N*-heterocycle-stabilized iodane
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
IBA	iodosobenzoic acid
IBX	iodoxybenzoic acid
L	ligand
*m*CPBA	*meta*-chloroperbenzoic acid
Mes	mesitylene
MO	molecular orbital
NHI	*N*-heterocycle-stabilized iodane
Nu	nucleophile
PIDA	phenyliodine diacetate
PIFA	phenyliodine bis(trifluoroacetate)
Pin	pinacol
S_N	nucleophilic substitution
TBAF	tetrabutylammonium fluoride
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFE	2,2,2-trifluoroethanol
Tf	triflyl
TGA	thermogravimetric analysis
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	tosyl
VBX	vinylbenziodoxolone
XB	halogen bond

Declaration on the contribution of the candidate to a multi-author article/manuscript which is included as a chapter in the submitted dissertation

Contribution of the candidate in % of the total workload with up to 100% for each of the categories.

Chapter:

3.1 Oxidation of benzylic alcohols to carbonyls using *N*-heterocyclic stabilized λ^3-iodanes

Project concept and design	ca. 90%
Experimental work and/or acquisition of data	ca. 100%
Data analysis and interpretation	ca. 90%
Preparation of Figures, Schemes and Tables	ca. 90%
Drafting of the manuscript	ca. 80%

3.2 Stabilization of Ethynyl-Substituted Aryl-λ^3-Iodanes by Tethered *N*-Heterocycles

Project concept and design	ca. 30%
Experimental work and/or acquisition of data	ca. 80%
Data analysis and interpretation	ca. 80%
Preparation of Figures, Schemes and Tables	ca. 90%
Drafting of the manuscript	ca. 80%

3.3 Synthesis and reactivity of azole-based iodazinium salts

Project concept and design	ca. 90%
Experimental work and/or acquisition of data	ca. 80%
Data analysis and interpretation	ca. 80%
Preparation of Figures, Schemes and Tables	ca. 100%
Drafting of the manuscript	ca. 90%

Bremen, 04.11.2024, Thomas Kuczmera

Further publications

Synthesis, Structure, Thermal Behavior and cis/trans Isomerization of 2,2′-(EMe3)2 (E = C, Si, Ge, Sn) Substituted Azobenzenes

J. Hoffmann, T. J. Kuczmera, E. Lork, A. Staubitz, *Molecules* **2019**, 24, 303.
DOI: 10.3390/molecules24020303

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DOI: 10.1107/s2056989019014592

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A. Boelke, T. J. Kuczmera, E. Lork, B. J. Nachtsheim, *Chem. Eur. J.* **2021**, 27, 13128.
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Site Selective Concerted Nucleophilic Aromatic Substitutions of Azole-Ligated Diaryliodonium Salts

Y. A. Vlasenko, T. J. Kuczmera, N. S. Antonkin, R. R. Valiev, P. S. Postnikov, B. J. Nachtsheim, *Adv. Synth. Catal*. **2023**, 365, 535.
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Synthesis of *N*-acyl carbazoles, phenoxazines and acridines from cyclic diaryliodonium salts

N. Clamor, M. Damrath, T. J. Kuczmera, D. Duvinage, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **2024**, 20, 12.
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DOI: 10.26434/chemrxiv-2023-cqfl6

Organocatalytic Friedel–Crafts arylation of aldehydes with indoles utilizing *N*-heterocyclic iod(az)olium salts as halogen-bonding catalysts

E. M. Galathri, T. J. Kuczmera, B. J. Nachtsheim, C. G. Kokotos, *Green Chem.* **2024**, 26, 825
DOI: 10.1039/d3gc03687a

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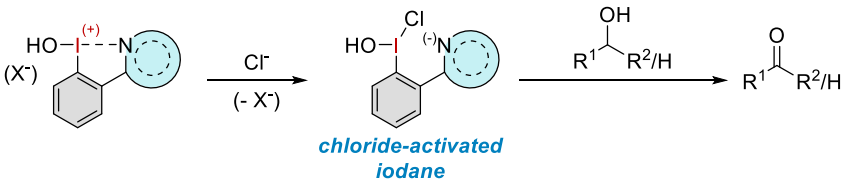
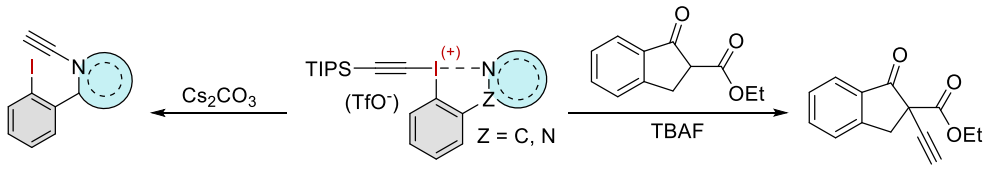
Abstract

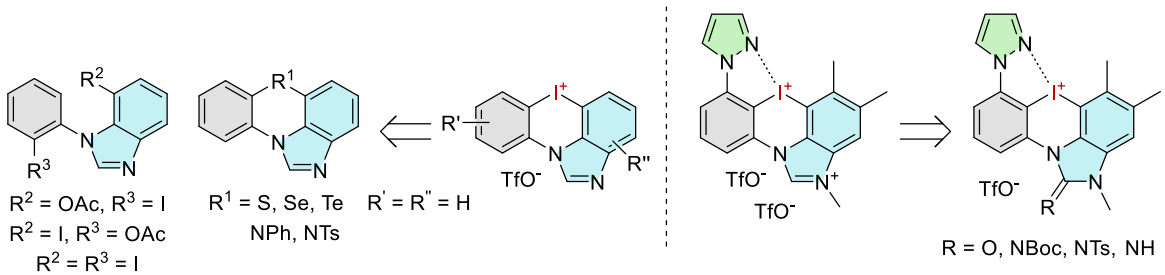
In this doctoral thesis, in-depth investigations were carried out regarding the influence of *N*-heteroarenes on iodine(III) compounds, and their applications. First, the potential of hydroxy-*N*-heterocycle-substituted iodanes (hydroxy-NHIs) were studied in oxidative transformations of alcohols. Adding halides (chlorides) as activating agents was the key to isolate the corresponding carbonyls in high yields and without overoxidation. A novel chloride-activated NHI could be detected as a reactive species in the reaction.



Furthermore, the addition of alkynes on *N*-heteroaromatic stabilized iodanes generated a range of (pseudo-)cyclic TIPS-ethynyl NHIs. Their properties as electrophilic alkynylation reagents were investigated in different model reactions, whereby quantitative conversion and a significant influence of the heteroaromatics on the reactivity of the iodane were determined. In addition, a selective intramolecular reactivity of these iodanes was observed and utilized for the selective synthesis of new structural motifs.

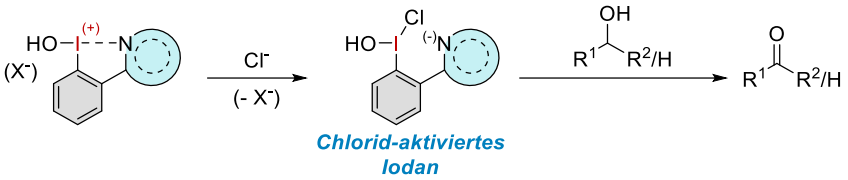


Finally, *N*-heterocycles were incorporated as part of cyclic diaryliodonium salts to obtain six-membered, *N*-heteroaromatic-bridged iodazinium salts in good yields *via* two protocols with a wide range of substituents. The possibilities as a synthetic building block were subsequently demonstrated in various mono- and bifunctionalizations of the hypervalent iodine center. Contrary to these conversions, further functionalization on the carbon backbone could be carried out while retaining the reactive hypervalent iodine center.

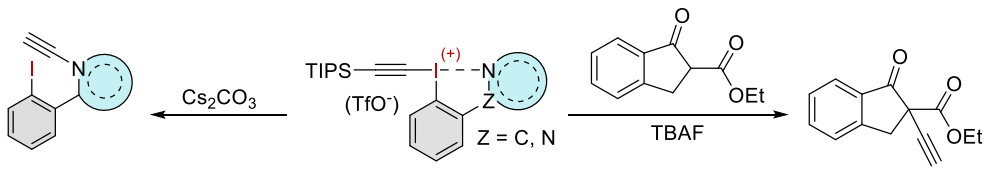


Zusammenfassung

In dieser Doktorarbeit wurde der Einfluss von *N*-Heterozyklen auf Iod(III) Verbindungen, sowie die sich daraus ergebenden Einsatzmöglichkeiten untersucht. Zunächst wurde das Potenzial von Hydroxy-*N*-Heterozyklus-substituierten Iodanen (Hydroxy-NHIs) für oxidative Transformationen von Alkoholen erforscht. Die Zugabe von Halogeniden (Chlorid) als aktivierendes Reagenz war der Schlüssel um die entsprechenden Carbonyle in hohen Ausbeuten und ohne Überoxidation zu isolieren. Ein Chlorid-aktiviertes NHI konnte als reaktive Spezies in der Reaktion nachgewiesen werden.



Weiterhin wurde durch Addition von Alkinen an *N*-heteroaromatisch stabilisierte Iodane eine Bandbreite von (pseudo-)zyklischen TIPS-ethinyl NHIs generiert. Deren Eigenschaften als elektrophile Gruppenübertragungsreagenzien wurden in Modellreaktionen untersucht, wobei quantitative Alkinylierungen und ein entscheidender Einfluss des Heteroaromaten auf die Reaktivität des Iodans festgestellt wurde. Zudem konnte eine selektive intramolekulare Reaktivität der Iodane beobachtet und zur gezielten Synthese neuer Strukturmotive genutzt werden.



Zuletzt wurden *N*-Heterozyklen als Teil zyklischer Diaryliodoniumsalze eingebaut, sodass sechsgliedrige, *N*-heteroaromatisch-verbrückte Iodaziniumsalze in guten Ausbeuten über zwei Protokolle mit einer großen Bandbreite and Substituenten erhalten wurden. Die Einsatzmöglichkeiten als synthetischer Baustein wurden anschließend in vielseitigen Mono- und Di-funktionalisierungen des hypervalenten Iodzentrums demonstriert. Konträr zu diesen Umsetzungen konnten weitere Funktionalisierungen am Kohlenstoffgerüst unter Erhalt des reaktiven hypervalenten Iodzentrums durchgeführt werden.

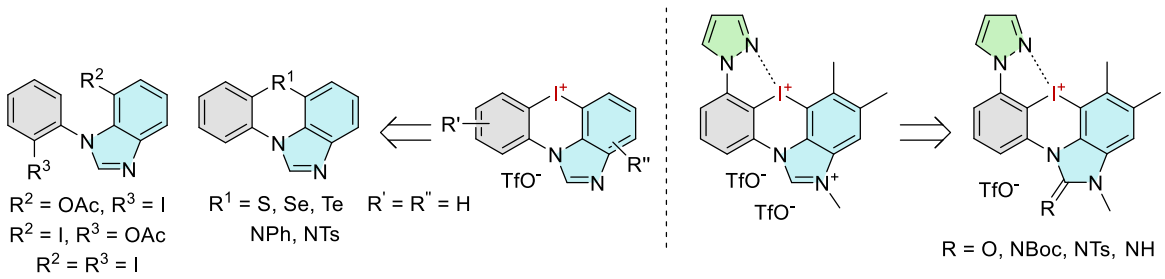


Table of Contents

1 Introduction

Iodine is the heaviest stable halogen and a vital element for higher organisms including humans.[1] Therefore it is not surprising that the first documented application of iodine was conducted by the Chinese medic *Sun Si-Miao* in the 7th century, treating goiter with the thyroid glands of animals, without knowing about iodine as the active part of his therapy.[2] It was not until twelve centuries later that the first isolation of iodine was succeeded by the French chemist *Bernard Courtois* in 1811, who observed the formation of violet crystals from vapor occurring after treatment of the ashes of seaweed with sulfuric acid.[3] However, two years later it was *Joseph Louis Gay-Lussac*[4] and *Sir Humphry Davy*[5] who introduced this new element to the general public, the latter giving it the name "iodine" (greek. ιοειδής, ioeides = violet).

Presently, iodine can be found in various applications such as medicine,[6] astronautics,[7] radiolabeling,[8] and industry.[9] In chemical synthesis, monovalent organoiodine compounds are popular reagents for cross-coupling reactions.[10] As an alternative to metal-catalyzed or hydrogen-bond mediated reactions, higher valent organoiodine compounds, so-called iodanes, have been established as another class of molecules with immense potential.[11,12,13]

1.1 Structure and reactivity of hypervalent iodine compounds

For a precise description of iodanes, appropriate terms are essential. For this, the *Martin-Arduengo* notation could be used, which defines the number of electrons E of the central atom A with L ligands (E-A-L).[14] The more common alternative nomenclature is the λ^x convention introduced by *Powell*, with x being the number of binding partners on the central atom, in this case iodine.[15]

In aryl-λ^3-iodanes, the hypervalent bond is described by a linear three-center-four-electron (3c-4e) bond, while in the case of aryl-λ^5-iodanes, another important class of hypervalent organic iodine species, two of such bonds are formed. Triggered by the electrostatic field of the ligands in aryl-λ^3-iodanes, a spin pairing of the p electrons occurs at the central iodine atom, where the electron configuration of this oxidation state is s^2p^4, resulting in a state of $p_x^2 p_y^2 p_z^0$. This produces a ring of negative polarization in the xy-plane

and a positive polarization along the z-axis (Figure 1a). The empty p_z orbital now bonds with the filled p orbital of the two ligands (L). This forms three molecular orbitals (MOs), wherein the bonding and non-bonding MOs are fully occupied (Figure 1b). The bonding MO thus formally ensures a bond order of 0.5 between the iodine and the ligands. In contrast, the non-bonding MO is localized on the ligands, therefore these electrons are not counted to the iodine and the octet rule is formally complied. Additionally, due to the negative polarization of the ligands, the most electronegative ligands preferentially form the hypervalent bond.[16,17]

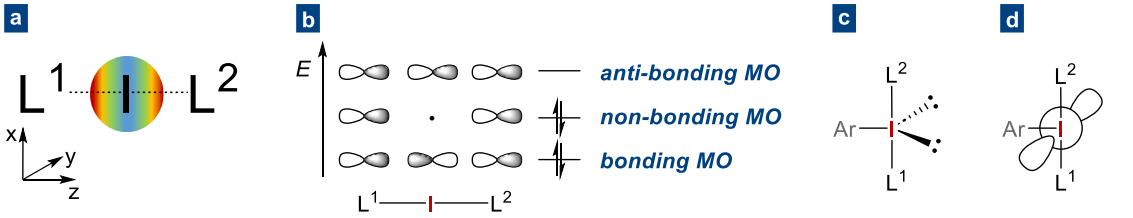


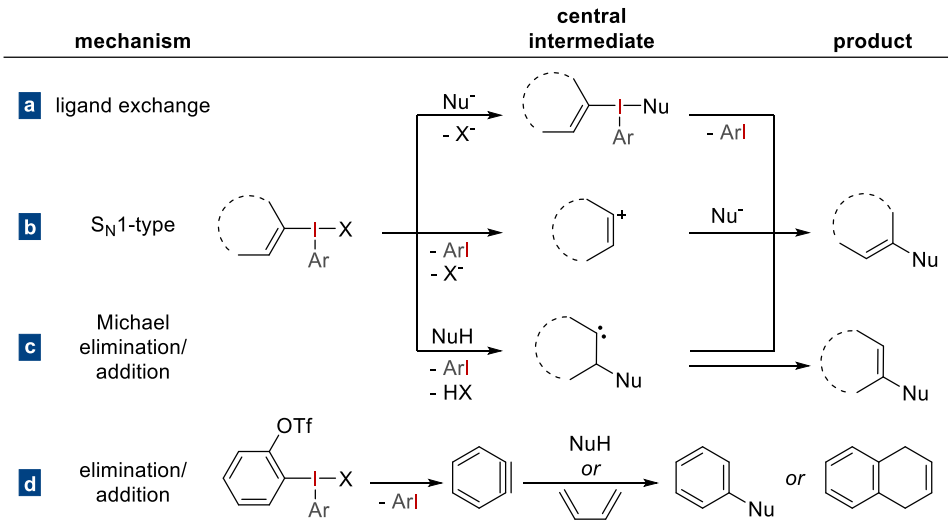
Figure 1: a) Electrostatic charge of an iodine-cation under the influence of ligands. Blue is repesenting a high electron desity, red a low. b) Molecular orbitals of a 3c-4e bond on iodine. c) Classical trigonal bipyramidal structure of an aryl-λ^3-iodane including two lone-pairs on the iodine. d) A revised structure, in which the lone-pairs are not hybridized, but the T-shape structure is preserved.

An alternative approach describes the hypervalent bond as a combination of a covalent bond and a halogen bond (XB). A halogen bond is defined as a non-covalent, approximately linear interaction R-X···Nu between an electropositive region of a halogen X (known as the σ-hole) and a nucleophile Nu, which is shorter than the sum of their van der Waals radii.[18] When the R-X bond is formed using the half-filled p_z orbital of the halogen, due to negatable hybridization, the remaining orbitals are approximately in the configuration $s^2p_x^2p_y^2$. The electrons form a ring of negative electrical potential around the center of the halogen atom, such that only the outermost region, the σ-hole, receives a positive polarization.[17,19] Evidently this explanation is similar to the concept of a 3c-4e bond, with the difference being that the former concept rather reflects a symmetrical hypervalent bond, while the latter is a more precise description of an asymmetric hypervalent bond, which is for example the case in iodonium salts. Thus, a rather complex nature of the hypervalent bond can be assumed. Lastly, the concept of hypervalency itself was discussed critically in the present literature, considering the use of terms such as “hypercoordination” or “trivalent/pentavalent” instead, as no significant bonding differences between lower and higher valent molecules could be determined.[20]

Nevertheless, “hypervalent” has been well established in the scientific community and is commonly used to describe the features of hypercoordinated iodine compounds.

Structurally, λ^3-iodanes have a trigonal bipyramidal geometry, with the arene and the lone pairs occupying the equatorial positions, while the ligands of the hypervalent bond are placed in the axial positions (Figure 1c).[21] Recent investigations on diaryliodonium salts revealed that the orbitals of the iodine lone pairs show almost no hybridization and are therefore located in an s and p orbital. In this revised concept the previously described T-shape structure remains intact (Figure 1d).[22]

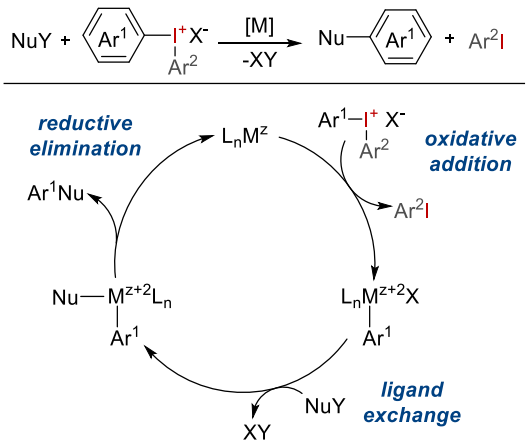
Due to the strong electron withdrawing properties of iodanes an “umpolung” of the ligands takes place, which changes the polarization of the usually electronegative substituents and let them react as electrophiles.[23] Under reductive elimination of the iodane, the hypernucleofuge ArI is released, which is known to be a 10^6 times stronger leaving group compared to the triflate anion.[24] This driving force results in a plethora of transformations developed for iodanes, using different mechanistic pathways.[25,26] The most prevalent is an associative pathway, which is proceeding *via* a ligand exchange of one of the substituents on the iodine center with a nucleophile (Scheme 1a). This intermediate can undergo reductive elimination or pseudorotation, followed by ligand coupling.[11] An alternative dissociative mechanism involves an S_N1-type formation of a carbocation, which is then trapped by a nucleophile (Scheme 1b).[24]



Scheme 1: General overview of metal-free reaction pathways of iodanes.

Furthermore, a Michael addition/elimination procedure can be applied for iodanes which contain carbenes as the central intermediate (Scheme 1c).[27] On diaryliodanes an elimination/addition pathway can also be applied, which forms an aryne as the central intermediate for the addition of nucleophiles, or undergoes [4+2] cycloaddition reactions (Scheme 1d).[28]

Besides metal-free transformations, metal-catalyzed reactions with iodanes were also established (Scheme 2). Mechanistically, the metal first undergoes an oxidative addition, where the more electron deficient ligand on the iodine center is transferred to the metal and the monovalent iodoarene is released. Afterward, a ligand exchange with a nucleophile takes place, followed by a reductive elimination with the release of the product and the regeneration of the catalyst.[21,29]



Scheme 2: General reaction mechanism of metal-mediated reactions of iodanes.

1.2 Aryl-λ^3-iodanes

The first known iodane was synthesized by *Willgerodt* in 1886 by treating iodobenzene with chlorine gas to obtain $PhICl_2$ (**1**) (Figure 2).[30] A few years later, iodosobenzene (**2**) was invented, which solidifies in a polymeric structure.[31] The hydroxy(tosyl)iodobenzene (**3**) was first published by *Nelland* and *Karele* in 1970,[32] but was investigated and made well-known by *Koser,* hence acquiring the name *Koser's reagent*.[33] Further prominent iodanes are bis(acetoxy)iodobenzene (PIDA, **4**),[34] as well as the analog bis(trifluoroacetoxy) iodobenzene (PIFA, **5**).[35] (Dicyano)iodobenzene (**6**) is the only λ^3-iodane with three carbon substituents which is stable under ambient conditions.[36]

Recently the isolation of iodane **7** with a free amine as ligand succeeded for the first time by the installation of an *ortho*-stabilizing carboxylic acid, which is forming a benziodoxolone (BX) ring.[37]

The simplest aryl-λ^5-iodane is iodylbenzene (**8**), which has little application due to its low solubility.[38] Other examples of this class of iodanes are iodoxybenzoic acid (IBX, **9**) and the prominent *Dess-Martin-Periodinane* (DMP, **10**).[39]

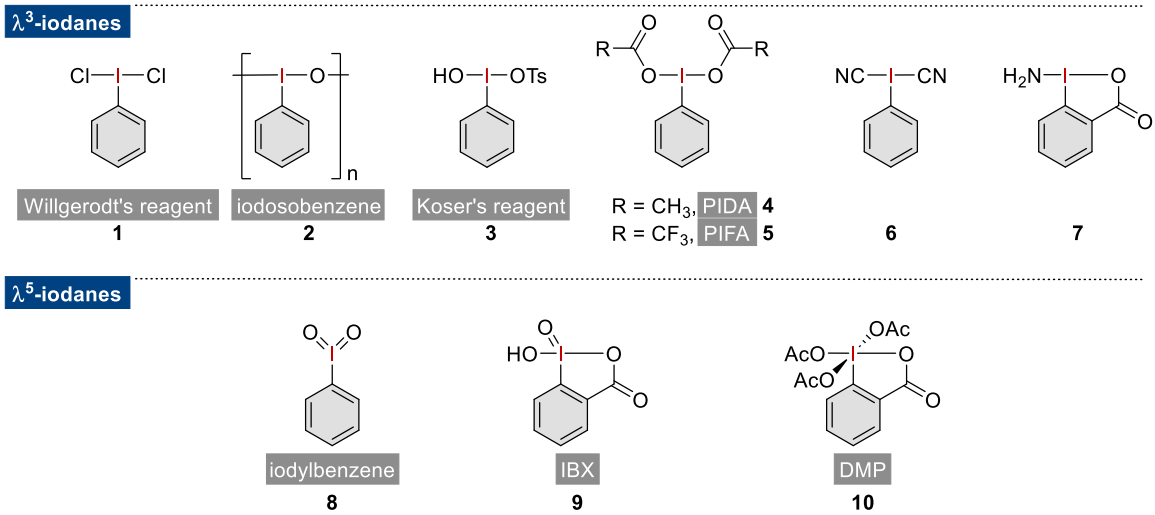
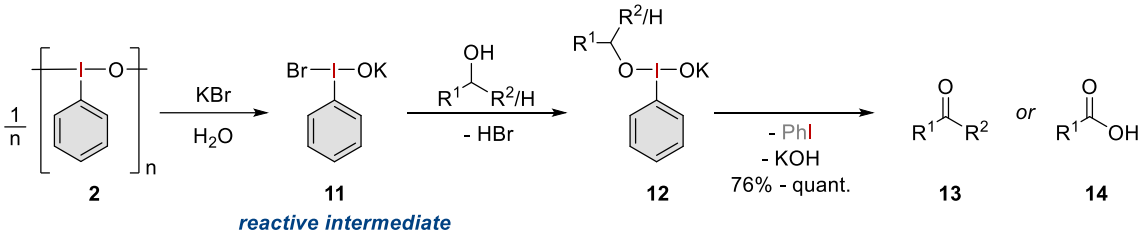


Figure 2: Prominent λ^3- and λ^5-iodanes.

Since reactions of iodanes often include reduction of the iodine, to no surprise, oxidative transformations represent the most prominent application. While halogen-substituted iodanes such as **1** are used for oxidative halogenations of organic[40] and metal-organic molecules,[41] oxygen-substituted tri- and pentavalent iodanes can be applied in the oxidation of alcohols.[42] Here, DMP (**10**) gained great popularity as a mild and selective commercially available reagent for the generation of aldehydes from primary alcohols, without overoxidation to carboxylic acids.[39,43] Additionally, DMP (**10**) is one of few polyvalent iodine compounds with application in industrial synthesis, such as for the H1 histamine receptor antagonist *Alcaftadine*. The synthesis includes a last-stage oxidation of a benzylic alcohol to the corresponding aldehyde.[44]

However, DMP (**10**) is hygroscopic and the synthetic intermediate IBX (**9**) is known for undergoing explosive decomposition.[45] Hence, trivalent iodanes were also established for alcohol oxidations. In contrast to the pentavalent analogs, λ^3-iodanes usually need harsh conditions[46] or a previous activation. *Kita* and co-workers introduced

iodosobenzene (**2**) for alcohol oxidations by breaking up the polymeric structure with catalytic amounts of KBr in an aqueous solution (Scheme 3; Table 1, Entry 1).[47,48] This *in situ* activated iodane **11** successfully oxidized secondary alcohols into ketones **13** at room temperature but failed in the synthesis of aldehydes due to overoxidation of primary alcohols to carboxylic acids **14**.



Scheme 3: Oxidation of alcohols using KBr-activated iodosobenzene (**2**).

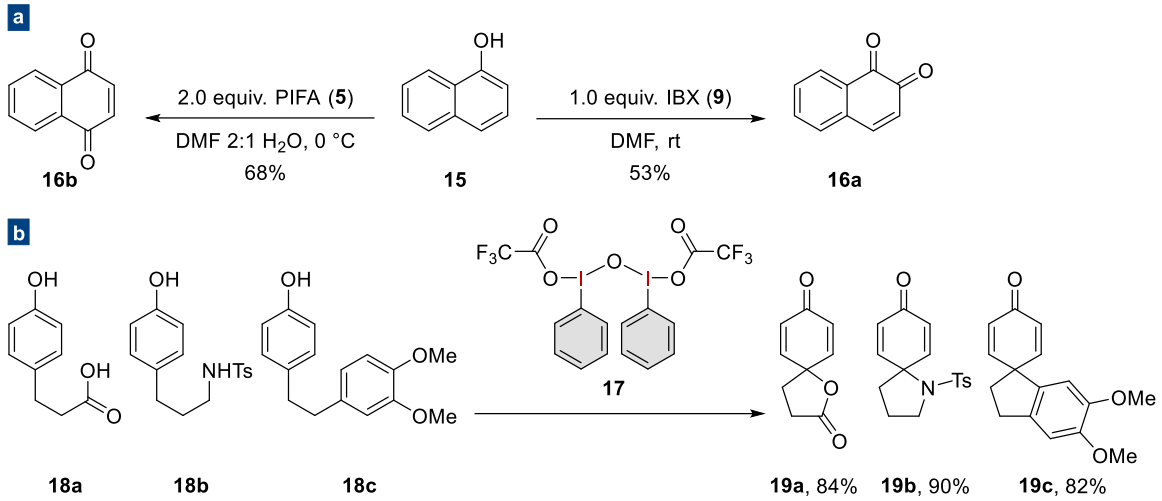
Mertis and co-workers applied **2** in a milder reaction system by using Ph_4PBr as a bromide source in DCM (Table 1, Entry 2).[49] With this procedure aldehydes could be generated in good yields, however secondary alcohols revealed low conversions into ketones. Similar observations were made when PIDA (**4**) was applied in alcohol oxidations. While bromide-activated reactions in water resulted in the formation of carboxylic acids (Table 1, Entry 3),[50] the use of EtOAc as an organic solvent gave the corresponding aldehydes (Table 1, Entry 4).[51] Additionally, with this method ketones could be isolated in high yields as well.

Table 1: Overview of alcohol oxidations using λ^3-iodanes.

Entry	Author	Oxidant	Additive	Solvent	Products
1[47,48]	*Kita*	$(PhIO)_n$ (**2**)	KBr	H_2O	ketones, carboxylic acids
2[49]	*Mertis*	$(PhIO)_n$ (**2**)	Ph_4PBr	DCM	ketones, aldehydes
3[50]	*Kita*	PIDA (**4**)	Et_4NBr	H_2O	ketones, carboxylic acids
4[51]	*Gruttadauria*	PIDA (**4**)	QBr, Q = Na, K, *n*Bu_4N	EtOAc	ketones, aldehydes
5[51]	*Gruttadauria*	PIDA (**4**)	TEMPO	DCM *or* EtOAc	ketones, aldehydes
6[52]	*Guan*	PIFA (**5**)	DDQ	DCM	ketones, aldehydes
7[53]	*Saini*	PIDA (**4**)	Al_2O_3	*neat*	ketones, carboxylic acids

A bigger range of alcohols was addressable using a radical pathway, which was mediated by (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) (Table 1, Entry 5).[51] As another redox mediator catalytic amounts of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) could be used with PIFA (**5**) as the terminal oxidant for selective formation of aldehydes (Table 1, Entry 6).[52] A procedure which activates PIDA (**4**) with Al_2O_3 without solvent was tested as well (Table 1, Entry 7).[53] All these methods obtained some of the products in more than 90% yield.

As another field of oxidative transformations, iodanes can be used for phenol-dearomatization reactions, in which an aromatic system is oxidized by the addition of an oxygen, nitrogen, or carbon nucleophile. Herein, the regioselectivity can be tuned by using different iodanes. While the pentavalent IBX (**9**) can transform 1-naphthol (**15**) into *ortho*-quinone (**16a**), the trivalent PIFA (**5**) yields the *para*-analog **16b** (Scheme 4a).[54] Intramolecular dearomatization reactions are known as well, where PIFA (**5**) or μ-oxo-bridged iodane **17** is used to generate oxo-, aza-, or carbo-spirocycles **19** in high yields of up to 90% (Scheme 4b).[55]



Scheme 4: a) Regioselective dearomatization reactions with polyvalent iodine reagents. b) Oxo-, aza- and carbo-spirocyclization with μ-oxo-bridged iodane **17**.

Unfortunately, the huge potential of higher coordinated iodine species in organic synthesis is often counteracted by low thermal stability and poor solubility.[56] By introducing an *ortho*-substituent to the iodine center the inherent low stability could be overcome, which resulted in further popularity of these reagents and led to a variety of novel applications in the field of hypervalent iodine compounds.

1.3 Stabilized aryl-λ^3-iodanes

Intramolecularly stabilized iodanes have become a widely applied concept, most commonly by introducing an *ortho*-benzoic acid moiety. After oxidation of the iodine center, the carboxylic acid part undergoes an intramolecular ligand exchange to form a benziodoxolone (BX) ring. The simplest derivative is iodosobenzoic acid (IBA, **20a**) (Figure 3). Moreover, benziodoxolones allow the stabilization of several other functionalities, such as halides, perfluorinated alkyl groups,[57] cyanides,[58] esters,[39] azides[59] or amines.[37]

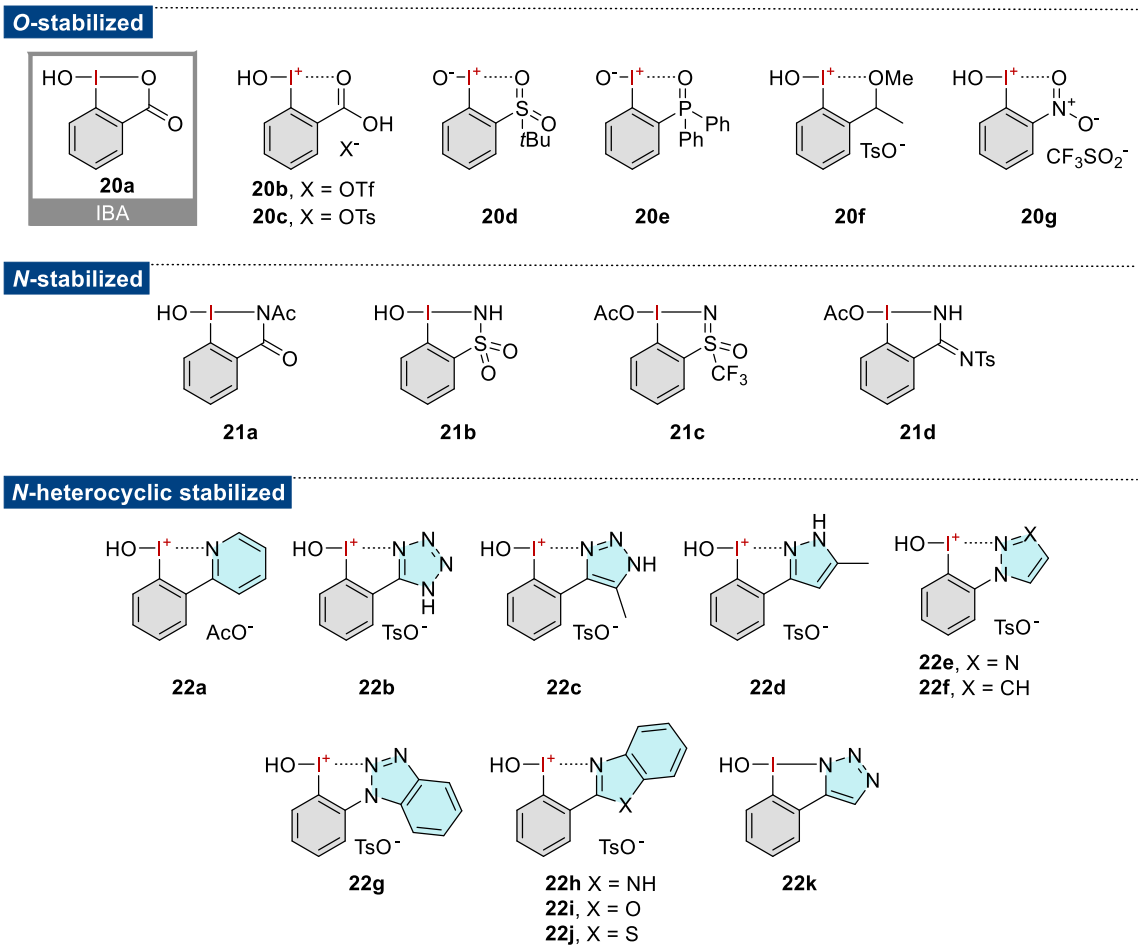
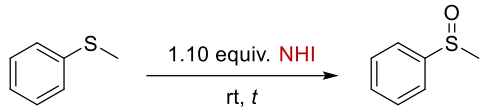


Figure 3: Overview of intramolecular oxygen-, nitrogen-, and *N*-heterocycle-stabilized hydroxy/acetoxy-iodanes.

Besides BX-substituted iodanes several other *O*-donor (pseudo)cyclic iodine(III) reagents **20** are known.[60] In contrast to oxygen-donors, nitrogen-stabilized iodanes of the type **21** enable a greater variability in their electronic and steric properties due to an additional bonding partner on the nitrogen.[61,62] Additionally, higher thermal stabilities could be measured for selected *N*-stabilized iodanes compared to their *O*-substituted analogs.[63]

In 2017, *Muñitz* and co-workers opened up a new class of *N*-stabilized iodanes by presenting the first hydroxy-*N*-heterocycle-substituted iodane (hydroxy-NHI) **22a**, in which the iodine atom is stabilized by an *ortho*-(2-pyridinyl) group.[64] In 2018, *Nachtsheim* and co-workers presented a systematic investigation of (pseudo)cyclic hydroxy-NHIs **22c-k**. By using *meta*-chloroperbenzoic acid (*m*CPBA) as the terminal oxidant in the presence of *para*-toluenesulfonic acid (TsOH) iodanes with a series of *C*- and *N*-bound triazoles, pyrazoles, benzotriazoles, benzimidazoles, benzoxazoles, and benzothiazoles as the *ortho*-stabilizing unit could be obtained.[65] One year later tetrazole-substituted salt **22b** was investigated as well.[66] Besides triazole and tetrazole derivatives, the NHIs were proven to have a high thermal stability in thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) measurements, therefore they are safe to handle reagents.[67] These compounds were tested in facile oxidative transformation reactions, such as the oxidation of thioanisole (**23**) (Table 2). Although excellent yields of sulfoxide **24** were obtained with all NHIs, the reaction rate could be accelerated in most cases in comparison to the *O*-stabilized iodane **20c**.

Table 2: Comparison of selected hydroxy-NHIs in the model oxidation reaction of thioanisole (**23**).



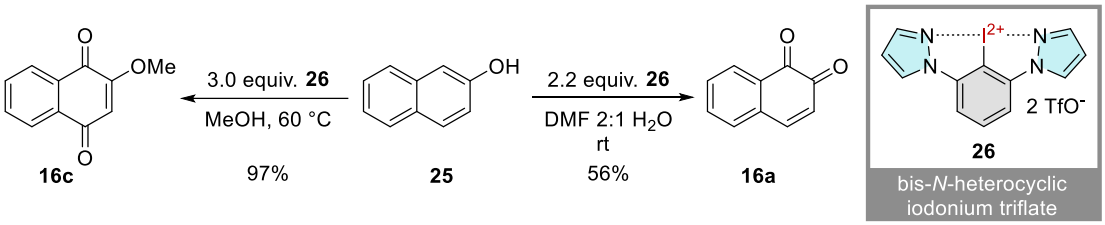
23 **24**

Entry	NHI	*t* [min]	Yield **24** [%]
1	**20c**	420	92
2	**22b**	45	94
3	**22c**	40	93
4	**22d**	135	96
5	**22e**	1	99
6	**22f**	75	99
7	**22h**	900 (65 °C)	86

These experiments clearly illustrate the crucial influence of the *N*-heterocycle on the reactivity of the iodane. In particular, a higher number of heteroatoms in the heterocycle is increasing the reactivity (Table 2, Entries 3 and 4, 5 and 6). Also, the connectivity to the iodine center is changing the performance of the NHI, showing that the respective *N*-bound heterocycles are superior (Table 2, Entries 3 and 5, 4 and 6).

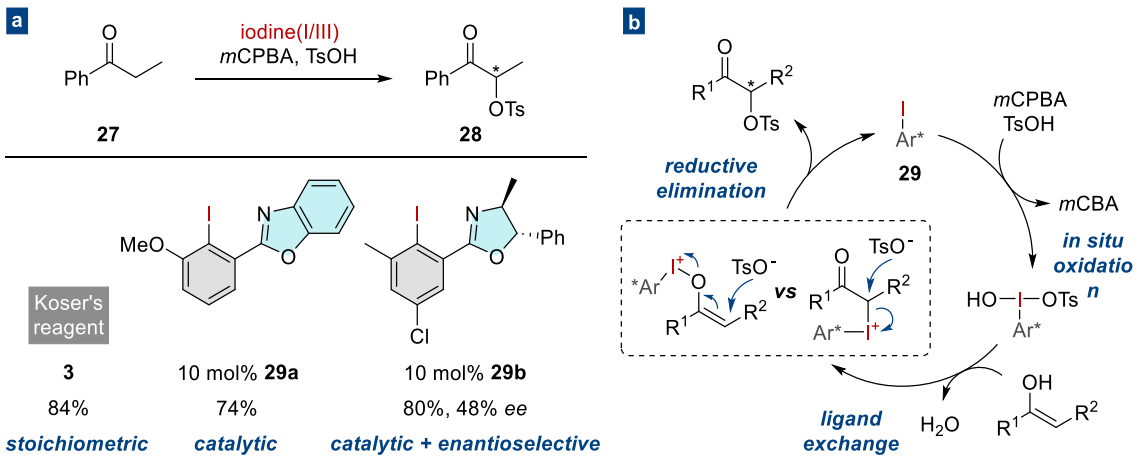
A further development of these NHIs led to an interesting oxidizing reagent, a pseudocyclic bis-*N*-heteroaromatic stabilized iodane **26**, which allowed to control the reaction product by employing different equivalents of the oxidant (Scheme 5).[68] When 2-naphthol (**25**) and 2.2 equiv. of **26** were combined in a DMF/water solvent system, the *ortho*-quinone (**16a**) was obtained. In contrast, 3.0 equiv. of iodane **26** in MeOH gave the higher oxidized 2-methoxynaphthalene-1,4-dione (**16c**) in an excellent yield of 97%.

Taking the displayed high reactivity and the knowledge about the NHIs design into account it is striking that NHIs were not further investigated in oxidative transformations.



Scheme 5: Product control by changing the reaction set up with bis-pyrazole-stabilized iodonium triflate **26**.

Aliphatic hydrocarbons can also be addressed for oxidative transformations with iodanes, such as for *α*-oxytosylation reactions of ketones **27** to **28**, classically carried out with *Koser's reagent* (**3**) (Scheme 6a).[69] Because the use of stochiometric quantities of iodanes is connected with high costs and low atom economy, catalytic applications were developed, using the benzoxazole-substituted iodoarene **29a**.[70] Additionally, an enantioselective protocol was developed by *Legault* and co-workers by using oxazolines **29b**.[71]

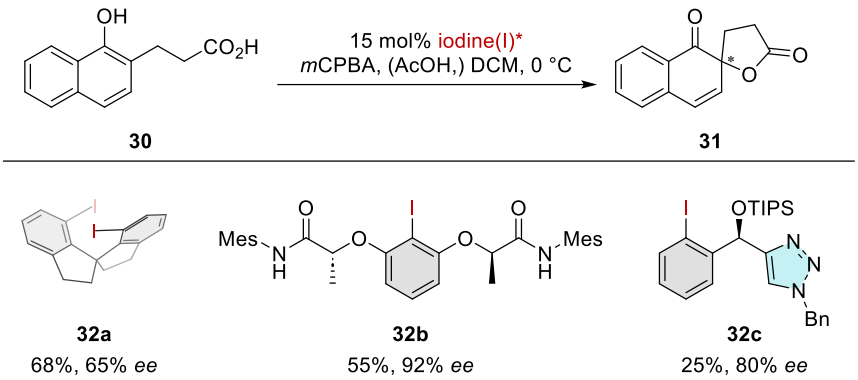


Scheme 6: a) Evolution of iodine-based reagents for the *α*-oxytosylation of ketones from a stoichiometric to catalytic and enantioselective application by the introduction of *N*-heterocycles. b) Mechanism of an enantioselective *α*-oxytosylation reaction, catalyzed by a chiral iodine(I/III) cycle.

In all shown examples the yield changed negligibly but the installation of *N*-heteroaromatic stabilizing substituents led to further development of these iodine(I/III) reagents, which increased their effectivity and expanded their field of application.

Mechanistically, the catalytic reaction is proceeding *via* an iodine(I) pre-catalyst, which is *in situ* oxidized by *m*CPBA to the corresponding λ^3-iodane (Scheme 6b). This active species then undergoes a ligand exchange reaction with the oxygen of the enol, or the *α*-carbon, to form the oxygen-bound intermediate or the higher enantioselective carbon-bound analog, respectively. Finally, the tosylate is introduced *via* a reductive elimination of the iodine(III).[72]

The previously described spiro-dearomatization was also further developed to include enantioselective procedures by using chiral iodine sources. *Kita* and co-workers presented a chiral iodine(I) catalyst **32a** and applied it in the spiro-lactonization reaction of **30** to the spiro-lactone **31** in good yields with moderate enantioselectivity of 65% *ee* (Scheme 7).[73]



Scheme 7: Chiral iodoarene catalysts, which are *in situ* transformed into the active iodine(III) species and utilized in an enantioselective *Kita* spirolactonization.

Ishihara and co-workers synthesized C_2-symmetric iodoarene **32b**, which gave slightly lower yields compared to catalyst **32a** but resulted in higher enantioselectivity (92% *ee*).[74] Finally, a C_1-symmetric, triazole-containing catalyst **32c** was developed by *Nachtsheim* and co-workers, which allows for the formation of **31** in 25% yield and with a good enantioinduction of 80% *ee*.[75]

Intramolecular stabilization does not only show a positive influence on oxygen- and nitrogen-based ligands, but it is also compatible with carbon-based substituents such as arenes, alkenes, and alkynes. The so-formed iodonium salts are a class of iodanes with a

huge field of application, in which stabilizing groups plays an important role in terms of stability and variability.

1.4 Iodonium salts

1.4.1 Alkynyl(aryl)iodonium salts

Alkynyl(aryl) and alkenyl(aryl)iodonium salts are a highly interesting class of iodanes, as an umpolung of the acetylenes and ethylenes allows for their application as versatile electrophilic carbon-group transfer reagents.[76] However, dialkynyliodonium salts such as **33** are poorly investigated and have shown a lack of application due to their low stability (Figure 4a).[77] The alkynyl(aryl)iodonium **34a** and alkenyl(aryl)iodonium analogs **34b** (Figure 4b) show a higher variety in their synthesis and are applicable in simple group transfer reactions, such as in the alkenylation or alkynylation of thiourea derivatives.[78] By introducing an *ortho*-stabilizing moiety, the ethynyl- and vinyl-benziodoxolone (EBX and VBX) analogs **35a,b** have shown an enhanced stability and could be used in several transfer reactions (Figure 4c).[26,79]

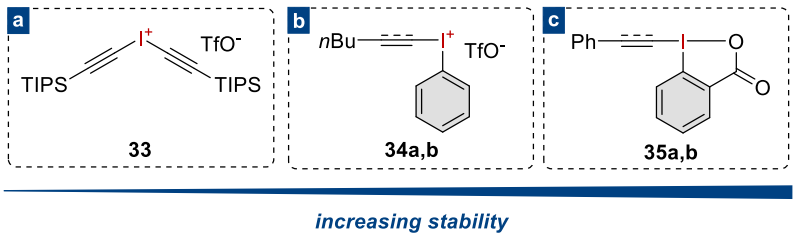
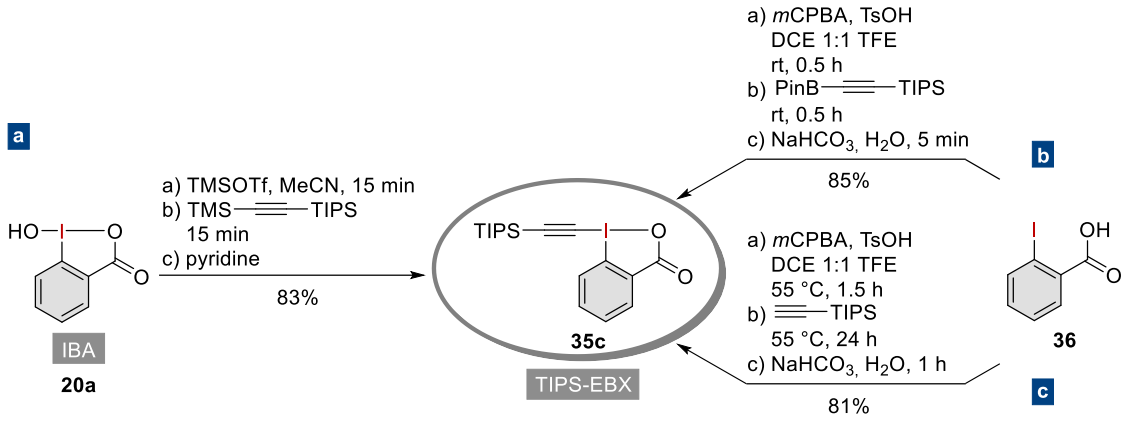


Figure 4: Increasing stability of different molecule designs for alkenyl- and alkynyl-iodanes.

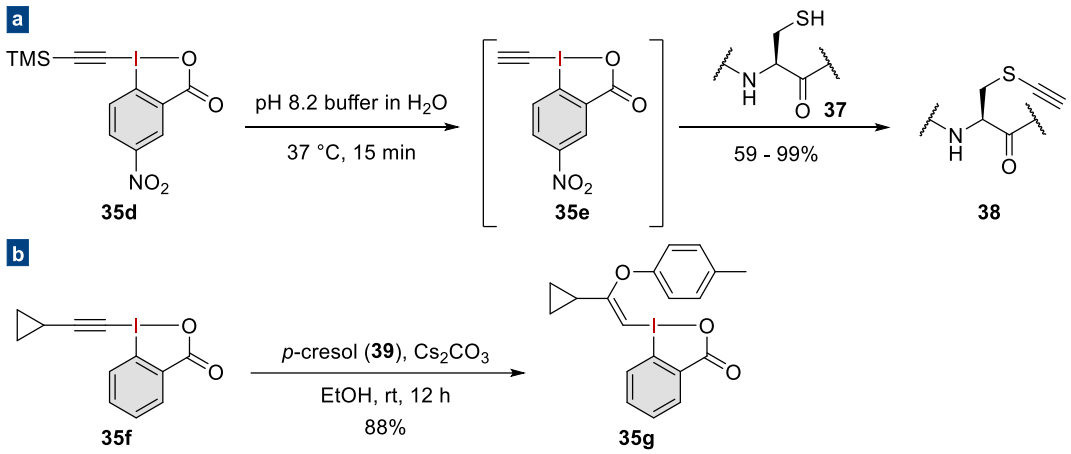
The classical synthesis of EBX-reagents such as TIPS-EBX (**35c**) starts with the activation of IBA (**20a**) with TMSOTf and subsequent treatment with TIPS-TMS-acetylene (Scheme 8a).[80] A one-pot protocol was developed by *Olofsson* and co-workers wherein 2-iodobenzoic acid (**36**) was first oxidized and afterward *in situ* coupled with TIPS-BPin-acetylene (Scheme 8b).[81] Later on, *Waser* and co-workers could further improve this one-pot procedure by using the commercially available TIPS-acetylene (Scheme 8c).[82]

EBX-reagents can be used for selective alkynylation reactions of *O*-, *N*-, *S*-, *P*-, *C*-, and metal-nucleophiles.[13]



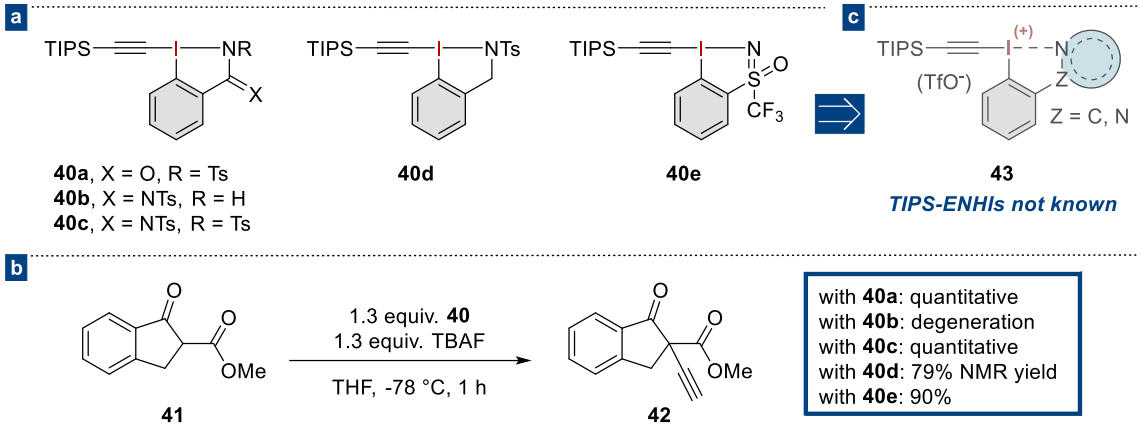
Scheme 8: Different synthetic approaches for the generation of TIPS-EBX (**35c**).

In oligopeptides **37** the free EBX (**35e**) allows for the selective transfer of a free acetylene moiety to cysteines (Scheme 9a).[83] For that **35e** is generated *in situ* by treating silyl-EBX **35d** with fluoride or aqueous basic solutions. Moreover, the addition of several nucleophiles such as *p*-cresol (**39**) to acetylene **35f** allows for post-functionalization of the iodane to form VBX **35g** (Scheme 9b).[84]



Scheme 9: Applications of EBX-reagents.

However, as mentioned before oxygen has a low ability to vary the reactivity. Here, in parallel to the hydroxy iodanes **20**-**22**, the change of oxygen- towards nitrogen-stabilization promises greater variability in molecular design. These benziodazolones (BZ), such as TIPS-EBZ **40a** were further developed by *Waser* and co-workers, who synthesized and investigated a series of amide, amidine, and sulfoximine *N*-stabilized alkynyl-iodanes **40b-e** (Scheme 10a).[62] The performance of these iodanes in alkynylation reactions of 1,3-dicarbonyl **41** revealed significant differences in the reaction outcome, from quantitative alkynylation to decomposition (Scheme 10b).



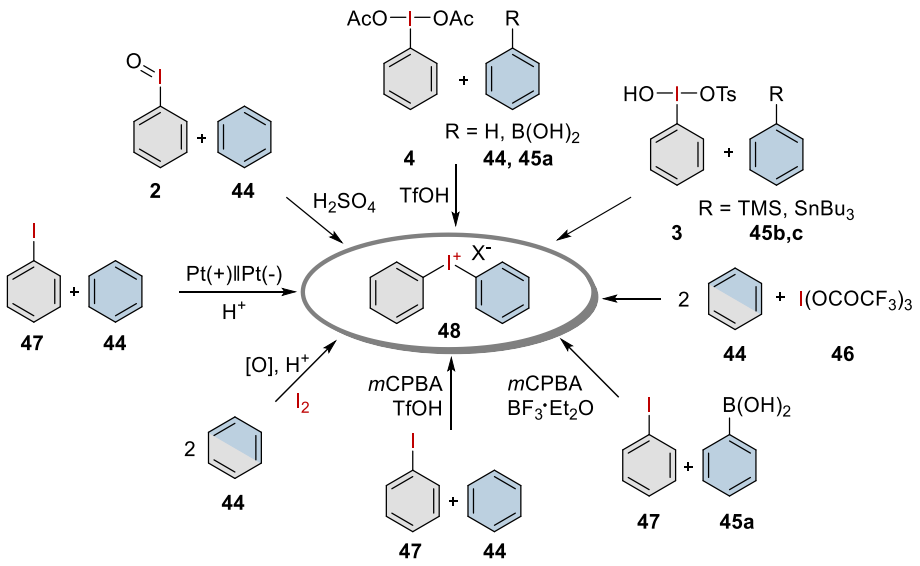
Scheme 10: a) TIPS-EBZ **40a** as an alternative to BX-reagents and further variation to the stabilizing group of TIPS-alkynyl-iodanes. b) Benchmark reaction with *N*-stabilized I(III) alkynylation reagents. c) TIPS-ethynyl-NHIs (TIPS-ENHIs), which are not known so far and represent further development for nitrogen-stabilized alkynyl(aryl)iodanes.

Although not all stabilizing motifs turned out to be suited to this test reaction, these experiments show the crucial influence of the substituent on the reactivity of the iodane. Therefore, it is surprising that *N*-heterocycles were not installed as *ortho*-stabilizing groups for ethynyl(aryl)iodanes to form ENHIs of the type **43** thus far (Scheme 10c), as they showed a positive influence on the reactivity in the case of hydroxy(aryl)iodanes **22** (see Table 2).

Instead of alkynyl-substituents, iodine(III) species with two arenes form another class of carbon-substituted iodine(III) reagents. While triaryliodanes are unstable under ambient conditions,[85] diaryliodonium salts are a highly investigated research area.[21]

1.4.2 Acyclic diaryliodonium salts

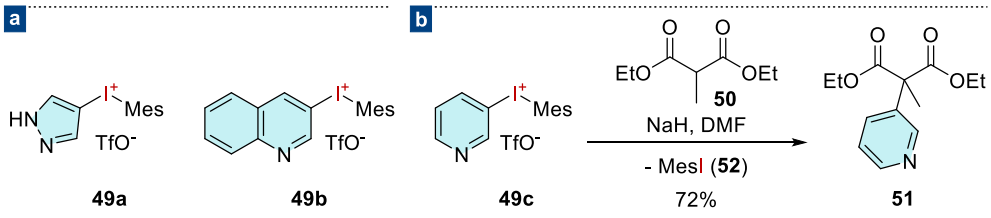
The first diaryliodonium salt was examined in 1894 by *Hartmann* and co-workers, who synthesized salts with different counter ions and complexes with metals.[86] Nowadays, several methods for generating diaryliodonium salts **48** are known (Scheme 11). The reaction of iodosobenzene (**2**) and arenes **44** under highly acidic conditions form in particular electron-deficient iodonium salts.[87] An improvement was achieved using trifluoromethanesulfonic acid (TfOH) to generate easy-to-handle iodonium triflates from PIDA-analogs **4** with either arenes **44** or aryl boronic acids **45a** as coupling reagents.[88] Substituted *Koser reagents* (**3**) can be coupled with trimethylsilyl- (TMS-)[89] or $SnBu_3$-substituted[90] arenes **45b,c** to form iodonium salts.



Scheme 11: Overview of different synthetic strategies towards diaryliodonium salts **48**.

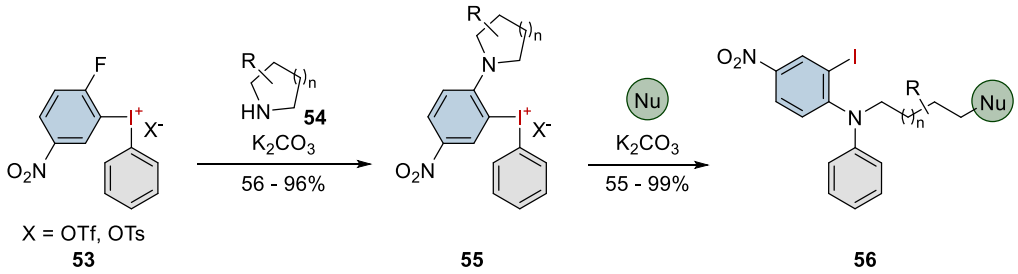
The synthesis of iodonium salts may become challenging if the substituents influence the electronic properties significantly. Strong electron-rich[91] and strong electron-deficient[92] diaryliodonium salts can be obtained by reacting iodine tris(trifluoroacetate) (**46**) with arenes **44**. Besides using iodine(III) precursors, modern methods apply a one-pot oxidation/arylation sequence. This is allowing the use of *m*CPBA as the terminal oxidant in the presence of $BF_3{\cdot}Et_2O$[93] or TfOH[94] to synthesize symmetric and asymmetric iodonium triflates from simple iodoarenes **47**. Additionally, one-pot procedures with molecular iodine were developed to simply access symmetrical diaryliodonium salts.[95] Instead of using chemical oxidants, electrochemical and flow-electrochemical procedures have also been developed as a cheap and atom economic alternative.[96]

Acyclic diaryliodonium salts can be applied as versatile electrophilic arylation reagents, with the transfer of the more electron deficient arene. Here, besides diaryliodonium salts, aryl(*N*-heteroaryl)iodonium salts **49** were also investigated, finding pyridine, quinoline, and pyrazole to be compatible heterocycles. The application of **49c** as heteroarylation reagent of 1,3-dicabonyl **50** yielded **51** in 72% (Scheme 12).[97]



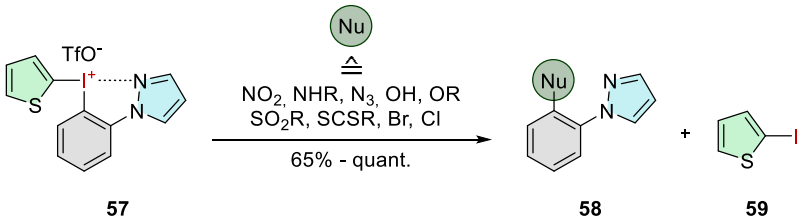
Scheme 12: a) *N*-Heteroaromatic diaryliodonium salts. b) Reactivity of **49c** in heteroarylation reactions.

The shown application has the disadvantage of iodoarene **52** being released as a side product. This results in a low atom economy of iodine(III)-mediated group transfer reactions. An elegant approach for this problem was presented by *Olofsson* and co-workers by synthesizing *ortho*-fluorinated diaryliodonium salts **53** (Scheme 13).[98] In the first step, an S_NAr reaction takes place to substitute the fluorine atom with an amine **54** while preserving the hypervalent iodine center. In the second step, an aryl shift occurs under reduction of iodane **55** and the intermediate could be quenched by several nucleophiles to form diarylamines **56** in an atom economically way.



Scheme 13: Atom-efficient di-functionalization protocol using *ortho*-fluorinated diaryliodonium salts **53**.

The concept of intramolecular stabilization was also applied on diaryliodonium salts. In addition to benziodoxolone-substituted iodanes,[99] *N*-heterocycles such as benzimidazoles, triazoles, imidazoles, or pyrazoles were also proven to be suitable stabilizing groups.[100] Also, heteroaromatic substituents influence the chemoselectivity of these iodanes and led to site-selective reactivity of pyrazole-stabilized iodonium salt **57** towards a wide variety of nucleophiles, giving arenes **58** in up to quantitative yields (Scheme 14). When the *N*-stabilization was hindered, the yield of the reaction dropped significantly and nucleophilic substitution on the thiophene-ring could be detected.



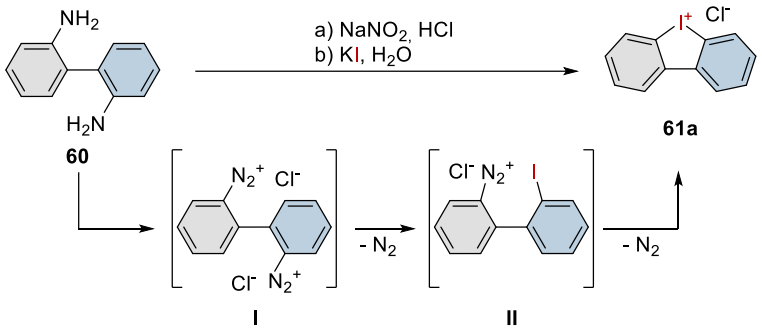
Scheme 14: Site-selective substitution of *N*-heterocycle stabilized iodonium salts with several nucleophiles.

If internal bonding of two arenes is present in iodonium salts, cyclic diaryliodonium salts with unique properties regarding sterics, thermodynamics and electronics is opened up with novel applications.

1.4.3 Cyclic diaryliodonium salts

In comparison to acyclic diaryliodonium salts, the arenes in their cyclic analogs are connected either directly or *via* a nitrogen, oxygen, sulfur or carbon bridge to form an iodo-heterocycle.[101] This class is showing different properties, such as higher stability or a more pronounced σ-hole. They are therefore suitable for applications, such as in halogen bond catalysis[102] or as building blocks.[103]

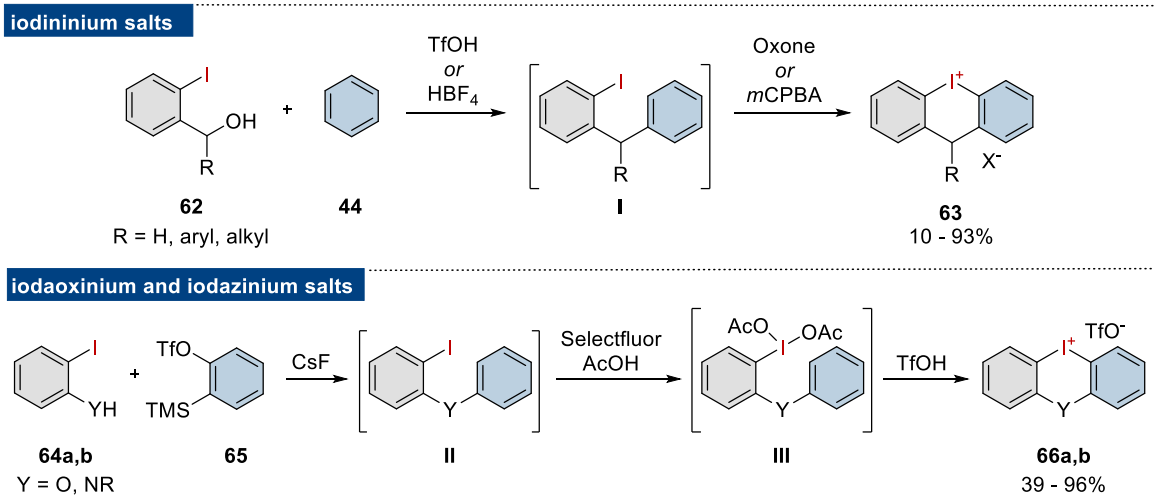
The first successful synthesis was performed using diamine **60**, yielding the cyclic iodolium chloride (**61a**) (Scheme 15). Initially, the bis(diazonium chloride) **I** is formed, which is then inserting iodine to form intermediate **II**. Finally, the iodine is undergoing ring closure *via* the release of N_2.[104]



Scheme 15: Synthesis of iodolium chloride (**61a**) *via* diazotization.

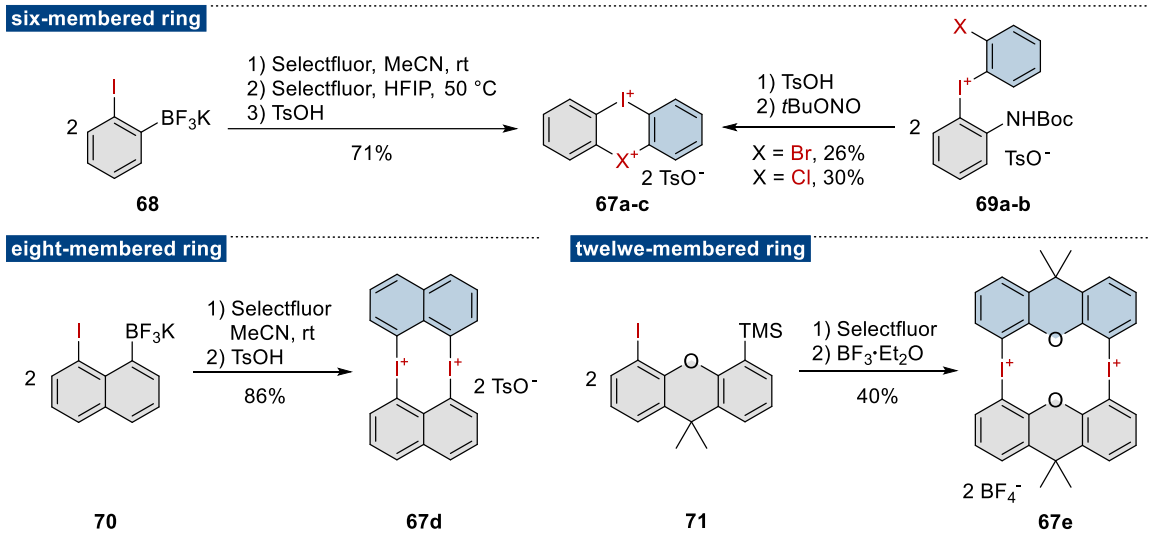
Many cyclic iodonium salts can be obtained by employing similar methods as their acyclic analogs, however, the use of *m*CPBA with TfOH is nowadays the most common pathway for the generation of five-membered cyclic diaryliodonium salts.[105]

Moreover, protocols have also been developed specifically for cyclic systems. Recently, *Nachtsheim* and co-workers developed efficient one-pot arylation-oxidation-cyclization protocols for the synthesis of six-membered carbon-,[106] oxygen- and nitrogen-bridged[107] iodonium salts **63** and **66a,b** (Scheme 16). After an initial arylation of iodoarene **62** by *Friedel-Crafts* reaction or **64a,b** *via* aryne formation, the coupled iodoarenes **I** and **II** were successively oxidized and cyclized toward diaryliodininium, -iodaoxinium, and -iodazinium salts in moderate to high yields.



Scheme 16: One-pot synthesis of six-membered carbon-, oxygen- and nitrogen-bridged diaryliodonium salts.

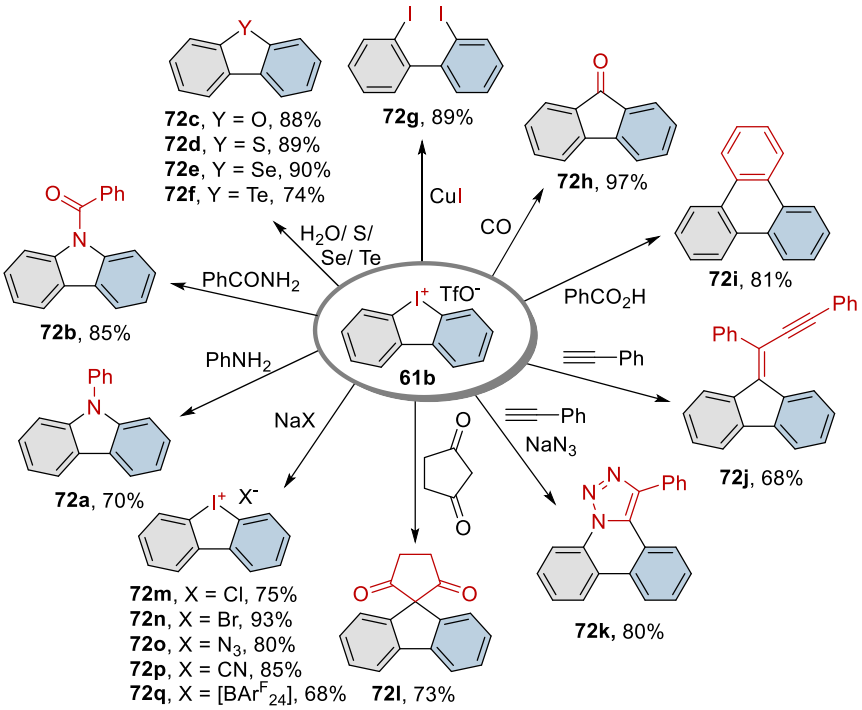
Recently, *Shafir* and co-workers presented several cyclic di-λ^3-diarylhalonium salts **67** from the precursors **68**-**71** (Scheme 17).[108] Various elegant methods were used to synthesize novel bis-halonium salts containing six-, eight- and twelve-membered rings.



Scheme 17: Synthesis of cyclic di-λ^3-diarylhalonium salts **67**.

Cyclic iodonium salts are versatile building blocks due to transformation of the reactive hypervalent iodine center into various structural motifs *via* ring-opening and ring-opening/closing protocols (Scheme 18). Compatible groups include amines[105] and amides,[109] forming carbazoles **72a,b**. Oxygen,[110] sulfur, selenium[111] and tellurium[112] give the chalcogen substituted products **72c-f**. Moreover, ring opening with iodide is leading to biphenyl **72g**,[113] whereas Pd-catalyzed CO-insertion allows to form carbonyl **72h**.[114] Pd-catalyzed decarboxylative coupling with benzoic acid leads to triphenylenes

72i,[115] while reactions with alkynes form alkenes **72j**[116] or triazoles **72k**[117] if azide is added additionally. 1,3-Dicarbonyls can also be coupled with cyclic diaryliodonium salts to yield **72l**.[118] Last but not least the hypervalent iodine center can stay intact while anion exchange reactions succeeded with various counterions.[119]



Scheme 18: Cyclic diaryliodonium salts as versatile building block and in counter ion exchange reactions.

Instead of two phenyl-moieties, aryl(heteroaryl)iodonium salts such as **73** introduce pyridine,[120] pyrazole,[121] imidazole,[122] or chromone[123] as heteroarenes and were all proven to be suitable building blocks for various *N*-heterocyclic compounds (Figure 5). It is noticeable that examples of six-membered, heteroaromatic substituted iodonium salts are rare. Isoxazole-substituted iodininium iodide **74** is the only known example, and no application of this molecule has been shown thus far.[124] Other motifs like heterocycle-substituted iodazinium salts are not known at all.

Besides their use as synthetic building blocks, heteroaryl-substituted iodonium salts were investigated and successfully applied as potent halogen-bond donors (XB-donors). Here the use of non-coordinating $[BAr^F_{24}]^-$ or $[B(C_6F_5)_4]^-$ anions is a prominent tool as these counterions are not inhibiting the iodine's σ-hole from coordination with nucleophiles. Thiophene-substituted bis-iodonium salt **75a** was synthesized by *Huber* and co-workers and could be applied as bidentate XB-donor.[125]

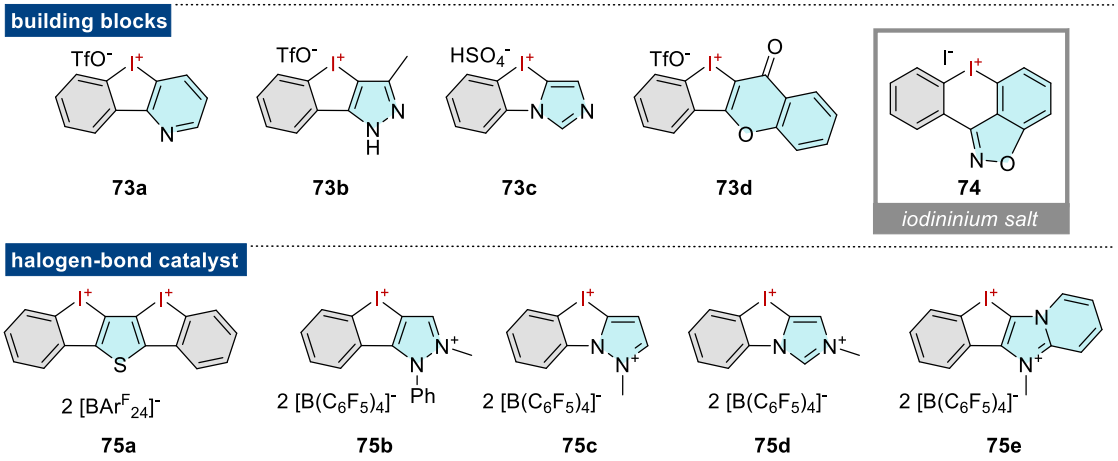
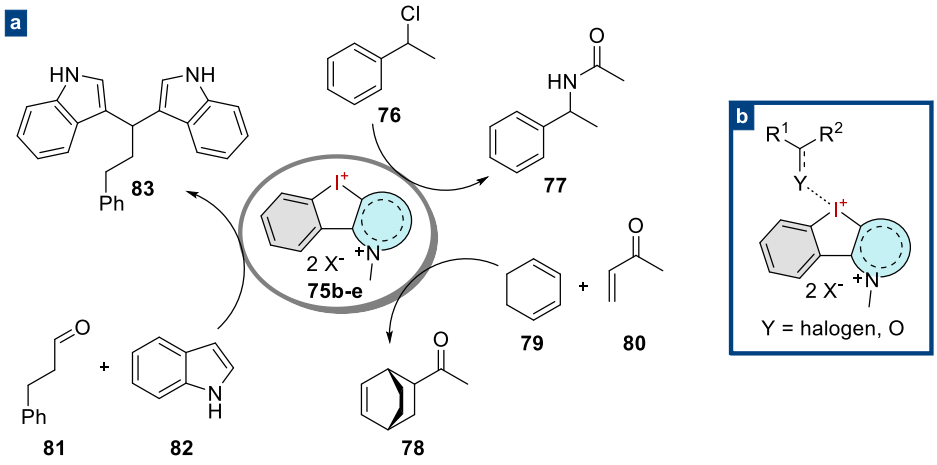


Figure 5: Heteroaryl-substituted cyclic iodonium salts as versatile building blocks and potent halogen bond donors.

Moreover, diaryliodonium salts **75b-e** with highly electron-withdrawing *N*-methylated heterocycles were synthesized by *Nachtsheim* and co-workers and were proven to be strong monodentate XB-donors.[102,126] Amongst others, they were suitable for *Ritter*-type halogen abstraction reactions, catalytic *Diels-Alder* reactions, or in *Friedel-Crafts* arylation reactions (Scheme 19a). In these reactions the XB-catalyst is activating the substrate by coordinating to a nucleophilic position *via* the more pronounced σ-hole, which is placed along the C-I bond of the stronger electron withdrawing arene (Scheme 19b).



Scheme 19: a) Application of *N*-heterocyclic diaryliodonium salts as versatile halogen bond donors. b) Activation mode of iodonium salts by coordinating the substrate with the more pronounced σ-hole.

2 Objectives

Over the last decade, *N*-heterocyclic substituted iodanes have shown growing interest by synthetic chemists regarding their application as oxidants, group transfer reagents or building blocks. These investigations produced promising results that can contribute to solving current limitations in the field of hypervalent iodine chemistry, such as selective oxidizing reagents or stronger halogen bond catalysts.

This dissertation aimed to further extend the applications of *N*-heteroaromatic substituted iodanes and investigate them in the full bandwidth of hypervalent iodine chemistry. Using the previously obtained results, in the first project, new hydroxy-*N*-heterocycle-stabilized iodanes (hydroxy-NHIs) were designed and used in the selective oxidation of benzylic alcohols to the corresponding carbonyls without overoxidation (Figure 6). In the second project, the potential of NHIs as electrophilic alkynylation reagents was investigated. Therefore, a batch of (pseudo)cyclic TIPS-alkynyl-NHIs were synthesized and their reactivity was comparatively investigated in group transfer reactions. Lastly, scarcely known azole-based, cyclic diaryliodininium salts were synthesized in a wide bandwidth of substituents and applied as versatile building blocks. As an outcome, a wider knowledge in terms of stability and reactivity of *N*-heterocyclic-substituted iodanes should enable a precise prediction regarding the design of the next generation of iodine(III) compounds and their application.

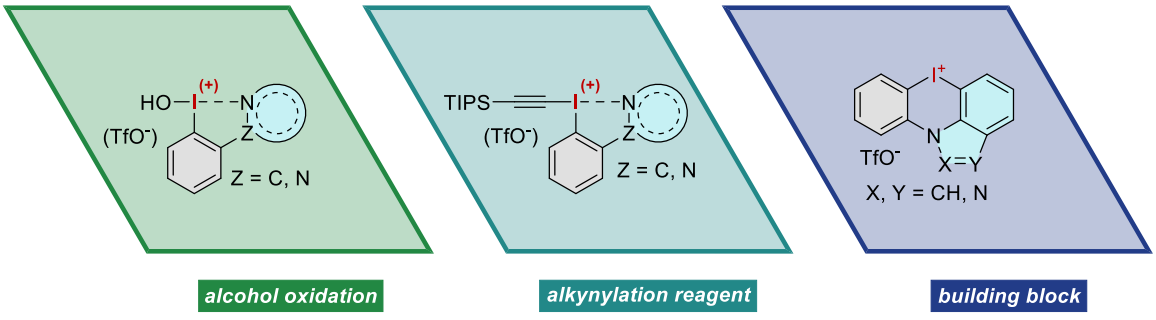


Figure 6: Overview of iodine(III) based structural motifs, which were investigated in the respective projects.

3 Results and discussion

3.1 Oxidation of benzylic alcohols to carbonyls using *N*-heterocyclic stabilized λ^3-iodanes

Thomas J. Kuczmera, Pim Puylaert, Boris J. Nachtsheim *Beilstein J. Org. Chem.* **2024**, 20, 1677–1683. DOI: 10.3762/bjoc.20.149

The manuscript and supporting information including experimental procedures, analytical data, X-ray crystallography data, and NMR spectra are available free of charge on the publisher's website.

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Declaration on the contribution of each author in % can be found on page XV.

Aim: The most prominent characteristic of hypervalent iodine compounds is their oxidative potential, which is applicable under mild and non-toxic reaction conditions. Surprisingly, to date oxidative transformations with *N*-heterocyclic-stabilized iodanes (NHIs) were only investigated with simple molecules. Therefore, the goal of this project was to introduce NHIs as oxidants in the oxidation of alcohols to carbonyls. Especially in the case of primary alcohols, where an overoxidation to carboxylic acids is possible, this can be a challenging transformation.

Abstract: We present *N*-heterocycle-stabilized iodanes (NHIs) as suitable reagents for the mild oxidation of activated alcohols. Two different protocols, both involving activation by chloride additives, were used to synthesize benzylic ketones and aldehydes without overoxidation in up to 97% yield. Based on MS experiments an activated hydroxy(chloro)iodane is proposed as the reactive intermediate.

Author Contribution to this Publication: The idea of this project and the synthetic routes were developed by me (T. J. Kuczmera) and B. J. Nachtsheim. I carried out all optimization experiments and prepared and characterized all compounds. I isolated the crystal for X-ray measurements. P. Puylaert performed the single crystal X-ray measurement and structure refinement. The manuscript and the supporting information were written by me. B. J. Nachtsheim was the principal investigator and edited the article.

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Oxidation of benzylic alcohols to carbonyls using *N*-heterocyclic stabilized λ^3-iodanes

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Full Research Paper

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Abstract

We present *N*-heterocycle-stabilized iodanes (NHIs) as suitable reagents for the mild oxidation of activated alcohols. Two different protocols, both involving activation by chloride additives, were used to synthesize benzylic ketones and aldehydes without overoxidation in up to 97% yield. Based on MS experiments an activated hydroxy(chloro)iodane is proposed as the reactive intermediate.

Introduction

The oxidation of alcohols to aldehydes and ketones is an essential transformation in organic chemistry [1,2]. Generating aldehydes is particularly challenging as they are easily overoxidized to carboxylic acids. Over the past decades a variety of methods have been developed, utilizing toxic heavy metals such as pyridinium dichromate (PDC) [3-5] or manganese dioxide (Figure 1) [6,7]. Molecular oxygen [8] and peroxides [9,10] can also be used as inexpensive terminal oxidants in combination with transition-metal catalysts. Metal-free methods employ chlorodimethylsulfonium compounds as the reactive species and have gained great popularity under the name Swern oxidation or the Corey–Kim oxidation [11]. Hypervalent iodine compounds have also been studied and are well established in several oxidative transformations including the synthesis of complex molecules and drugs [12,13]. The most prominent examples are the pentavalent derivatives 2-iodoxybenzoic acid (IBX) and Dess–Martin periodinane (DMP) [14,15]. Although mild and selective oxidants, these highly oxidized λ^5-iodanes have drawbacks, in particular low solubility and moisture sensitivity [11]. Hypervalent iodine compounds in a lower oxidation state (λ^3-iodanes), such as iodosobenzene $(PhIO)_n$ or phenyliodine(III) diacetate (PIDA) have been reported in alcohol oxidations but they often result in overoxidation to the corresponding carboxylic acids [16]. Additives such as bromide salts or Al_2O_3 can eliminate this problem and allow selective oxidation to some extent [17-20].

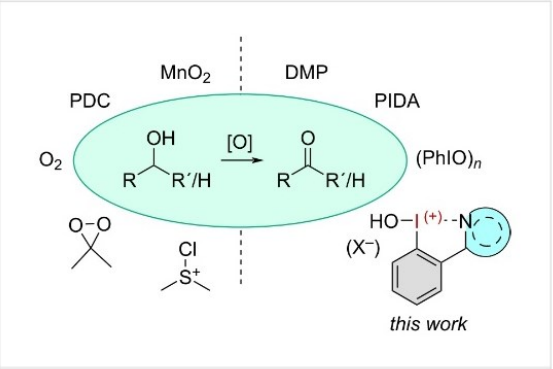


Figure 1: Overview of common non-iodine-based (left) and iodine-based (right) oxidizing reagents for the generation of carbonyls from the corresponding alcohols.

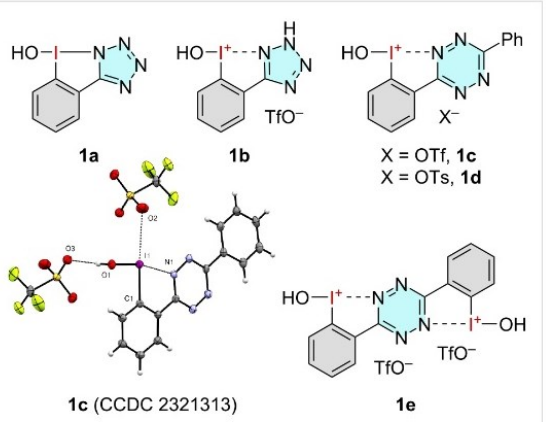


Figure 2: NHIs investigated for the oxidation of benzylic alcohols and the crystal structure (ORTEP drawing) of **1c** (CCDC 2321313), showing the coordination of the triflate to two positions of the iodane. Thermal ellipsoids are displayed with 50% probability. Selected bond lengths and angles: I1–N1: 2.44(4) Å; I1–O1: 1.94(9) Å; I1–O2: 3.04(1) Å; C1–I1–N1: 73.5(8)°; O1–I1–N1: 166.6(5)°; N1–I1–C1–O1: 177.8(3)°.

During the past years, *N*-heterocycle-stabilized iodanes (NHIs) were demonstrated as suitable tools for various applications among them group transfer reactions [21] and as building blocks [22-24]. The synthetic potential of NHIs has been previously studied in model transformations such as thioanisole oxygenation, oxidative lactonization, or diacetoxylation of alkenes [25-28]. In this work, we want to apply NHIs in a mild oxidation of primary and secondary benzylic alcohols to aldehydes and ketones as an alternative to λ^5-iodanes.

Results and Discussion

Initially, we investigated a variety of pyrazole-, triazole-, and oxazole-substituted hydroxy-NHIs previously developed by our group [25]. However, none of them proved to be effective in a model oxidation reaction of *n*-octanol (**2**). Since previous investigations have repeatedly shown that the number of heteroatoms in the *N*-heterocycle correlates with the NHIs activity, a series of tetrazole- and tetrazine-substituted NHIs **1a–e** was synthesized (Figure 2) [29,30]. A crystal structure was additionally obtained for tetrazine **1c**. Bond lengths and angles were similar to those of known five-membered NHIs [25], including a strong intramolecular interaction between the nitrogen of the tetrazine and the hypervalent iodine atom (I1–N1: 2.44(4) Å; the sum of VdW radii: 3.61 Å [31]).

Beginning with the electron-deficient and thereby highly reactive NHIs **1a** and **1c**, we explored the potential for a ligand-exchange process on the iodane via ^{1}H NMR spectroscopy by combining equimolar quantities of NHI and *n*-octanol (**2**). When the tetrazole-substituted hydroxy(aryl)iodane **1a** was added, no significant shifts in the NMR spectral signals were detected, probably due to the poor solubility of the iodane. Conversely, with the addition of the red tetrazine salt **1c**, a significant downfield shift was observed for the *alpha*-carbon protons from 3.51 ppm to 4.55 ppm, as illustrated in Figure 3a.

This indicates a ligand exchange of the hydroxy group resulting in a loss of electron density and the formation of the alkoxy-NHI **2'**. The chemical shift is consistent with previously measured alkoxyiodanes [32].

The experiments were repeated using activated *p*-tolylmethanol (**3a**), again showing no reaction with iodane **1a**. Utilizing the tetrazine **1c**, *p*-methylbenzaldehyde (**4a**) was observed as a new species at 9.94 ppm (Figure 3b). The reaction reached 31% conversion after 72 h, however, *p*-methylbenzoic acid (**4a'**) was formed in 35% as well, showing an undesired overreaction. In this experiment no formation of an alkoxyiodane was observed, indicating that the formation of this ligand-exchanged intermediate is slower than the dehydrogenation. As a consequence, we attempted to accelerate the ligand exchange through the addition of a Lewis acid and the performance of the NHIs was compared with common iodine(III) reagents by ^{1}H NMR spectroscopy (Figure 4). After 60 h the measurements revealed a higher yield of aldehyde **4a** using **1a** (68%) compared to **1c** (30%) under the influence of $AlCl_3$. As a comparison, the use of PIDA (**5b**) and IBA (**5c**) with the additive resulted in a significantly lower oxidation of the alcohol. Only small amounts of benzoic acid **4a'** were observed in all reactions with additional $AlCl_3$, suggesting that the additive inhibits the previously observed overoxidation.

Surprisingly $AlCl_3$ activated the cyclic tetrazole iodane **1a** but had almost no influence on the reactivity of the tetrazine salt **1c**. Based on these results, the reaction conditions were further optimized using NHI **1a** with the benzyl alcohols **3a** (electron-rich)

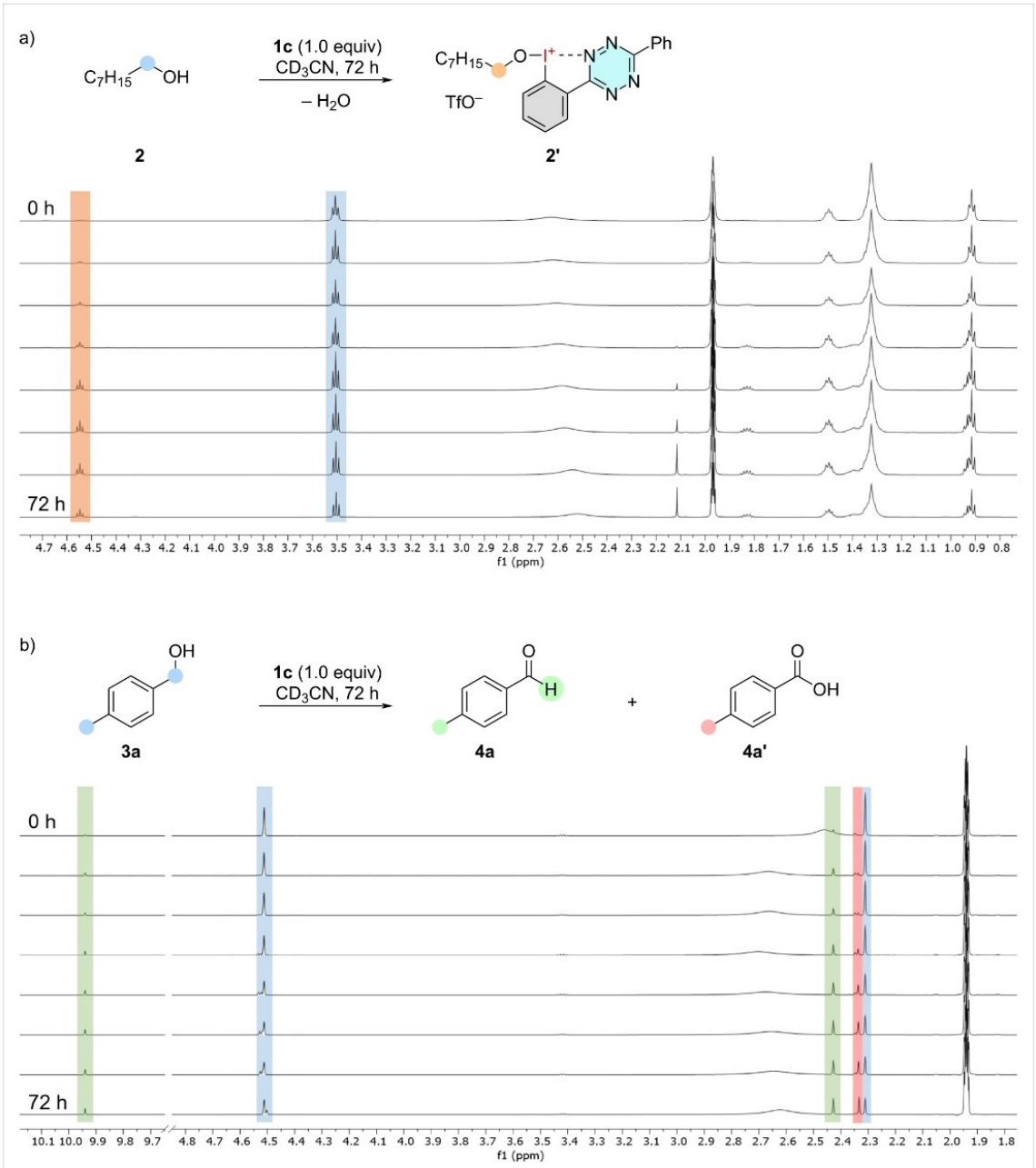


Figure 3: ^{1}H NMR spectra of the time-dependent formation of a) an alkoxy-NHI which is causing a significant downfield shift of the protons in *alpha*-position (orange) compared to the free alcohol **2** (blue) and b) oxidation of *p*-tolylmethanol (**3a**, blue) to the aldehyde **4a** (green) and carboxylic acid **4a'** (red). Reaction conditions: An equimolar mixture of NHI **1c** (10.0 µmol) and alcohol (**2** or **3a**, 10.0 µmol) were dissolved in CD_3CN (600 µL) and ^{1}H NMR spectra were recorded.

and **3b** (electron-poor) as the model substrates. First, the reaction temperature was increased, finding 60 °C to be the optimal value in EtOAc (Table 1, entry 1). At this temperature, the reaction time was significantly reduced to 2.5 h. A variety of other additives were tested next, revealing TsOH or NaOTs inhibiting the reaction (Table 1, entries 2 and 3). The addition of tetrabutylammonium halides showed the chloride salt being superior, giving comparable or even better yields than $AlCl_3$ (Table 1,

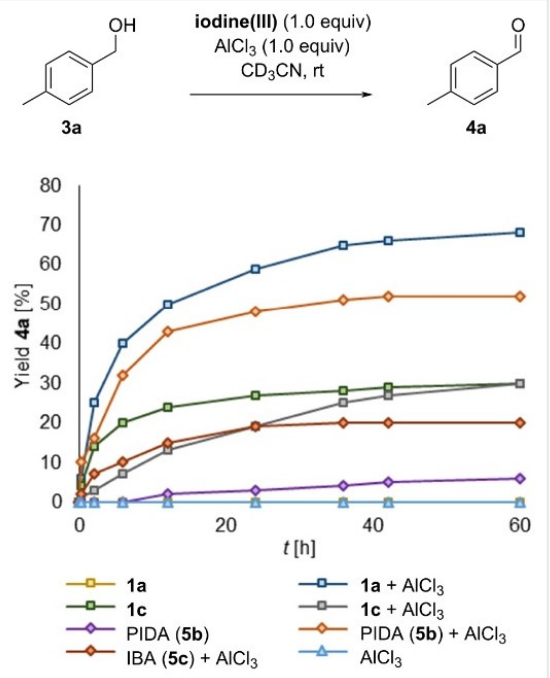
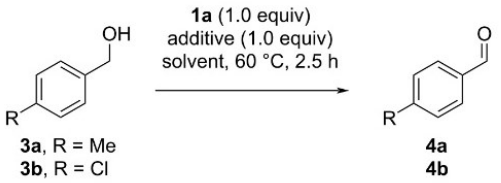


Figure 4: Oxidation of **3a** to **4a** using different iodine(III) reagents with $AlCl_3$ as an additive. Conditions: The turnover of an equimolar mixture of **3a**, iodine(III), and $AlCl_3$ (10.0 µmol, respectively) in CD_3CN (500 µL) was monitored via ^1H NMR spectroscopy.

Table 1: Varying the additive and solvent in the oxidation of electron-rich and electron-deficient benzylic alcohols with **1a**.[a]



3a, R = Me
3b, R = Cl
4a
4b

Entry	Additive	Solvent	Yield [%]	
			4a	**4b**
1	$AlCl_3$	EtOAc	65	39
2	$TsOH·H_2O$	EtOAc	1	1
3	NaOTs	EtOAc	1	1
4	TBAF	EtOAc	9	19
5	TBACl	EtOAc	67	62
6	TBABr	EtOAc	58	47
7	TBAI	EtOAc	40	36
8	NH_4Cl	EtOAc	37	26
9	HCl	EtOAc	82	44
10	TBACl	MeCN	64	69
11[b]	TBACl	MeCN	74	78
12[b]	HCl	EtOAc	90	53

[a]Reaction conditions: **1a** (100 µmol), **3a**/**3b** (100 µmol), and the additive (100 µmol) were stirred in the given solvent (1 mL) at 60 °C for 2.5 h and quenched with Me_2S (200 µmol). [b]Optimum reaction conditions were used: **1a** (100 µmol), **3a**/**3b** (100 µmol), and the additive (100 µmol) were stirred in the given solvent (0.5 mL) at 60 °C for 2.5 h and quenched with Me_2S (200 µmol). The yield was determined via ^1H NMR using tetraethylsilane as an internal standard.

Table 2: Testing different NHIs under the optimum conditions for oxidation of electron-deficient substrate **3b**.[a]

Iodane	Yield of **4b** [%]
1a	78
1b	71
1c	46
1d	29
1e	41

[a]Reaction conditions: NHI (**1a–d**: 140 µmol, **1e**: 70.0 µmol), *p*-chlorobenzyl alcohol (**3b**, 100 µmol) and TBACl (100 µmol) in MeCN (500 µL) were stirred at 60 °C for 2.5 h and quenched with Me_2S (200 µmol). The yield was determined via ^1H NMR with tetraethylsilane as an internal standard.

entries 4–7). Investigation of other chloride sources resulted in a reduced yield in the case of ammonium chloride and an improved yield of 82% of **4a** when concentrated aqueous HCl was added (Table 1, entries 8 and 9). Other solvents did not further increase the yield (see the full table in Supporting Information File 1).

However, when electron-deficient *p*-chlorobenzyl alcohol (**3b**) was used the highest yield of **4b** (69%) was achieved with TBACl as the chloride source in MeCN (Table 1, entry 10). These optimizations lead to the conclusion that $AlCl_3$, as proposed in the initial experiments is not a Lewis acid activator but just a chloride source. Further optimization studies improved the yield to 78% of **4b** using a concentration of 0.20 M of the alcohol and 1.4 equiv of **1a** (see Supporting Information File 1). Finally, all NHIs were tested under the optimized conditions, revealing the tetrazole-substituted iodane **1a** to be the best oxidant for this reaction (Table 2).

The two suitable methods (A: HCl in EtOAc; B: TBACl in MeCN) were then applied to a variety of activated alcohols. The best option is shown in Figure 5. Model substrate **4a** could be isolated in a high yield of 84% with reisolation of the 5-(2-iodophenyl)-1*H*-tetrazole (**6**) in 90% yield. Other *para*-halogenated benzaldehydes **4b–f** were isolated in good yields of up to 88%. *ortho*-Substitution led to a lower yield of the iodinated product **4g** (43%) compared to the *para*-iodinated analogues **4d** (75%). The *ortho*-phenyl-substituted aldehyde **4h** was isolated in 85% yield, while the *ortho*-methoxy substrate did not convert to **4i**.

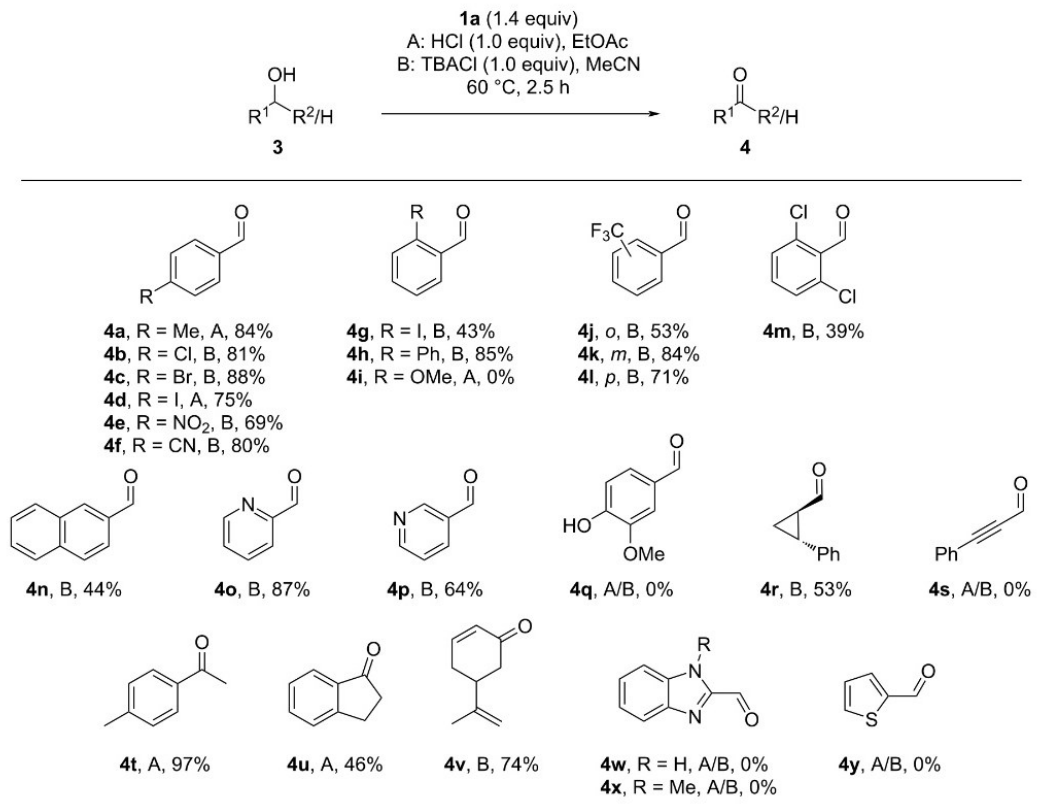
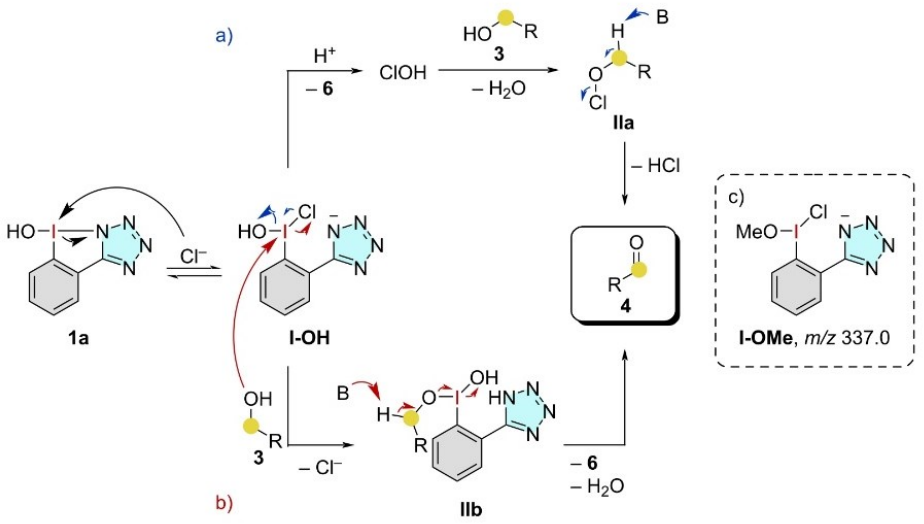


Figure 5: Substrate scope of aldehydes and ketones synthesized from the corresponding alcohols. Isolated yields. Reaction conditions: **1a** (700 µmol), alcohol (500 µmol), and method A HCl (37%, 500 µmol) in EtOAc (2.5 mL) or method B TBACl (500 µmol) in MeCN (2.5 mL), respectively, were stirred at 60 °C for 2.5 h and quenched with Me_2S (1.40 mmol).

The *ortho*-, *meta*- and *para*-permutation of a CF_3 group showed lower reactivity for the *ortho*-substituted **4j** (53%), while the *meta*- and *para*-derivatives **4k** and **4l** gave higher yields of 84% and 71%, respectively. The steric inhibition of a doubly substituted phenyl ring was observed in a diminished formation of 2,6-dichlorobenzaldehyde (**4m**) in 39% yield. Naphthalen-2-ylmethanol gave aldehyde **4n** in 44% yield. Pyridines **4o** and **4p** were also compatible and gave good yields of 87% and 64%, respectively. Unfortunately, the synthesis of vanillin (**4q**) was unsuccessful due to undesirable oxidation reactions of the electron-rich arene. The cyclopropane derivative **4r** was generated from the cyclopropylmethanol in 53% yield. The acetylene derivative **4s** could not be isolated due to undesired oxidations of the triple bond. The behavior of secondary benzylic alcohols was tested next, giving 4-methylacetophenone (**4t**) in an excellent yield of 97% and 1-indanone (**4u**) in 46%. It is worth noting that for some derivatives oxidized by method A, an acylation of the alcohol was detected as a side reaction via mass spectrometry. Vinyl alcohols were also studied, giving carvone (**4v**) in 74% yield without oxidation of the double bonds. Finally, other heterocyclic benzylic alcohols were investigated, which led to undesired chlorinations in the case of benzimidazoles **3w** and **3x** and decomposition for thiophenylmethanol **3y**.

Regarding the reaction mechanism, two plausible pathways can be discussed based on literature examples (Scheme 1, path a [17] and path b [33]). In either path, initial ligand exchange to the hydroxy(chloro)iodane **I-OH** is proposed. For getting an indication of a chloride-activated iodane of this type, a mixture of NHI **1a** and HCl in EtOAc was stirred for 1 h at 60 °C and an ESI(−) mass spectrum was recorded afterward, showing an ion **I-OMe** with *m/z* 337.0 [**1a** – OH + MeO + Cl]$^-$ (Scheme 1c). It is known that methanol, which is used as a solvent in the mass spectrometer, can be exchanged with the hydroxy group of the NHI [21]. No such ion was measured in the mixture before heating. This ion therefore indicates an I–Cl bond in the activated iodane. Starting from **I-OH**, in a potential path a) formation of hypochlorous acid is suggested, which consequently



Scheme 1: Possible reaction mechanisms via the formation of a) a Cl(I) species and b) the formation of an alkoxyiodane **IIb**. Both are initialized by the activated iodane **I-OH**, which was observed as c) **I-OMe** species in the ESI(–) MS.

oxidizes the alcohol through the alkyl hypochlorite **IIa**. The second mechanism (path b) requires a direct ligand exchange of **I-OH** with the alcohol and subsequent β-elimination of the alkoxy(hydroxy)iodane **IIb** to form the desired aldehyde **4**.

Conclusion

In conclusion, this study has successfully introduced *N*-heterocycle-stabilized iodanes (NHIs) as effective λ^3-iodane oxidants for the selective synthesis of ketones and aldehydes, avoiding overoxidation to carboxylic acids. The developed protocols proved particularly effective for benzylic alcohols, yielding good to excellent results. The beneficial role of chloride salt additives was investigated, potentially leading to the formation of a hydroxy(chloro)iodane intermediate. This intermediate either liberates hypochlorous acid as the terminal oxidant or undergoes a direct ligand exchange with the alcohol, followed by oxidative elimination to form the aldehyde. Thus, these reagents offer a viable alternative to traditional aryl-λ^5-iodane-based oxidants, although further studies are necessary to fully understand their reaction mechanisms.

Experimental

General procedure for oxidation of benzylic alcohols

1a (700 µmol, 201 mg, 1.40 equiv), benzylic alcohol (**3**, 500 µmol, 1.00 equiv) and method A: aqueous HCl (37%, 500 µmol, 41.6 µL, 1.00 equiv) in EtOAc (2.5 mL) or method B: TBACl (500 µmol, 137 mg, 1.00 equiv) in MeCN (2.5 mL), respectively, were stirred at 60 °C for 2.5 h, quenched with Me_2S (2.00 equiv) and the reaction mixture was purified via flash column chromatography on silica.

Supporting Information

Supporting Information File 1

Experimental part and copies of spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-20-149-S1.pdf]

Author Contributions

Thomas J. Kuczmera: investigation; writing – original draft. Pim Puylaert: investigation. Boris J. Nachtsheim: conceptualization; funding acquisition; project administration; resources; supervision; writing – review & editing.

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Data Availability Statement

All data that supports the findings of this study is available in the published article and/or the supporting information to this article

Preprint

A non-peer-reviewed version of this article has been previously published as a preprint: https://doi.org/10.26434/chemrxiv-2024-t3b6h

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3.2 Stabilization of Ethynyl-Substituted Aryl-λ^3-Iodanes by Tethered *N*-Heterocycles

Thomas J. Kuczmera, Andreas Boelke, Boris J. Nachtsheim *Eur. J. Org. Chem.* 2022, e202200276. DOI: 10.1002/ejoc.202200276

The manuscript and supporting information including experimental procedures, analytical data, X-ray crystallography data, and NMR spectra are available free of charge on the publisher's website

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Declaration on the contribution of each author in % can be found on page XV.

Aim: During the past years, NHIs have been studied in several fields of hypervalent iodine chemistry. However, there is a lack of knowledge in their application as electrophilic group transfer reagents. The aim of this project was to efficiently synthesize TIPS-acetylene NHIs followed by investigation as novel alkynylation reagents.

Abstract: A systematic investigation of ethynyl *N*-heterocycle-substituted-λ^3-iodanes (ENHIs) is presented. In a straightforward one-pot synthesis these novel reagents can be obtained in high yields bearing a variety of N-heterocycles. Their reactivity as electrophilic alkyne group transfer reagents was benchmarked in well-established and novel inter- and intramolecular group transfer reactions.

Author Contribution to this Publication: The idea of this project as well as synthetic routes were developed by A. Boelke and B. J. Nachtsheim. He carried out initial experiments to synthesize the NHIs, while possible applications were developed by me (T. J. Kuczmera). I carried out the optimization and prepared and characterized 70 compounds. Two compounds were generated by A. Boelke and 21 additional compounds were synthesized by both of us. I isolated the two crystals for X-ray measurements. The manuscript and the supporting information were written by me. B. J. Nachtsheim was the principal investigator and edited the article.

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Stabilization of Ethynyl-Substituted Aryl-λ^3-Iodanes by Tethered *N*-Heterocylces**

Thomas J. Kuczmera,[a] Andreas Boelke,[a] and Boris J. Nachtsheim*[a]

In memory of Klaus Hafner

A systematic investigation of ethynyl *N*-heterocycle-substituted-λ^3-iodanes (ENHIs) is presented. In a straightforward one-pot synthesis these novel reagents can be obtained in high yields bearing a variety of *N*-heterocycles. Their reactivity as electrophilic alkyne group transfer reagents was benchmarked in well-established and novel inter- and intramolecular group transfer reactions.

Introduction

In recent years, the chemistry of hypervalent iodine compounds experienced an immersive growth resulting in a plethora of applications in organic synthesis,[1,2] including the oxidation of alcohols,[3,4] CH-oxidations[4] and phenol dearomatizations.[5] Besides their remarkable reactivity as dehydrogenative oxidants, in particular aryl-λ^3-iodanes turned out to be potent electrophilic group transfer reagents.[6] The most prominent representatives are diaryliodonium salts as electrophilic arylating reagents,[7] alkenyl(aryl)iodonium salts as electrophilic vinyl motives[8] and alkynyl(aryl)iodonium salts for electrophilic alkyne transfer reactions.[9] In the latter, thermal stability is a latent problem.[10] Here, intermolecular stabilization by oxygen-based donors in the form of ethynyl-benziodoxol(on)es (EBX) revealed a significantly increased thermal stability and hence an improved synthetic utilization of alkynyl-substituted iodanes (Figure 1).[11] Benziodoxol(on)es (BX) motifs also allow the stabilization of a large range of other transferable substituents at the hypervalent iodine atom such as halides,[12,15] esters,[13] cyanides,[14] CF_3-groups[15] or azides.[16] Intrinsically, BX-based iodanes allow only a limited chemical variation to modify and fine-tune thNe reactivity of these substituents in umpolung reactions. However, the oxygen atom itself can be substituted by other heteroatoms, in particular nitrogen.[17] These contemporary benziodazol(on)e (BZ) reagents tolerate a wider range of functional substituents, even the highly delicate SCF_3 group.[18] Recently, Waser and co-workers presented the corresponding ethynyl benziodazol(on)es (EBZ), benziodazolimines (EBZI) and benziodosulfoximines (EBS).[19] Their reactivity in electrophilic alkynyl transfer reactions strongly depends on the electron density distribution along the I–N-bond and the resulting *trans*-effect on the σ-hole.

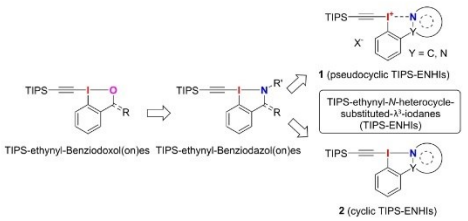

Figure 1. Pseudocyclic and cyclic TIPS-ethynyl *N*-heterocycle-substituted-λ^3-iodanes (TIPS-ENHIs) as a further development based on ethynyl benziodoxol(on)e (EBX)[11] and ethynyl benziodazol(on)e (EBZ)[18,19] reagents.

Our group is interested in the chemistry of *N*-heterocycle-stabilized iodonium salts (NHIs), in which regard we systematically investigated pseudocyclic hydroxy(aryl)-NHIs as potent oxidizing reagents.[20] Based on these initial findings, we were interested to systematically describe the chemistry of these potentially useful reagents and herein present a variety of novel (pseudo)cyclic ethynyl *N*-heterocycle-substituted-λ^3-iodanes (ENHIs). We demonstrate their application in inter- and intramolecular group transfer reactions and in the synthesis of novel heteroaromatic compounds.

Results and Discussion

Initially, we were focused on the synthesis of pseudocyclic TIPS-ENHIs. Because of our previous results for the synthesis of cyclic diaryliodonium salts using one-pot procedures,[21,22] we intended to directly develop a convenient oxidation/alkynylation reaction. One-pot procedures for unsubstituted TIPS-ethynyl

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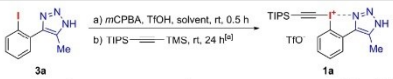
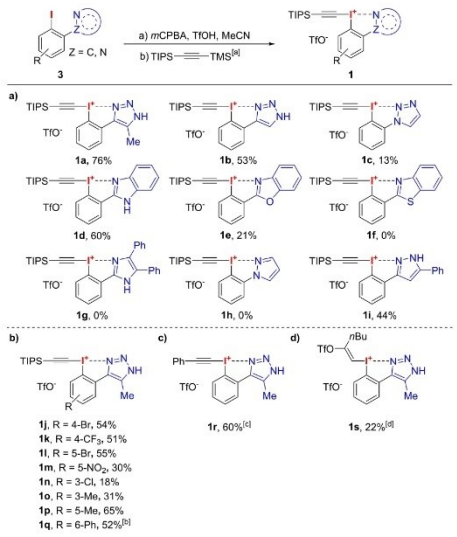
iodonium salts and EBX reagents have already been described, using *meta*-chloroperbenzoic acid (*m*CPBA) as the terminal oxidant in the presence of strong acids such as TfOH or TsOH and the subsequent addition of an alkyne to the *in situ* formed hydroxy(aryl)iodonium salt.[23] Based on these procedures the reaction conditions were optimized for TIPS-ENHIs (Table 1).

Table 1. Optimization of the reaction conditions for the one-pot synthesis of TIPS-ENHIs.[a]



Entry	Solvent	TfOH [equiv.]	Yield [%][b]
1	TFE	4.5	50
2	TFE	3.5	53
3	TFE	2.5	61
4	DCM/TFE	2.5	71
5	DCM	2.5	(55)[c]
6	$CHCl_3$	2.5	(24)[c]
7	MeCN	2.5	76
8	MeCN	1.6	(11)[c]
9[d]	MeCN	2.5	69
10[d]	MeCN	3.0	71

[a] Reaction conditions: **3a** (0.20 mmol, 1.0 equiv.) was dissolved in the indicated solvent (1 mL) and *m*CPBA (0.24 mmol, 1.2 equiv.) and TfOH were added. The mixture was stirred at rt for 0.5 h, then TIPS-TMS-acetylene (0.28 mmol, 1.4 equiv.) was added and stirring was continued at rt for 24 h. [b] Isolated yield. [c] Incomplete conversion of the oxidized intermediate. [d] 1.00 mmol scale, oxidation time 1 h.



Scheme 1. [a] 2-Iodoarene **3** (1.0 equiv.), *m*CPBA (1.1 equiv.) and TfOH (2.5 equiv.) were stirred in MeCN (0.20 M) at room temperature for 1 h, then TIPS-TMS-acetylene (1.4 equiv.) was added and stirred for 42 h. [b] reaction temperature 50 °C, [c] Ph-TMS-acetylene (1.4 equiv.), [d] **1s** was synthesized via a two-step procedure due to a failed one-pot synthesis. The given yield refers over both steps. *n*Bu-TMS-acetylene (1.4 equiv.) was added as alkynylation reagent.

First, the equivalents of TfOH were varied using 2,2,2-trifluoroethanol (TFE) as a solvent. The best yield of 61% was achieved using 2.5 equiv. of TfOH (entry 1–3) after suspending the crude product in Et_2O, while column chromatography turned out to be not suitable due to decomposition of the product. Next, the influence of the solvent was investigated. A 1:1 mixture of DCM and TFE gave an increased yield of 71% (entry 4), while in pure DCM or chloroform only incomplete conversion of the oxidized intermediate was observed (entries 5–6). Finally, MeCN was found to be the best solvent for this transformation, giving **1a** in 76% yield (entry 7). Even in this solvent the amount of added TfOH could not be decreased (entry 8). On a 1 mmol scale, 3 equiv. of TfOH were slightly superior (entries 9–10). It is worth mentioning that the use of $TsOH{\cdot}H_2O$ as acid leads to no alkynylation of the oxidized intermediate and even the addition of an excess of TfOH during the alkynylation step does not lead to a quantitative counter ion exchange when previously $TsOH{\cdot}H_2O$ was used in the oxidation.

Under these optimized conditions different TIPS-ENHIs **1** were synthesized (Scheme 1a). The unsubstituted triazole **1b** was isolated in 53% yield, whereas the *N*-bound triazole **1c** could only be obtained in 13% yield. The benzimidazole **1d** was smoothly synthesized in 60% yield, while the benzoxazole **1e** gave a moderate yield of 21%. The absence of an NH-function leads to the tendency to form oils and a better solubility of the salts **1c** and **1e**, which caused problems in the purification process and rationalizes the observed low yields. Moreover, in the case of benzoxazole **1e** a partial addition of TfOH to the acetylene moiety was observed, which could be removed by addition of water and lead to lose of product. The alkynylation of the benzothiazole **1f** and *N*-bound pyrazole **1h** failed despite a successful oxidation. With diphenylimidazole **3g** as substrate, TfOH was not tolerated due to decomposition. Furthermore, the successful synthesis of the *C*-bound pyrazole **1i** in a good yield of 44% was a great success, as the competing ring closure to the cyclic iodolopyrazolium salt under similar conditions had recently been described.[21] It is worth mentioning, that a two-step protocol was also tested with those substrates. These results can be found in the ESI.

After the successful synthesis of ENHIs with different *N*-heterocycles, the tolerance of various functional groups at the iodoarene was investigated, using the methylated *C*-bound triazole as a model substrate (Scheme 1b). Most electron withdrawing halogen- and CF_3-substituted iodoarenes **3j–3l** yielded the desired products **1j–l** in good yields of 51–55%, while the NO_2-derivative gave **1m** in a diminished yield. The low yield of 18% for the chlorinated salt **1n** can be explained by steric effects between the substituent and the alkyne. A similar tendency was observed for the methylated derivatives **1o–p**. Here, *para*-methylation gave a yield twice as high as the *ortho*-substituted salt (31% and 65%). The biphenyl **1q** was also obtained in a good yield of 52%, so that an overall high functional group tolerance of the pseudocyclic salts could be demonstrated.

Finally, other alkynylation reagents were investigated (Scheme 1c and Scheme 1d), giving the moisture sensitive Ph-acetylene salt **1r** in 60% yield. For the 1-hexyne derivative the

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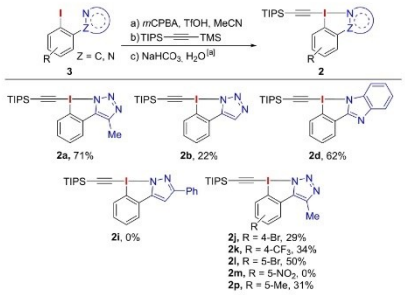
one-pot procedure was not successful, so that the oxidized intermediate was isolated and used for the alkynylation. Here, only the vinyl species **1s** could be obtained due to the addition of TfOH to the alkyne. This behavior has previously been described for other unsubstituted[24] as well as stabilized[25] iodonium salts.

For salts containing a free NH-function in the *N*-heterocycle, the corresponding cyclic ENHIs were synthesized through addition of aqueous $NaHCO_3$-solution to the reaction mixture after the alkynylation step (Scheme 2). Accordingly cyclic triazole **2a** was isolated in a good yield of 71%. The non-methyl derivative **2b** was obtained in only 22%, again due to a better solubility of this derivative and the related difficulties during work-up. In contrast the again insoluble cyclic benzimidazole **2d** was isolated in 62% yield. Pyrazole **2i** could not be obtained due to cleavage of the TIPS-acetylene moiety. The cyclization of the substituted iodanes revealed yields between 29–50% for the iodanes **2j–l** and **2p**, while the cyclization of the NO_2-salt **2m** failed due to a cleavage of the alkyne as observed for **2i**.



Scheme 2. One-pot synthesis of cyclic ENHIs. [a] 2-Iodoarene **3** (1.0 equiv.), *m*CPBA (1.1 equiv.) and TfOH (2.5 equiv.) were stirred in MeCN (0.20 M) at room temperature for 1 h, then TIPS-TMS-acetylene (1.4 equiv.) was added and stirred for 42 h. Afterwards aq. $NaHCO_3$-solution (4.0–6.0 equiv.) was added and stirred for 1–3 h at room temperature.

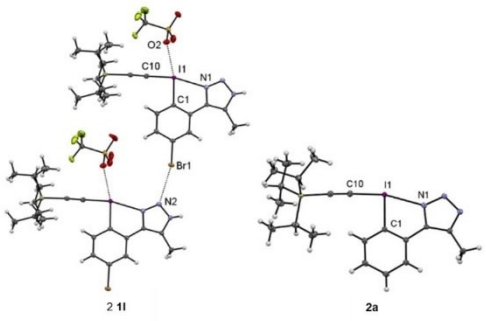
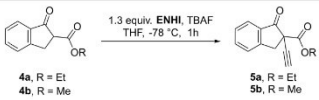


Figure 2. Crystal structures (ORTEP drawing) of **1l** (CCDC 2120075) and **2a** (CCDC 2120074). Thermal ellipsoids with 50% probability. For **1l**: C1–I1: 2.183 Å, I1–C10: 2.035 Å, I1–N1: 2.517 Å, C1–I1–C10: 92.40°, C1–I1–N1: 73.38°, N1–I1–C10: 165.78°, C1–I1–N1–C10: 0.27°. For **2a**: C1–I1: 2.143 Å, I1–C10: 2.071 Å, I1–N1: 2.431 Å, C1–I1–C10: 90.04°, C1–I1–N1: 74.38°, N1–I1–C10: 164.77°, C1–I1–N1–C10: 17.26°.

Single crystal structure analysis of the two ENHIs **1l** and **2a** (Figure 2) revealed the expected T-shape structure of the hypervalent iodine center[1] (N1–I1–C10 angles of 165.78° for **1l** and 164.77° for **2a**) and an expected longer N1–I1 distance in the pseudocyclic salt (2.517 Å) compared to the cyclic iodane (2.431 Å). While the alkyne group of the pseudocyclic salt **1l** is nearly in plane with the aromatic system, **2a** is significantly twisted with a C1–I1–N1–C10 dihedral angle of 17.26°. This twist was previously observed for other bis-*N*-heterocyclic substituted-λ^3-iodanes.[26] Additionally, in **2a** 1/6 equiv. of NaOTf is included in the crystal structure (see ESI). Significant intermolecular interactions in ENHI **1l** between Br1–N2 (3.149 Å, sum of VdW-radii 3.38 Å) and I1–O2 (2.828 Å, sum of VdW-radii 3.50 Å) indicates substantial halogen bonding between those atoms.

After the successful synthesis of a range of new (pseudo)cyclic ENHIs, their potential in electrophilic alkynyl transfer reactions was investigated. First, a relative performance test of all ENHIs was accomplished on the alkynylation of β-ketoester **4a** via the *in situ* formed free alkynyl-NHI (Table 2). This reaction has been previously investigated by Waser and coworkers using TIPS-EBX and TIPS-EBZ reagents.[19,27] Starting with the triazole **1a**, quantitative formation of the desired product **5a** could be observed after 1 h (entry 1). The cyclic derivative **2a** gave **5a** in 79% yield, which could be significantly increased to 94% after a prolonged reaction time of 18 h (entries 2–3). The non-methylated triazole salt **1b** gave an improved yield of **5a** after 1 h reaction time (70%, entry 4). Similar to the Me-triazoles, the cyclic iodane **2b** gave a lower yield of 60% in direct comparison with the corresponding pseudocyclic salt **1b** (entry 5). The same tendency was observed with the benzimidazoles (entries 6–7). This reactivity can be derived from the crystal structures. The shorter I1–C10-

Table 2. Alkynylation of 1,3-dicarbonyle **4a, b** by *in situ* formation of the free ethynyl-NHI.



Entry	R	ENHI	Yield **5** [%]	Yield iodoarene **3** [%]
1	Et	**1a**	quant.	88
2	Et	**2a**	79	69
3	Et	**2a**	94[a]	86
4	Et	**1b**	87	70
5	Et	**2b**	60	93
6	Et	**1d**	76	(57)[b]
7	Et	**2d**	48	85
8	Et	**1c**	quant.	(>100)[b]
9	Et	**1e**	quant.	43
10	Et	**1i**	quant.	61
11	Et	**6**	quant.	–
12	Et	**1r**	0[c]	–
13	Me	**1a**	71	–
14	Me	**6**	quant.	–

[a] Reaction time 18 h. [b] Not clean after column chromatography. [c] Without TBAF.

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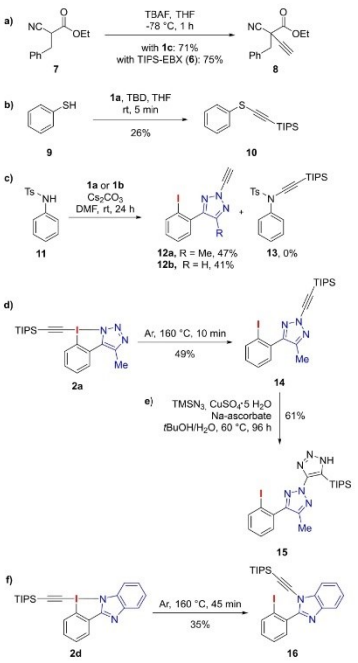
distance of the pseudocyclic derivative **1l** (2.035 Å) compared with the cyclic iodane **2a** (2.071 Å) indicates a stronger *trans*-effect of the pseudocyclic salts and therefore a higher reactivity in group transfer reactions.[19] With the salts **1c**, **1e** and **1i** a quantitative formation of the alkynyl product **5a** was observed (entries 8–10) and showed a similar reactivity to TIPS-EBX (**6**) (entry 11). It is worth mentioning that in many reactions the iodoarenes **3** could be recovered in moderate to high yields. The Ph-alkynyl salt **1r** was not reactive in this type of transfer reaction (entry 12). Unfortunately, the reaction of methyl ester **4b** with the triazole **1a** leads to a slightly lower yield of **5b** (71%), while TIPS-EBX (**6**) again gave quantitative product formation (entries 13–14).

After these promising results, we were eager to test the ENHIs in other group transfer reactions (Scheme 3). Reaction of ethyl 2-cyano-3-phenylpropanoate[27] (**7**) (Scheme 3a) with the *N*-bound triazole **1c** gave the alkynylated product **8** in a good yield of 71% which is a comparative reactivity to TIPS-EBX (**6**). The alkynylation of thiophenole (**9**)[28] with 1,5,7-triazabicyclo(4.4.0) dec-5-ene (TBD) to **10** gave only a low product formation of 26% and therefore a significant lower reactivity than TIPS-EBX (Scheme 3b).[29] Waser and co-workers also observed a low reactivity of their *N*-heterocyclic iodanes in this reaction. Calculated MEP-maps of those iodanes reveal a lower electron density of the N–I-bond and assumes a decreased σ-hole compared to TIPS-EBX as a putative reason.[19]

Finally, the alkynylation of amines was tested using *N*-tosylaniline (**11**).[30] Instead of an aniline alkynylation, *N*-alkynylation of the ENHI **1a**, **b** was observed, giving *N*-alkynylated triazoles **12a** and **12b** in 47% and 41% (Scheme 3c). Here, first the transfer of the TIPS-acetylene moiety was observed (TLC-MS), which then was slowly deprotecting to the free alkyne **12**. The cyclic salt **2a** reveals no reactivity in this conversion. MS/MS experiments of **12a** strongly indicated a selective alkynylation of the triazoles N2 (see ESI). Interestingly the absence of *N*-tosylaniline leads to only a low intramolecular conversion. Based on this observation, the direct thermolysis as another intramolecular transformation pathway was investigated. While using the pseudocyclic salts **1a** and **1d** the emerging TfOH leads to no product formation, the cyclic NHIs **2a** and **2d** gave the TIPS-acetylene triazole **14** in 49% (Scheme 3d) and benzimidazole **16** in 35% yield (Scheme 3f). Those *N*-alkynyl heteroaromatic iodoarenes reveal the possibility for further functionalization, either through the iodine or alkyne. The latter was demonstrated in a click-reaction of the triazole **14** with TMS-N_3,[31] yielding the bi-triazole **15** in 61% (Scheme 3e). To the best of our knowledge this is the first direct C–N connection of two triazoles described so far.



Scheme 3. Intra- and intermolecular group transfer reactions of the ENHIs and further application.

Conclusion

In this work, we demonstrated the systematic synthesis of pseudocyclic and cyclic TIPS-ethynyl NHIs via a one-pot procedure, which revealed a wide range of different heterocycles and substituents to be suitable. The reactivity of those ENHIs was investigated in inter- and intramolecular group transfer reactions, which showed a comparable reactivity to TIPS-EBX. It further enables access to novel N-substituted heteroaromatic compounds and bi-triazole motives. Other promising applications of *N*-heteroaromatic substituted-λ^3-iodanes are under current work in our laboratory.

Experimental Section

General procedure for synthesis of (pseudo)cyclic TIPS-ENHIs: The corresponding iodoarene (**3**, 1.0 equiv.) was dissolved/suspended in MeCN (5 mL/mmol) and *m*CPBA (85%, 1.1 equiv.) was added followed by the dropwise addition of TfOH (3.0 equiv.). The mixture was stirred for 1 h at room temperature, then triisopropyl((trimethylsilyl)ethynyl)silane (1.4 equiv.) was added and stirring continued for 24/42 h at room temperature. For cyclic derivatives afterwards a solution of $NaHCO_3$ (4.0–6.0 equiv.) in H_2O (2.5 ml/mmol) was added and the reaction was stirred for another 1–3 h. The solvent was removed *in vacuo* and the residue was suspended in H_2O (5 ml), decantated, and the crude residue was either washed with Et_2O or recrystallized from the indicated solvent to give pure TIPS-ethynyl-λ^3-iodonium triflates **1** or the cyclic analogues **2**.

Crystallographic data: Deposition Number 2120075 (for **1l**) and 2120074 (for **2a**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszen-

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Group transfer reactions · Heterocycles · Hypervalent compounds · Iodonium salts · Synthetic methods

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3.3 Synthesis and reactivity of azole-based iodazinium salts

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The manuscript and supporting information including experimental procedures, analytical data, X-ray crystallography data, and NMR spectra are available free of charge on the publisher's website

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Declaration on the contribution of each author in % can be found on page XV.

Aim: Six-membered cyclic diaryliodonium salts are usually bridged oxygen-, nitrogen-, carbon-, or sulfur- atoms. In this project, six-membered cyclic diaryliodonium salts should be generated, where the bridge is the nitrogen of an azole-based heterocycle. They were applied as building blocks, as well as in functionalizations under retention of the iodane.

Abstract: A systematic investigation of imidazo- and pyrazoloiodazinium salts is presented. Besides a robust synthetic protocol that allowed us to synthesize these novel cyclic iodonium salts in their mono- and dicationic forms, we gained in-depth structural information through single-crystal analysis and demonstrated the ring opening of the heterocycle-bridged iodonium species. For an exclusive set of dicationic imidazoiodaziniums, we show highly delicate post-oxidation functionalizations retaining the hypervalent iodine center.

Author Contribution to this Publication: The idea of this project and the synthetic routes were developed by me (T. J. Kuczmera) and B. J. Nachtsheim. I carried out the optimization for electron rich substrates and A. Dietz for electron deficient derivatives under my supervision. I prepared and characterized 74 compounds. 14 compounds were generated by A. Dietz and seven additional compounds were synthesized by both of us. I isolated three crystals for X-ray measurements. A. Boelke prepared one reaction and gave helpful ideas. The manuscript and the supporting information were written by me. B. J. Nachtsheim was the principal investigator and edited the article.

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Synthesis and reactivity of azole-based iodazinium salts

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Full Research Paper

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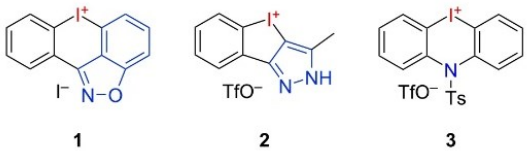
Abstract

A systematic investigation of imidazo- and pyrazoloiodazinium salts is presented. Besides a robust synthetic protocol that allowed us to synthesize these novel cyclic iodonium salts in their mono- and dicationic forms, we gained in-depth structural information through single-crystal analysis and demonstrated the ring opening of the heterocycle-bridged iodonium species. For an exclusive set of dicationic imidazoiodaziniums, we show highly delicate post-oxidation functionalizations retaining the hypervalent iodine center.

Introduction

The chemistry of hypervalent iodine compounds, in particular aryl-λ^3-iodanes, is highly versatile, and a wide range of applications is meanwhile established in organic synthesis [1-5]. They can be applied as mild oxidants [6-8], in phenol dearomatizations [9] or in α-oxygenation reactions [10]. In a complemental reactivity, diaryliodonium salts are potent electrophilic aryl donors [11-16]. Their cyclic derivatives have a proven utility as precursors for the synthesis of hetero- and carbocycles [17-21], and their pronounced σ-holes [22] render them efficient halogen-bond donors (XB donors in XB catalysis) [23]. Despite their great potential in organic synthesis and catalysis, their structural variation is still limited. In particular, heteroarene-bridged cyclic iodonium salts are rare. Examples include the benzisoxazole-containing iodonium salt **1** described by Lisichkina and Tolstaya (Figure 1) [24,25]. Our group is interested in the chemistry of hypervalent iodine species in all their variety, particularly those containing *N*-heterocycles either as tethered stabilizing ligands or as an inclusive part of a cyclic



1 **2** **3**

Figure 1: Nitrogen-containing iodolium and iodonium salts.

iodonium salt [26-31]. We prepared five-membered, *N*-heterocycle-containing iodoliums **2** and investigated their reactivity and utility in XB catalysis. We also established one-pot methods for generating six-membered carbon-, oxygen-, and nitrogen-bridged iodonium salts, such as the iodazinium triflate **3** [32,33]. Based on these promising findings, we further wanted to elaborate this chemistry and herein we present the first synthesis and application of more sophisticated imidazo- and pyrazoloiodazinium salts.

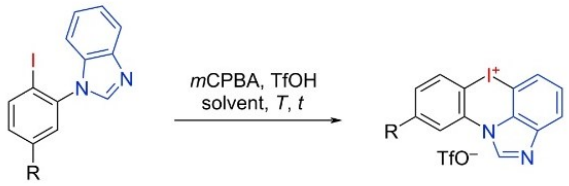
Results and Discussion

Initially, we focused on developing a mild oxidation procedure starting from iodoarene precursors. Previous studies on five-membered heteroaromatic iodonium salts revealed *m*-chloroperoxybenzoic acid (*m*CPBA) as the oxidant of choice in the presence of triflic acid (TfOH) [27,29]. Based on these promising results, the conditions were optimized using *o*-benzimidazole-substituted iodoarenes **4aa** and **4ah** (Table 1).

While running the reaction in MeCN as solvent resulted in no product formation, the reaction of **4aa** in DCE at 50 °C gave the product **5aa** in 23% yield (Table 1, entries 1 and 2). A larger amount of TfOH turned out to increase the solubility of the product and therefore impeded the purification process. However, an excess of acid is required for the electrophilic aromatic substitution to take place. With 2.5 equivalents of TfOH as the optimum amount of acid the product **5aa** was obtained in a yield of 69% (Table 1, entry 3). Similar results were observed with DCM at 40 °C (Table 1, entry 5). A higher amount of *m*CPBA did not lead to a better yield due to more washing required to remove the *m*-chlorobenzoic acid (Table 1, entry 6). When we employed the chlorinated, electron-deficient iodoarene **4ah**, the yield of the product **5ah** dropped significantly (Table 1, entry 7). Combining an electron-deficient heterocycle and an iodoarene with electron-withdrawing substituents results in a significantly decreased reactivity. Thus, for those substrates, harsher reaction conditions were required. A slight adaption of the original conditions to elevated temperatures (65 °C) and prolonged reaction times of 14 d finally resulted in the formation of product **5ah** in 52% yield using DCM as the solvent (Table 1, entry 8).

Next, various substituted iodoarenes **4** were oxidized and cyclized using the optimized conditions to generate a diverse set of azoiodazinium salts **5** (Figure 2). The *ortho*-methylated salt **5ab** was obtained in a low yield of 19%, and the fluorinated derivative **5ac** could be obtained in 55%. Unfortunately, the MeO-substituted derivative **5ad** did not form. Except for the acetamide **5ae**, which could not be obtained due to decomposition, other *meta*- and *para*-substituted derivatives **5af–ak**, among them derivatives with strong electron-withdrawing functionalities, could be synthesized in 39–69% yield. The electron-rich

Table 1: Optimization of reaction conditions for the synthesis of azoiodazinium salts **5aa** and **5ah**.[a]



4aa (R = H)
4ah (R = Cl)

5aa (R = H)
5ah (R = Cl)

Entry	R	*m*CPBA (equiv)	TfOH (equiv)	*T* (°C)	*t* (d)	Solvent	Yield (%)
1	H	1.1	3.0	50	3	MeCN	0
2	H	1.1	3.0	50	3	DCE	23
3	H	1.1	2.5	50	3	DCE	69
4	H	1.1	2.0	50	3	DCE	19
5	**H**	**1.1**	**2.5**	**40**	**3**	**DCM**	**69**
6	H	1.5	2.5	40	3	DCM	53
7	Cl	1.1	2.5	40	3	DCM	9[b]
8	**Cl**	**1.3**	**5.0**	**65**	**14**	**DCM**	**52**

[a]Iodoarene **4aa** or **4ah** (200 µmol) and *m*CPBA were dissolved in the given solvent (1 mL) in a screw cap vial, TfOH was added, and the reaction mixture was stirred under the corresponding conditions. For full table, see Supporting Information File 1. [b]Incomplete conversion, product not clean.

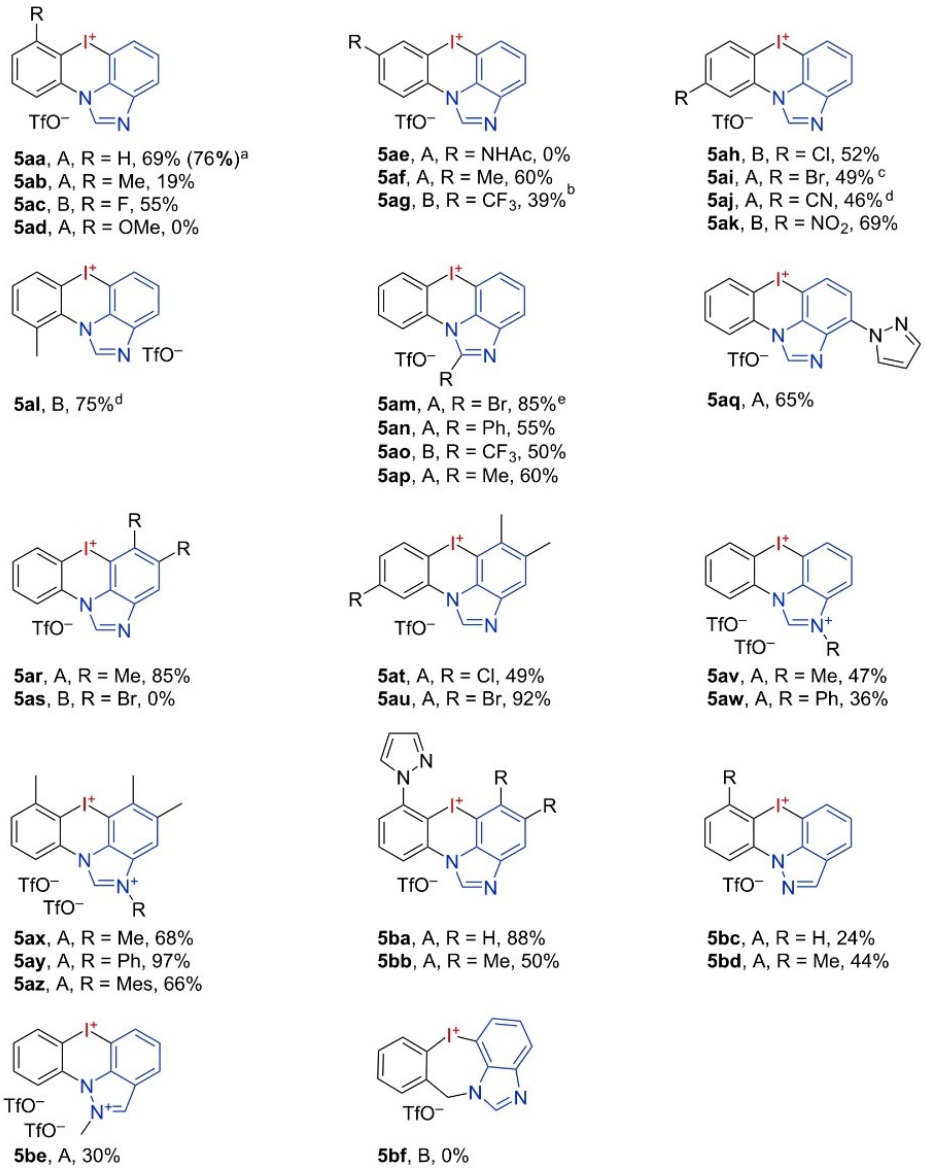


Figure 2: Synthesis of a set of azoiodazinium salts **5**. Method A: Iodoarene **4** (200 µmol) and *m*CPBA (1.1 equiv) were dissolved/suspended in DCM (1 mL), TfOH (2.5 equiv) was added, and the reaction mixture was stirred for 72 h at 40 °C. Method B: Iodoarene **4** (200 µmol) and *m*CPBA (1.3 equiv) were dissolved/suspended in DCM (1 mL), TfOH (5.0 equiv) was added, and the reaction mixture was stirred for 14 d at 65 °C. [a]6.00 mmol scale, T = 50 °C, [b]T = 40 °C, [c]T = 80 °C, t = 6 d, [d]t = 7 d, [e]0.3 equiv of DCM were included in the product.

salt **5al** was obtained in 75% yield using modified reaction conditions B. The harsher conditions were probably required due to a sterically hindered rotation of the benzimidazole moiety in the plane of the iodophenyl, which could also be observed in two rotamers of the starting iodoarene **4al** (see Supporting Information File 1).

Next, we investigated substrates **4** having various substituents in the benzimidazole motif. Starting from 2-bromo-derivative **4am**, the moisture-sensitive, brominated salt **5am** was obtained in an excellent yield of 85%. Also, the C2-alkyl- and phenyl-substituted benzimidazoles gave the expected products **5an–ap** in 50–60% yield. The pyrazole-substituted salt **5aq** was ob-

tained with 65% yield. Using an electron-rich 5,6-dimethylbenzimidazole substrate yielded dimethylated product **5ar** in 85% yield. Unfortunately, even under harsher reaction conditions, the corresponding electron-deficient dibrominated salt **5as** could not be obtained. This further demonstrated the crucial influence of the electronic properties on the reactivity of those substrates. Especially, electron deficiency is particularly counterproductive for the final cyclization step. To prove the influence of the electron-rich dimethylated benzimidazole, this moiety combined with the chlorinated and brominated iodoarene gave the corresponding salts **5at** and **5au** in good yields under milder reaction conditions, in particular in direct comparison to the unsubstituted analogs **5ah–aj**. *N*-Substituted iodoarenes were then used to create dicationic iodonium salts. The *N*-Me and *N*-Ph-iodonium-benzimidazolium salts **5av** and **5aw** were obtained in 47% and 36% yield, respectively. The introduction of additional *ortho*-methyl groups resulted in the formation of the σ-hole-protected *N*-substituted salts **5ax–az** in up to 97% yield. Next, the iodonium center was stabilized through an additional *N*-coordination via *ortho*-pyrazole substitution, giving the iodonium salts **5ba** and **5bb** in 88% and 50% yield. When replacing imidazoles by indazoles the oxidation was not as efficient giving the products **5bc** and **5bd** with only 24% and 44% yields. In the latter case, the initially generated hydroxy-iodonium salt is stabilized via the indazole nitrogen [26] and the steric hindrance by the methyl group is likely destabilizing this intermediate by an out-of-plane distortion [28,34] and hence accelerating the cyclization. The dicationic indazole salt **5bc** was isolated in 30% yield and the benzyl-bridged, seven-membered salt **5bf** could not be obtained under our optimized reaction conditions.

Single crystal structures of selected salts were obtained to gain a better understanding of the bonding situation and the coordination states in these novel azoiodazinium salts (Figure 3). An N4–I1 distance of 2.540 Å with a typical T-shape structure (N4–I1–C1 angle 185.74°) implies a significant interaction between the *N*-heterocycle and the iodine atom for the *ortho*-pyrazole-substituted derivative **5bb** [35]. However, the presence of an *ortho*-methyl group significantly disturbs the triflate coordination to the other iodine σ-hole, which results in a C15–I1–O5 angle of 145.50°. In contrast to other six-membered iodonium salts, this molecule is nearly in plane with an I1–C1–C15–N4 dihedral angle of 2.03° [30,32]. For the dicationic salt **5av**, we observed a coordination of the triflates along the C–I axis with distances of 2.705 Å (I1–O1) and 2.898 Å (I1–O5). For the *ortho*-methyl-substituted analogue **5ax**, no halogen bonding to the triflates was observed, indicating an effective steric protection of the σ-holes [36]. Instead, there were only two weak interactions with one of the triflates (I1–O3: 3.354 Å, I1–O5, 3.078 Å).

We finally investigated the further reactivity of the synthesized azoiodazinium salts to elaborate their potential as synthetic building blocks (Scheme 1). Treatment of **5aa** with Ac_2O led to a non-selective ring opening at both C–I bonds giving the iodi-

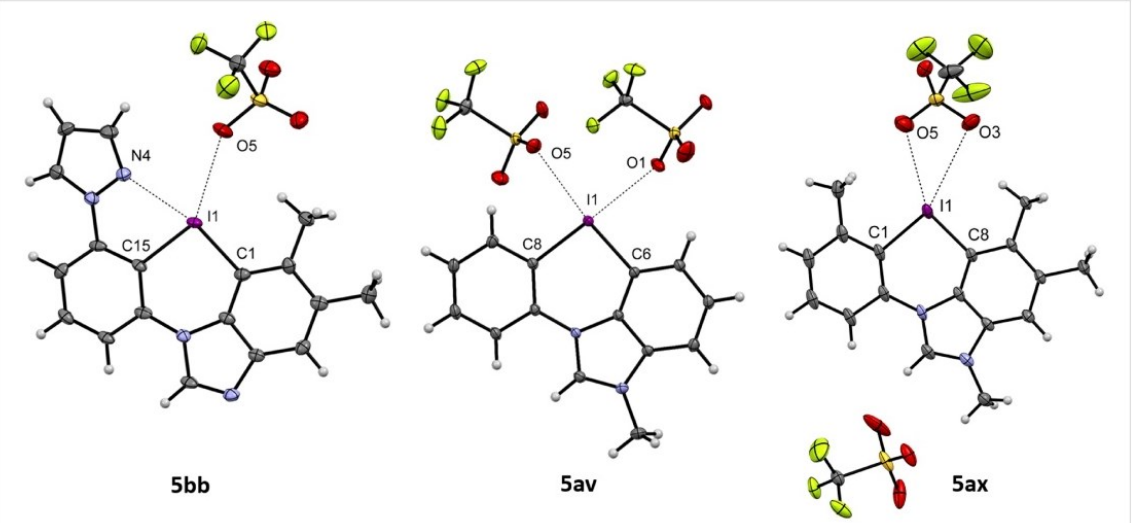
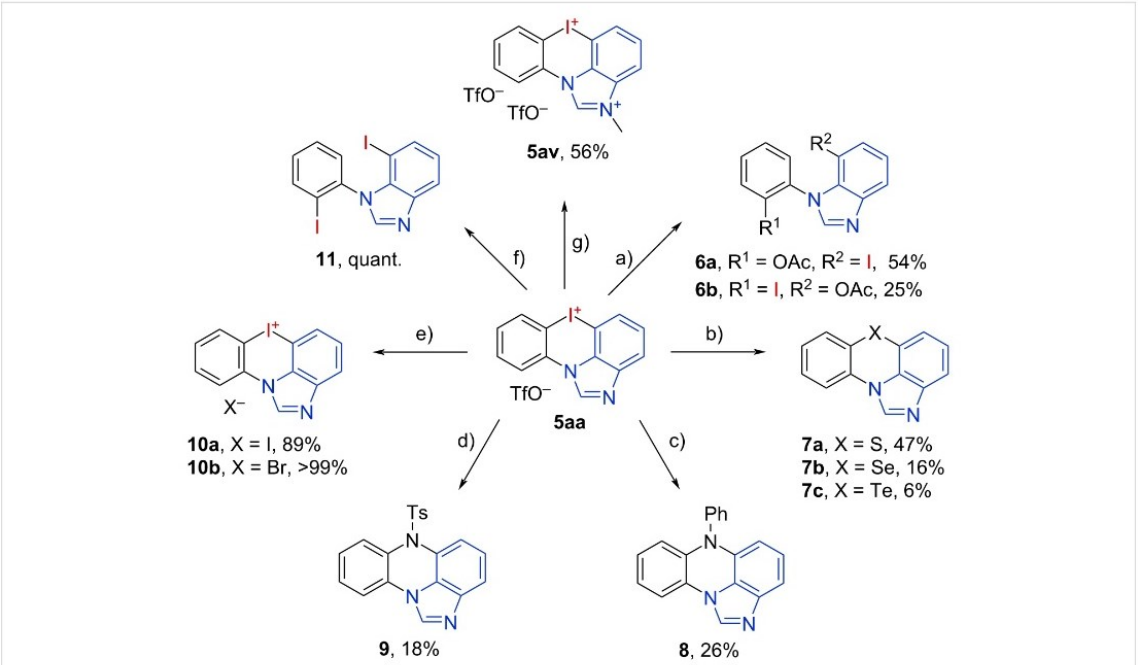


Figure 3: Single crystal structures (ORTEP drawing with 50% probability) of the pyrazole-coordinated salt **5bb** (dimer, a second structure was omitted for clarity. For full structure, see Supporting Information File 1; CCDC 2216124) and the two *N*-methylated, dicationic salts **5av** (CCDC 2216134) and **5ax** (CCDC 2216127). Selected bond lengths and angles: For **5bb**: N4–I1: 2.540 Å, I1–O5: 2.905 Å, N4–I1–C1: 185.74°, C15–I1–O5: 145.50°; for **5av**: I1–O1: 2.705 Å, I1–O5: 2.898 Å, C8–I1–O1: 173.80°, C6–I1–O5: 167.75°, C6–I1–C8: 94.05°; for **5ax**: I1–O3: 3.354 Å, I1–O5, 3.078 Å, C1–I1–O3: 154.71°, C8–I1–O5: 148.91°, C1–I1–C8: 94.53°.



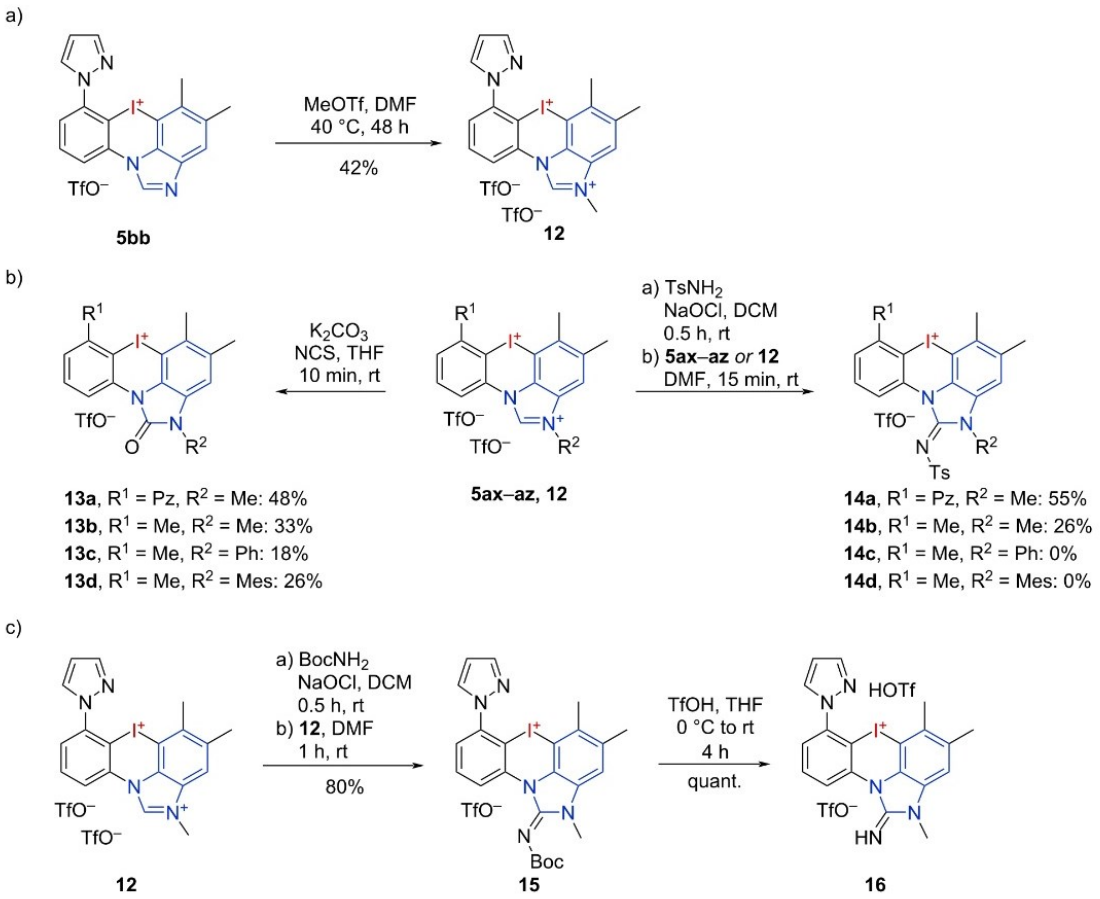
Scheme 1: Derivatizations of the iodonium salt **5aa**. a) Ac_2O, $CuSO_4·5H_2O$, NaOAc, AcOH, 120 °C, 5 h; b) S_8/Se/Te, Cs_2CO_3, DMSO, rt–100 °C, 2.5–24 h; c) I: $PhNH_2$, $Cu(OAc)_2·H_2O$, Na_2CO_3, iPrOH, 40 °C, 17 h, II: CuI, Cs_2CO_3, DMF, 120 °C, 40 h; d) $TsNH_2$, $(CH_2OH)_2$, iPrOH, Na_2CO_3, 100 °C, 24 h, e) KX, H_2O, EtOH, reflux; f) CuI, DMEDA, 1,4-dioxane, TBAI, rt, 24 h; g) MeOTf, DMF, 40 °C, 24 h.

nated *N*-arylbenzimidazoles **6a** and **6b** as a mixture with 54% and 25% yield [37]. A ring opening/closing cascade reaction with elemental sulfur resulted in the formation of the imidazo[4,5,1-*kl*]phenothiazine (**7a**) in 47% yield.

The corresponding phenoselenazine **7b** and the phenotellurazine **7c** were isolated in lower yields of 16% and 6%, likely due to undesired oxidations of selenium and tellurium [38]. Substitutions with nitrogen nucleophiles were performed, giving the *N*-phenylphenazine **8** in 26% yield [39,40] and the *N*-tosyl derivative **9** in 18% yield [41]. Anion exchange reactions to iodide and bromide were performed giving the salts **10a** and **10b** in excellent yields [27]. A copper-catalyzed iodination gave the diiodinated product **11** in quantitative yield [42]. Finally, *N*-methylation of **5aa** was performed, to yield the dicationic salt **5av** in 56% yield without decomposition of the iodonium center [43]. In this reaction, however, no complete conversion could be achieved, even by adding excess MeOTf.

Inspired by the latter results, we were interested to investigate other post-oxidation functionalizations on the benzimidazole ring while keeping the highly reactive hypervalent iodine center intact. Treatment of the *ortho*-pyrazole-substituted salt **5bb** with MeOTf resulted in a selective benzimidazole *N*-methylation. A reaction on the pyrazole nitrogen is impeded due to its coordination with the iodane's σ-hole (Scheme 2a). Besides nitrogen-substitution, the benzimidazole C-2 position of the dicationic salts is a reactive site for oxidative transformations [44,45]. The reaction of the iodine-protected benzimidazolium salts **5ax–az** and **12** with different oxygen sources revealed K_2CO_3 and NCS as the optimal system to form the benzimidazole-2-ones **13a–d** in 18–48% yield, with the best result obtained when using the stabilized salt **12** (Scheme 2b) [44]. Here, no counter-ion exchange to chloride was observed. The favored counter ion is determined by the pK_a value of the corresponding acids but not by halogen bonding due to the steric hindrance at the iodines' σ-holes. The reaction of $TsNH_2$ in combination with NaOCl as an oxidant was investigated next. Under these conditions, the *N*-Me salts **5ax** and **12** gave the desired products **14a** and **14b** in 55% and 26% yield, respectively. The corresponding *N*-Ph- and *N*-Mes-derivatives **5ay** and **5az** failed to give products **14c** and **14d** and only underwent undesired ring openings.

Treating **12** with $BocNH_2$ resulted in the formation of protected guanidine **15** in 80% yield (Scheme 2c), which would not be possible to obtain via an oxidative cyclization of the corresponding iodine(I) species due to a carbamate cleavage with acid. The other dicationic salts underwent ring openings in this reaction. This reactivity demonstrates the highly stabilizing effect of *N*-heterocycles on hypervalent iodine species. Further-



Scheme 2: Post-functionalization of mono- and dicationic iodonium salts under preservation of the hypervalent iodine center.

more, the formed 2-aminobenzimidazoles reveal new access to potential bioactive compounds [46,47]. Even the formation of the free guanidine **16** via cleavage of the Boc-group was possible in quantitative yield.

Conclusion

In this work, we prepared azoiodaziniums as a new class of six-membered heterocyclic iodonium salts with a wide range of substituents. Derivatizations of the reactive iodonium center allow for the formation of new heterocyclic compounds based on azol-based iodazinium as reactive intermediates. Most interestingly, functionalization of the heteroarene salts was achieved without an undesired attack of the delicate C–I bond at the hypervalent iodine center.

Experimental

General procedure for the synthesis of azoiodazinium salts (method A): To a stirred solution of the corresponding (2-iodophenyl)-1*H*-benzo[*d*]imidazole or -indazole (200 µmol, 1.0 equiv) and *m*CPBA (85%, 44.8 mg, 220 µmol, 1.1 equiv) in DCM (1 mL) was added TfOH (44.2 µL, 500 µmol, 2.5 equiv) and the resulting solution was stirred for 72 h at 40 °C. The solvent was removed under reduced pressure. The residue was suspended in Et_2O (1 mL) or another solvent if necessary, stored at 4 °C for 30 min, filtered, washed with Et_2O (3 × 1 mL) and dried in vacuo.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data and copies of spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-19-27-S1.pdf]

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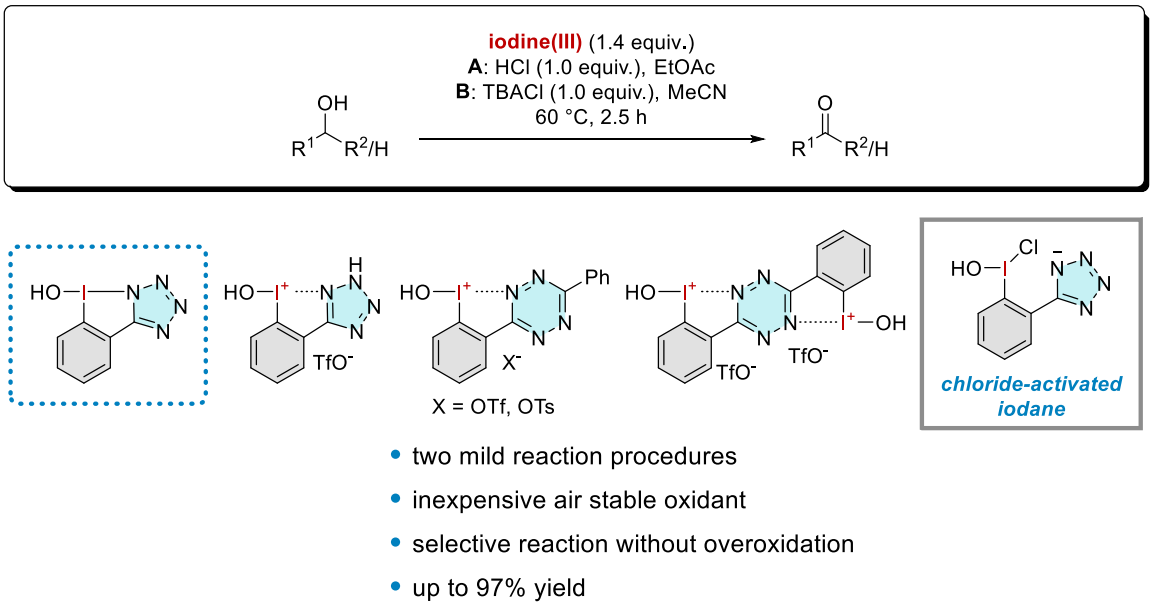
4 Summary

4.1 Oxidation of benzylic alcohols to carbonyls using *N*-heterocyclic stabilized λ^3-iodanes

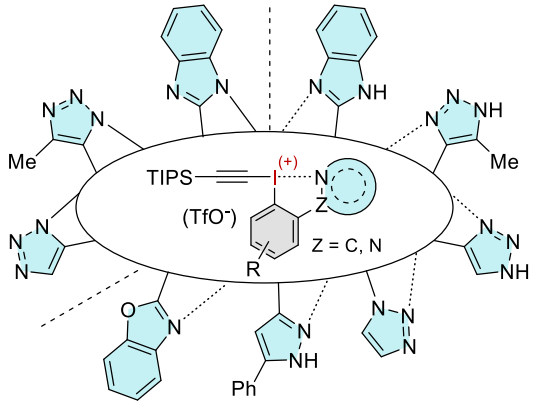
Previous studies investigated *N*-heterocycle-stabilized iodanes (NHIs) in simple oxidative test reactions. To further develop their applications, the goal of this project was to introduce NHIs in the selective oxidation of alcohols to aldehydes and ketones, while preventing an overoxidation to carboxylic acids. Novel NHIs, with tetrazoles and tetrazines as stabilizing *N*-heterocycles, were synthesized and systematically investigated in the oxidation of alcohols. After extensive optimization, two methods for either electron-rich or electron-poor alcohols were developed and allow for the selective transformation to the corresponding carbonyls in up to 97% yield. Systematic investigations *via* NMR spectroscopy and mass spectrometry revealed insight that chloride-activated species were part of a plausible reaction mechanism.



- two mild reaction procedures
- inexpensive air stable oxidant
- selective reaction without overoxidation
- up to 97% yield

4.2 Stabilization of Ethynyl-Substituted Aryl-λ^3-Iodanes by Tethered *N*-Heterocycles

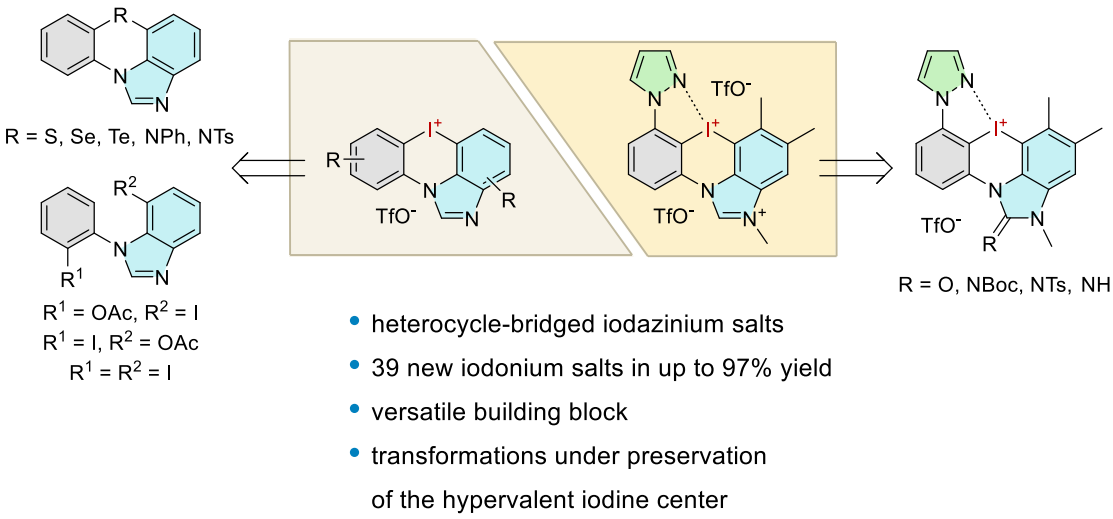
In a subsequent project, NHIs were established as electrophilic group transfer reagents. As a synthetically useful and versatile electrophilic building block, alkynyl groups were chosen and a systematic investigation of these ethynyl-NHIs (ENHIs) was performed. In a straightforward one-pot synthesis, these novel reagents were obtained in up to 76% yield bearing a variety of *N*-heteroarenes and substituents on the arene. The ENHIs could be isolated as pseudocyclic iodonium triflates as well as cyclic iodanes. Single crystal X-ray measurements showed strong I-N-coordination and therefore a crucial influence of the *N*-heterocycle on the hypervalent iodine center, which revealed a way to fine-tune their reactivity. This reactivity as electrophilic alkyne group transfer reagents was then demonstrated in well-established and novel inter- and intramolecular group transfer reactions, revealing a comparable reactivity to common iodane-based alkynylation reagents such as TIPS-EBX.



- 24 new iodanes in up to 76% yield
- robust one-pot synthesis
- pseudocyclic and cyclic ENHIs
- up to quantitative alkynylation of nucleophiles
- intramolecular transformations

4.3 Synthesis and reactivity of azole-based iodazinium salts

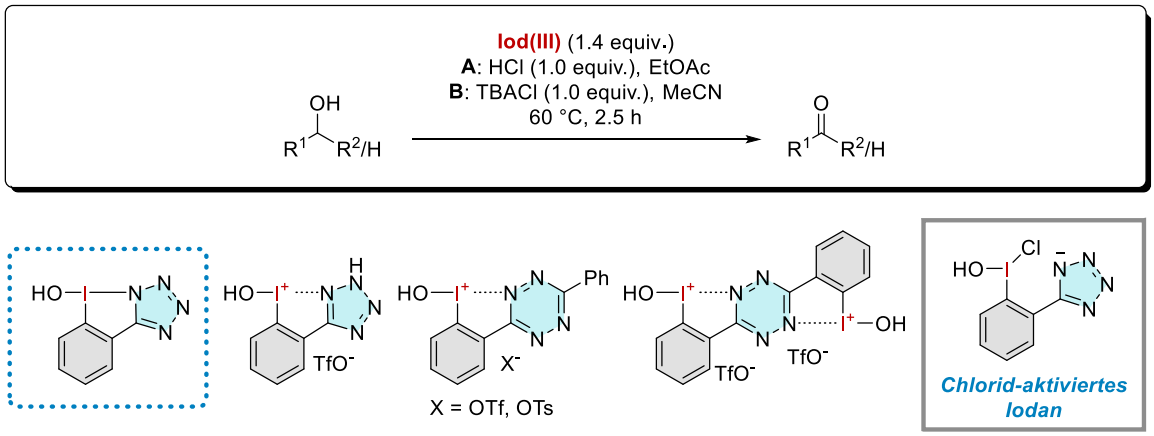
While most six-membered diaryliodonium salts are bridged by single carbon- or heteroatoms, in this work azoiodazinium salts were presented as a new class of six-membered iodonium salts. The salts were obtained in their mono- and dicationic forms with a wide range of substituents in up to 97% yield. Additionally, structural information obtained through X-ray analysis revealed a strong halogen bond of the hypervalent iodine to an *ortho*-pyrazole substituent. Derivatizations of the reactive iodonium center allow for the formation of new heterocyclic compounds and therefore demonstrate their application as versatile synthetic building blocks. Additionally, outstanding post-functionalizations with a rigidified iodonium center were possible, leaving the delicate hypervalent C-I bonds intact.



5 Zusammenfassung

5.1 Oxidation von benzylischen Alkoholen zu Carbonylen mittels *N*-Heterozyklus stabilisierten- λ^3-Iodanen

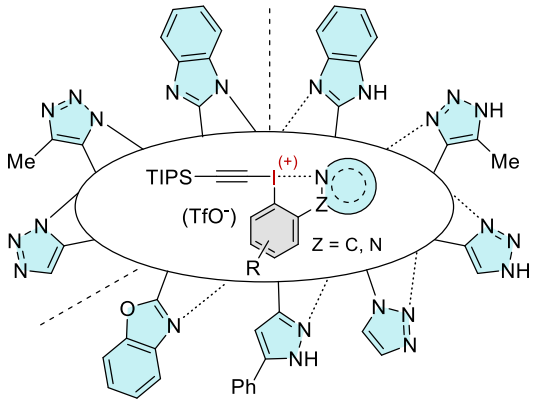
In früheren Studien wurden *N*-Heterozyklus-stabilisierte Iodane (NHIs) in einfachen oxidativen Testreaktionen untersucht. Um dieses Gebiet weiterzuentwickeln, bestand das Ziel dieses Projekts darin, NHIs in die selektive Oxidation von Alkoholen zu Aldehyden und Ketonen unter Verhinderung einer Überoxidation zu Carbonsäuren einzuführen. Neue NHIs mit Tetrazolen und Tetrazinen als stabilisierenden *N*-Heterozyklen wurden synthetisiert und systematisch in der Oxidation von Alkoholen untersucht. Nach umfangreichen Optimierungen wurden zwei Methoden, entweder für elektronenreiche oder elektronenarme Alkohole, entwickelt und erlaubten die selektive Transformation zu den entsprechenden Carbonylen in bis zu 97% Ausbeute. Systematische Untersuchungen mittels NMR Spektroskopie und Massenspektrometrie enthüllten Einblicke in eine Chlorid-aktivierte Spezies als Teil eines plausiblen Reaktionsmechanismus.



- zwei milde Reaktionsvorschriften
- günstiges, luftstabiles Oxidanz
- selektive Reaktion ohne Überoxidation
- bis zu 97% Ausbeute

5.2 Stabilisierung von Ethinyl-Substituierten Aryl-λ^3-Iodanen durch Angebundene *N*-Heterozyklen

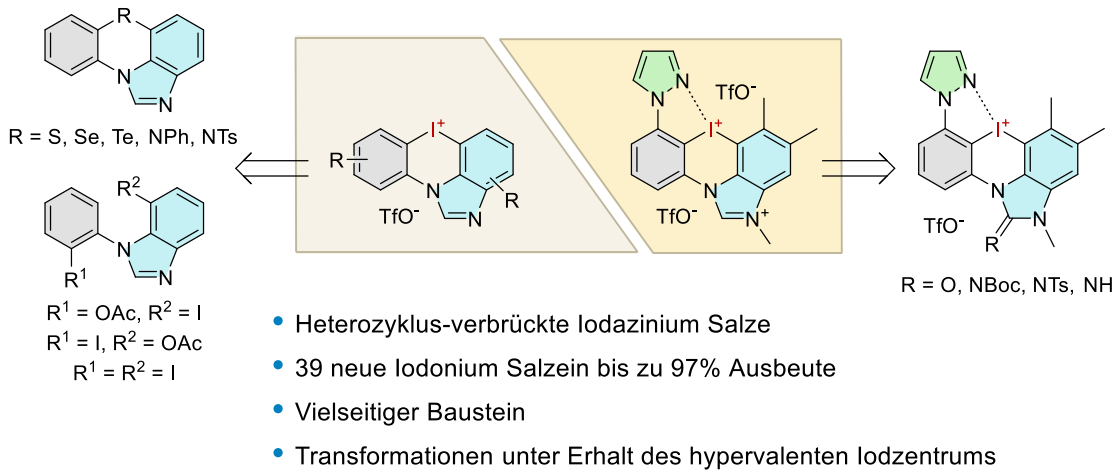
In einem Folgeprojekt wurden NHIs als elektrophile Gruppentransferreagenzien etabliert. Als synthetisch nützliche und vielseitige elektrophile Bausteine wurden Alkinylgruppen ausgewählt und eine systematische Untersuchung dieser Ethinyl-NHIs (ENHIs) durchgeführt. In einer simplen Eintopfsynthese wurden diese neuartigen Reagenzien mit einer Vielzahl von *N*-Heteroaromaten und Substituenten am Aren in bis zu 76% Ausbeute erhalten. Die ENHIs konnten als pseudozyklische Iodoniumtriflate sowie als zyklische Iodane isoliert werden. Einkristall-Röntgenmessungen zeigten eine starke I-N-Koordination und damit einen entscheidenden Einfluss des *N*-Heterozyklus auf das hypervalente Iodzentrum, was eine Möglichkeit zur Feinabstimmung ihrer Reaktivität aufzeigte. Diese Reaktivität als elektrophile Alkin-Gruppenübertragungsreagenzien wurde anschließend in etablierten und neuartigen inter- und intramolekularen Gruppenübertragungsreaktionen demonstriert, welche eine vergleichbare Reaktivität mit herkömmlichen Alkinylierungsreagenzien auf Iodanbasis wie TIPS-EBX aufwies.



- 24 neue Iodane in bis zu 76% Ausbeute
- robuste Eintopftsynthesen
- pseudozyklische und zyklische ENHIs
- teilweise quantitative Alkinylierung von Nukleophilen
- intramolekulare Transformationen

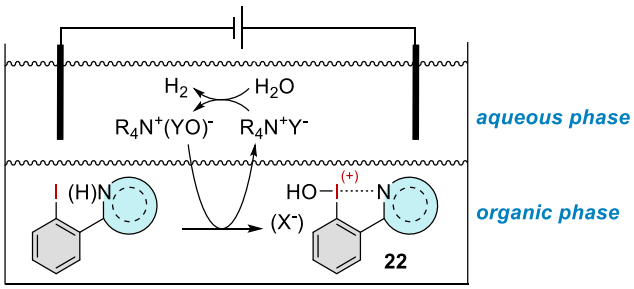
5.3 Synthese und Reaktivität von Azol-basierten Iodaziniumsalzen

Während die meisten sechsgliedrigen Diaryliodoniumsalze durch einzelne Kohlenstoff- oder Heteroatome verbrückt sind, wurden in dieser Arbeit Azoiodaziniumsalze als neue Klasse sechsgliedriger Iodoniumsalze vorgestellt. Die Salze wurden in ihren mono- und dikationischen Formen mit einer weiten Bandbreite an Substituenten in bis zu 97% Ausbeute erhalten. Darüber hinaus konnte durch Röntgen-Einkristallanalyse eine starke Halogenbindung des hypervalenten Iods zu einem *ortho*-Pyrazol-Substituenten aufzeigt werden. Derivatisierungen des reaktiven Iodoniumzentrums ermöglichen die Bildung neuer heterozyklischer Verbindungen und haben daher die Anwendung als vielseitige Synthesebausteine demonstriert. Zudem war eine hervorragende Nachfunktionalisierung der starren Iodoniumverbindungen möglich, wobei die empfindlichen C-I-Bindungen des hypervalenten Iodzentrums intakt blieben.



6 Outlook

Despite NHIs being successfully applied in several fields of hypervalent iodine chemistry their potential is far from being exhausted. As the synthesis of NHIs requires (super)stochiometric amounts of chemical oxidants, the development of electrochemical methods represents an economic alternative. However, initial investigations revealed undesired oxidation reaction on most heterocycles.[127] An elegant solution is the use of a mediator which avoids direct contact between the substrate and electrodes. *Vasudevan* and co-workers and *Raja* and co-workers used an electrochemical Cl^-/OCl^-[128] or $NO_3^-/NO_3^{\cdot}$[129] redox couple in a $H_2O/CHCl_3$ biphasic media for the selective oxidation of alcohols to carbonyls. Adapting this method to NHIs might be a promising attempt for their electrochemical synthesis (Scheme 20).



Scheme 20: Potential reaction set-up for the redox couple mediated electrochemical generation of NHIs.

Besides this, a wider variety of substituents would be interesting, as NHIs were proven to be versatile electrophilic group transfer reagents in the case of ethynyl-groups. In particular, the amine **84d** is a highly interesting electrophilic N1-precursor (Figure 7). Other carbon-based substituents such as the CF_3-derivate **84f** or the iodonium ylide **84h** are also not known so far.

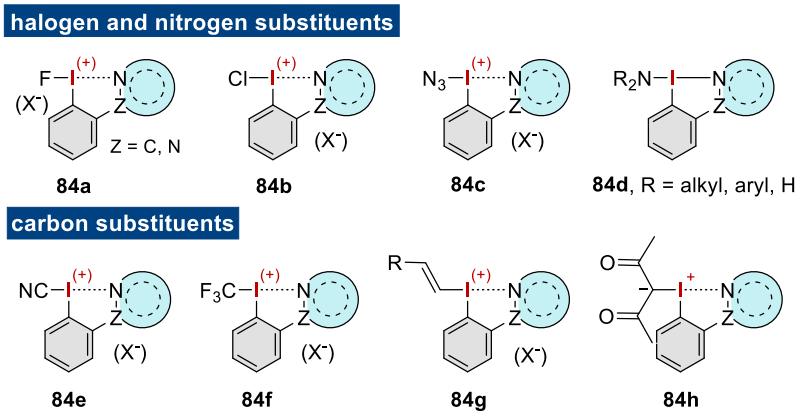


Figure 7: Introducing new substituents to NHIs, to expand their application as group transfer reagents.

7 Literature

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