Pseudocyclic Bis-*N*-Heterocycle-stabilized Iodanes – Synthesis, Characterization and Applications

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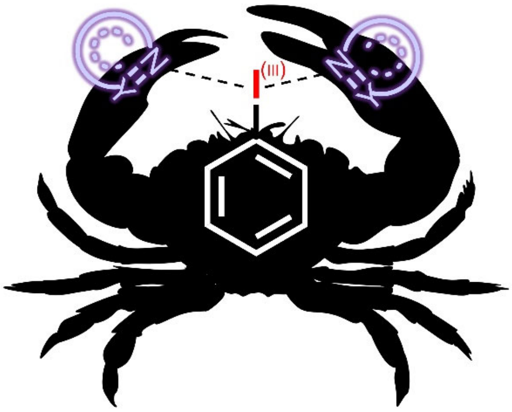

Bis-*N*-heterocycle-stabilized λ^3-iodanes (BNHIs) based on azoles are introduced as novel structural motifs in hypervalent iodine chemistry. A performance test in a variety of benchmark reactions including sulfoxidations and phenol dearomatizations revealed a bis-*N*-bound pyrazole substituted BNHI as the most reactive derivative. Its solid-state structure was characterized via X-ray analysis implying strong intramolecular interactions between the pyrazole nitrogen atoms and the hypervalent iodine centre.

Over the last three decades, hypervalent iodine compounds have received increasing interest and their chemistry witnessed an unprecedented growth. By now, they have been established as easy to handle, readily available, diverse, and environmentally benign reagents for a plethora of oxidative transformations.[1–9]

Despite a convenient reactivity as mild oxidants, the most puristic examples (iodoso- and iodylbenzene) suffer from unfavourable features such as poor solubility and thermal lability. Therefore, strategies to overcome these drawbacks came into focus recently. Due to the electrophilic nature of the hypervalent iodine centre, heteroatoms in its vicinity should alter the structure, reactivity, and selectivity of these reagents through beneficial non-covalent intramolecular interactions.[10,11] Historically, the so formed pseudocyclic compounds included oxygen-containing stabilizing units, such as sulfonyl-groups, carboxylic acids, ethers or carbonyls.[12–20] *N*-heterocycles as stabilizing functional groups have been widely neglected, despite their high synthetic versatility. Recent years showed growing interest in the investigation of λ^3-iodanes containing heterocycles, not only as free ligands, as in the bispyridinium derivatives,[21–23] but even more important as an intramolecular anchored stabilizing moiety.[24–29] The first confirmation about a direct intramolecular N-I interaction in hydroxy-λ^3-iodanes was presented in 2017 by Muñiz and co-workers for a 2-pyridinyl-substituted reagent which showed an improved reactivity in the catalytic diacetoxylation of alkenes.[30] Our group systematically investigates related *N*-heterocycle-stabilized iodanes (**NHIs**, Figure 1) based on azoles.[31–34]

Although 2,6-bis-heterocyclic systems are long known as pincer-ligands (so-called phebox) in transition metal complexes,[35,36] their effective transfer to the chemistry of hypervalent iodine has not been described so far. Only in one initial investigation by Legault and co-workers a 2,6-bisoxazoline-substituted iodoarene was tested as a catalyst in the α-oxytosylation of ketones but was found to be inefficient.[27]

Herein, we want to present the first systematic investigations of bis-*N*-heterocycle-stabilized iodanes (**BNHIs**) by describing their synthesis, characterization and finally their application as highly potent oxidants.

Starting with the preparation of the corresponding iodoarenes, two different strategies divided into *N*- and *C*-bound derivatives were chosen. First, 2,6-difluoronitrobenzene (**1**), which is either commercially available or easily prepared on a decagram-scale (see ESI), was reacted with pyrazole or 1,2,4-triazole via S$_N$Ar to **2** and **3**. A subsequent Sandmeyer-sequence gave the bis-pyrazole **4** (X=CH) and the bis 1,2,4-triazole **5** (X=N) in 77% and 40% yield over three steps on a multigram scale, without the need for column chromatography (Scheme 1, a). *C*-bound derivatives were obtained starting from 2-iodoisophthalonitrile (**6**) which was transformed into the corresponding aldehyde **7** via an iodination- and reduction

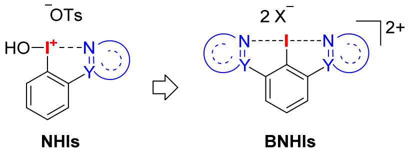

Figure 1 General structures of mono- and bis-*N*-heterocycle-stabilized λ^3-iodanes.

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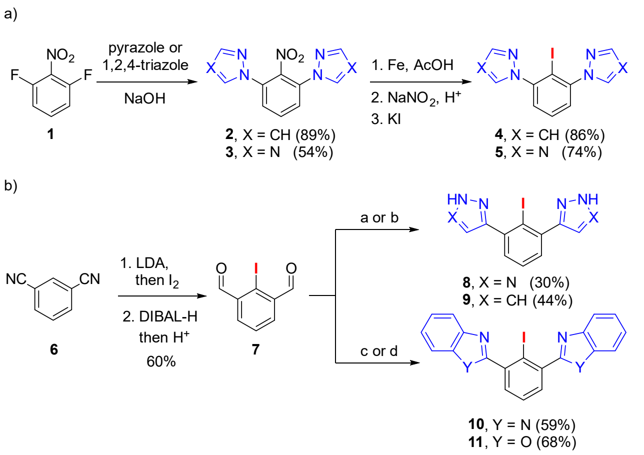
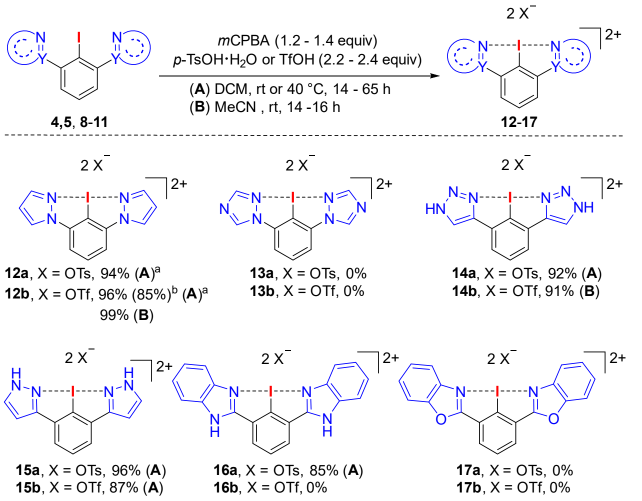


Scheme 1 Synthesis of heterocyclic bis-*N*-bound (a) and *C*-bound (b) iodoarenes. a: 1. $MeNO_2$, NaOH, then H^+, 2. NaN_3, *p*-TsOH; b: 1. $TsNHNH_2$, 2. NaOEt, then TMS-acetylene, then TBAF; c: *o*-phenylenediamine, then NaOH, I_2; d: 2-aminophenol, then DDQ.



Scheme 2 Oxidation of bis-*N*-heterocycle-substituted iodoarenes into iodanes **12-17**. [a]at 40 °C. [b]after recrystallization from MeOH/Et_2O, 8.0 mmol scale.

sequence in 60% overall yield. A final two-step sequence gave bis-*NH*-triazole **8** and bis-*NH*-pyrazole **9** in 30-44% yield. Benzimidazole **10** and benzoxazole **11** were obtained in 59% and 68% yield, in one step (Scheme 1, b).

With these six structurally diverse iodoarenes in hand the oxidation to the corresponding hypervalent iodine compounds was investigated using *meta*-chloroperbenzoic acid as the oxidant in the presence of *p*-toluenesulfonic acid or triflic acid (Scheme 2). Bis-Pyr-I-OTs **12a** was obtained using DCM as the solvent in 94% (2.0 mmol scale). Under similar conditions Bis-Pyr-I-OTf **12b** was synthesized in 96% yield (85% after recrystallization from MeOH/Et_2O) on a multigram-scale. For this compound, a solvent exchange for MeCN proved to be highly beneficial, cutting the reaction time to only 16 h at rt and giving **12b** in near quantitative yield. In contrast, bis-1,2,4-triazole **5** could either not be oxidized – even under harsh conditions (65 h at 75 °C) – or not be isolated in its oxidized form **13**. In contrast, *C*-bound 1,2,3-triazole **8**, was oxidized smoothly giving bis-NH-Tria-I-OTs **14a** and bis-NH-Tria-I-OTf **14b** in 92% and 91% yield, respectively, after 14 h. Bis-NH-Pyr-I-OTs **15a** and Bis-NH-Pyr-I-OTf **15b** were obtained in 87-96% - even though after elongated reaction times (24-42 h). Benzimidazole **10** was also suitable for the oxidation employing *p*-toluenesulfonic acid (85% yield of **16a**), but mainly decomposition was observed using triflic acid. The oxidized bis-benzoxazole **17** appeared to be unstable under any tested condition. In contrast, isolated **BNHIs** (**12, 14, 15** and **16**) were throughout shelf-stable for at least several months without any signs of decomposition.

The solid-state structure of the recrystallized Bis-Pyr-I-OTf **12b** was investigated by X-ray crystallography, which confirmed the expected T-shaped pseudo-bicyclic benziodazole structure with two short dative bonds between the iodine atom and the coordinating pyrazole-nitrogens (I1-N1 = 2.2301(12) Å; I1-N3: 2.1944(12) Å) with a N1-I1-N3 bond angle of 150.93(5) ° (Figure 2). In comparison, these coordinative bonds are only slightly longer than the reported covalent bonds in bicyclic benziodoxoles and benziodazoles, while the distorted T-shaped geometry appears to be the most bent among bicyclic hypervalent iodine compounds.[37–40] Furthermore, the coordination of one MeOH molecule (2.712 Å) and a weak interaction of the two expected triflate counterions (2.808 Å and 3.206 Å) with the iodine atom were observed.

Finally, we investigated the reactivity of these hypervalent iodine compounds. As a model reaction the oxidation of thioanisole (**18**) to sulfoxide **19** was chosen (Figure 3). In MeOH/H_2O (conditions **A**) Bis-Pyr-I-OTs **12a** showed remarkably high reactivity with a full conversion of **18** almost instantly (>30 sec, 95%) at 0 °C, but was inefficient in MeCN (conditions **B**). In comparison, the triflate salt **12b** showed an outstanding performance giving **19** instantly (<30 sec) in near quantitative

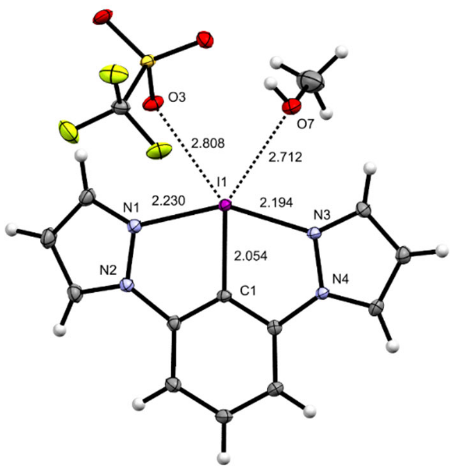


Figure 2 Crystal structure (ORTEP drawing) of **12b** (CCDC 2086526) with coordination of MeOH. Second triflate counterion omitted for clarity (see ESI). Thermal ellipsoids displayed with 50% probability. Selected bond length: I1-C1: 2.0533 (13) Å; I1-N1: 2.2301(12) Å; I1-N3: 2.1944(12) Å; I1-O3: 2.808 Å, I1-O7: 2.712 Å, I1-O6: 3.206 Å (second triflate). Selected bond angles: N1-I1-N3: 150.93(4)°; C1-I1-N1: 75.05(5)°; C1-I1-N3: 75.89(5)°.

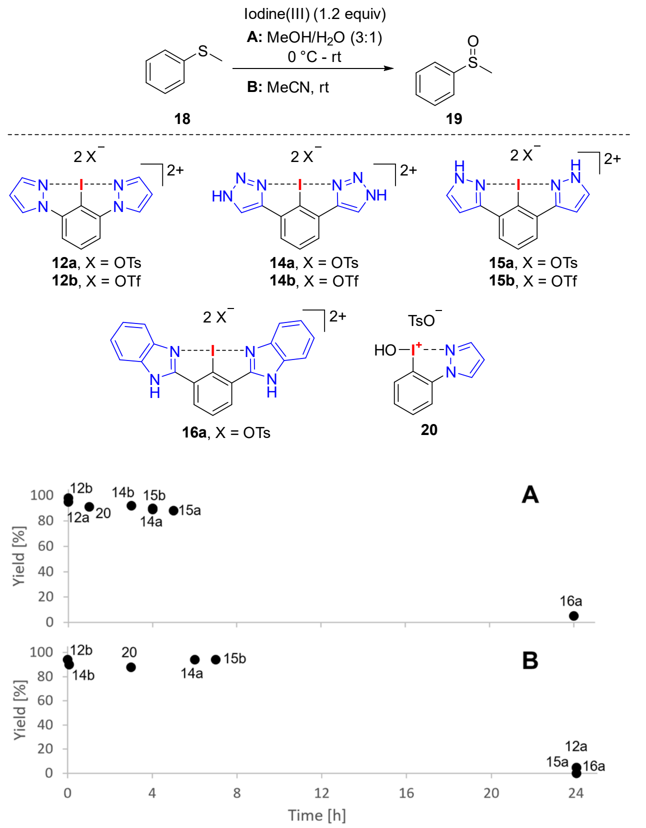
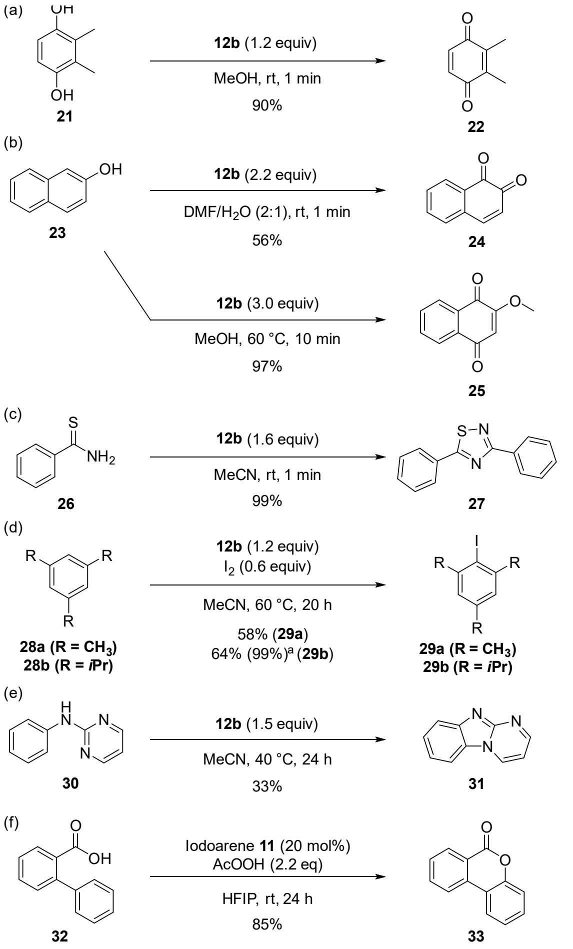


Figure 3 Oxidation of thioanisole (**18**) to sulfoxide **19** and the yield-vs.-time profile for the investigated iodanes in MeOH/H_2O (**A**) or MeCN (**B**).

yields in both chosen solvent systems. Both triazole-substituted **BNHIs 14a** and **14b** showed a significantly lower reactivity under both conditions (5 min – 6 h, 89-94%). As expected from the previous results for the **NHIs**,[33] bis-NH-pyrazoles **15a** and **15b** were less reactive than the triazole derivatives (4-7 h, 88-94%), with **15a** being inefficient in MeCN. Bis-benzimidazole-substituted **BNHI 16a** proved to be nearly unreactive in both solvents. These results were compared to the previously introduced mono-pyrazole stabilized iodane **20**.[33] In comparison to bis-pyrazole **12a**, **20** showed a much slower conversion in MeOH/H_2O (1 h, 91%), but an enhanced reactivity in MeCN (3 h, 88%). However, in both reaction media **20** was drastically outperformed by the triflate derivative **12b**.

With its high reactivity, **BNHI 12b** appears to be among the most potent pseudocyclic λ^3-iodanes reported so far for this oxidation.[12–14,20,31,33] Due to these promising results, we were eager to investigate the versatility and potency of **12b** in a variety of other oxidative transformations (Scheme 3, a-f). 2,3-Dimethylhydroquinone (**21**) was efficiently oxidized to *p*-chinone **22** in 90% yield in only one minute.[41] Similarly, the reaction of 2-naphthol (**23**) with 2.2 equivalents of Bis-Pyr-I-OTf **12b** gave *o*-dione **24** in 56%.[42] When the same reaction was performed with 3.0 equivalents of **12b** in MeOH under elevated temperature, 2-methoxynaphthalene-1,4-dione **25** was directly obtained in one step from 2-naphthol. This is the first example for this reaction with quantitative results (97%). Furthermore, for the oxidative cyclization of thiobenzamide (**26**) again outstanding reactivity was observed, yielding thiadiazole **27** in 99% after only one minute.[12,14,20,31] In the iodination of arenes (Scheme 3, d), iodomesitylene (**29a**) and 1-iodo-2,4,6-triisopropylbenzene (**29b**) were obtained in 58-64% from the corresponding arenes. However, with increased equivalents of Bis-Pyr-I-OTf **12b** and iodine the triisopropyl derivative **29b** was obtained in quantitative yield.[43,44] In contrast, Bis-Pyr-I-OTf **12b** showed only a moderate performance in the oxidative cyclization of aminopyrimidine **30**, yielding imidazopyrimidine **31** in 33%.[45] As expected, similarly to the report of Legault and co-workers, **12b** was found to be inefficient in the α-functionalization of ketones, most probably due to its highly stabilized and planar structure.[27]



Scheme 2 Further applications of Bis-Pyr-I-OTf **12b** and the catalytic application of bis-benzoxazole 17. [a]1.5 equiv of **12b** and I_2 for 16 h.

In addition, although bis-benzoxazole **11** did not form a stable hypervalent iodine species, it was found to be an efficient catalyst for the lactonization of biphenylcarboxylic acid **32**, giving chromenone **33** in 85% yield (Scheme 3, f).[46]

In conclusion, we synthesized seven pseudocyclic bis-*N*-heterocycle stabilized iodanes (**BNHIs**) and elucidated the solid-state structure of the bis-pyrazole derivative **12b**. The X-ray analysis revealed a highly bent T-shaped structure and strong intramolecular interactions between the iodine and pyrazole-nitrogen atoms (2.2301 Å and 2.1944 Å). Furthermore, **12b** is easily prepared in four steps from commercially available starting materials in 76% overall yield and was found to be the most potent reagent in the oxidation of thioanisole among these novel λ^3-iodanes. Beside the oxidation of sulfides, **12b** was demonstrated to be an efficient reagent in further oxidative transformations, like the oxidation of phenols.

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There are no conflicts to declare.

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