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Indole- and Pyrrole-BX: Bench-Stable Hypervalent Iodine Reagents for Heterocycle Umpolung

Paola Caramenti, Stefano Nicolai and Jerome Waser*

Abstract: The one-step synthesis of the bench-stable hypervalent iodine reagents IndoleBX and PyrroleBX using mild Lewis acid catalyzed conditions is reported. The new reagents are stable up to 150 °C and were applied in the C-H arylation of unactivated arenes using either rhodium or ruthenium catalysts. A broad range of heterocyclic systems of high interest for synthetic and medicinal chemistry was accessed in high yields. The developed C-H functionalization could not be achieved using reported reagents or methods, highlighting the unique reactivity of Indole- and Pyrrole-BX.

Pyrrole and indole heterocycles are omnipresent in natural and synthetic biologically active compounds and have found countless applications in the pharmaceutical and agrochemical industries.[1] Therefore, synthetic chemists have invested unceasing efforts towards their synthesis and functionalization.[2] As indoles and pyrroles are highly nucleophilic, the broad majority of functionalization methods is based on reactions with electrophiles, which limits the structural diversity of compounds in medicinal chemistry studies. In order to allow indoles and pyrroles to react with nucleophiles and discover new chemical space, an *Umpolung* of the innate reactivity of the heterocycles would be highly useful. However, accessing electrophilic indole and pyrrole synthons constitutes a formidable challenge. Most approaches rely on the substitution of the heterocycles with one or several electron-withdrawing groups or on reactive electrophilic indolyl intermediates generated *in situ*.[3] More stable halogenated indoles have been used only in cross-coupling reactions with activated partners.[4] Clearly, the development of better indole and pyrrole electrophilic synthons combining high reactivity with enhanced stability is needed.

In this context, hypervalent iodine reagents are recognized for their high reactivity, which can lead to the formal *Umpolung* of functional groups.[5] The introduction of reactive yet stable aryl iodonium salts (Scheme 1A) has led to the development of broadly applicable arylation reactions.[6] Nevertheless, there are only few reports on indole and pyrrole-based iodonium salts. Pioneering works by Neiland, Kost, Moriarty and co-workers required a multi-step procedure via a potentially explosive betaine intermediate to access NH unprotected indole iodonium salts.[7]

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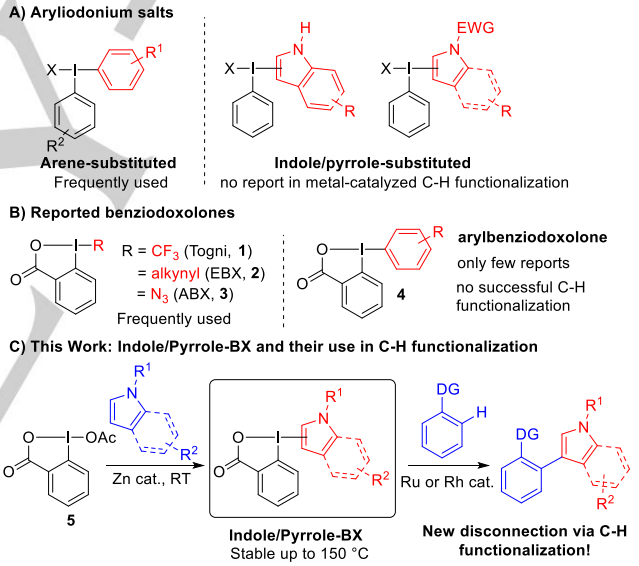
Recently, more stable indole and pyrrole iodonium salts were reported by Moriyama and co-workers[8] and Kita and co-workers[9] respectively, based on the introduction of an electron-withdrawing group on the nitrogen. The electrophilic character of these reagents was used for direct reactions with nucleophiles, such as alkyl lithium reagents,[7c] azides,[10a] amines[10b] and electron-rich arenes.[9] There is only one report on the use of indole iodonium salts involving a transition metal: the copper-catalyzed de-aromatization of indoles reported by You and co-workers.[11] This stands in stark contrast with the hundreds of transformations reported for other aryl iodonium salts,[6] and is probably due to the lower stability of indole and pyrrole iodonium salts in presence of metals and/or at higher temperature.



Scheme 1. Aryliodonium salts, benziodoxolones and Indole/Pyrrole-BX reagents.

The enhanced stability of cyclic hypervalent iodine reagents in particular those obtained from 2-iodobenzoic acid and its derivatives – the benzidoxol(on)es - has been established since several decades (Scheme 1B).[12] The use of reagents such as benziodoxolones **1-3** in group-transfer reactions (trifluoromethylation, alkynylation and azidation) has been investigated only more recently.[13] In the short time since their introduction, they have already had a strong impact in the fields of synthetic and medicinal chemistry. Aryl benziodoxolones **4** have also displayed enhanced stability and are easily accessible, but they have not found broad application in synthesis.[14] Indeed, in most reactions with nucleophiles, the benzoic acid group is transferred, limiting the scope of those transformations.[14c,15] There is no report on indole or pyrrole based benziodoxol(on)e

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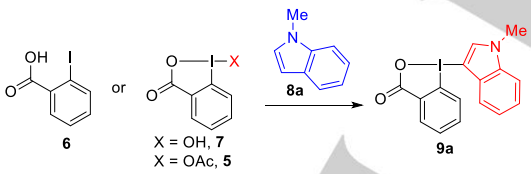
reagents, however, and the strongly acidic or oxidizing methods used for the introduction of other aryl groups cannot be used for these more sensitive heterocycles.

Herein, we report the first synthesis of pyrrole- and indole-based benziodoxolone reagents in one step from the heterocycles, based on a mild zinc-catalyzed direct iodonium transfer from acetoxy benziodoxolone (**5**) (Scheme 1C). The new reagents are air- moisture- and thermally stable. They were applied in the directed *ortho* C-H functionalization of arenes using rhodium and ruthenium catalysts, resulting in bond formations that could not be achieved using reported methods and reagents.

To access the targeted Indole- and Pyrrole-BX reagents, we first applied recently reported methods for aryl benziodoxolone synthesis based on the oxidation of iodobenzoic acid (**6**) followed by reaction with N-methyl indole (**8a**) in presence of triflic or sulfuric acid (Table 1, entries 1-2).[14] However, only decomposition of the indole was observed. To avoid the use of oxidants, iodine(III) precursors were then examined. Starting from hydroxy benziodoxolone **7** with trimethylsilyl triflate (TMSOTf) as activating agent,[16] decomposition was still occurring (entry 3). If a lower amount of TMSOTf was used, no conversion was observed (entry 4). A promising result was obtained with acetoxy benziodoxolone **5** as precursor: the desired indole-BX could be obtained in 16% yield using 20 mol% of TMSOTf (entries 5 and 6).[17] This compound could be purified by silica gel column chromatography and was thermally stable up to 150 °C.[18] No conversion was observed in absence of TMSOTf (entry 7). Better results were obtained with $Zn(OTf)_2$ and $Cu(OTf)_2$ as Lewis acids (entries 8 and 9), giving **9a** in 36% yield. Changing to dichloromethane as solvent with $Zn(OTf)_2$ as catalyst, **9a** was obtained in 97% yield with complete C3 selectivity (entry 10). This synthesis could be easily scaled up to give **9a** in 87% yield on the 10 mmol scale (entry 11).

Table 1. Optimization of the synthesis of Indole-BX **9a**.



Entry	Iodine precursor	Reaction Conditions[a]	Yield[b] (%)
1	**6**	*m*CPBA, TfOH, CH_2Cl_2, then NH_3[14b]	<5[c]
2	**6**	Oxone, H_2SO_4, CH_2Cl_2, then $NaHCO_3$[14c]	<5[c]
3	**7**	1 equiv TMSOTf, CH_3CN, then pyridine	<5[c]
4	**7**	20 mol% TMSOTf, CH_3CN	<5[d]
5	**5**	1 equiv TMSOTf, Et_2O	<5[c]
6	**5**	20 mol% TMSOTf, Et_2O	16
7	**5**	Et_2O	<5[d]
8	**5**	20 mol% $Zn(OTf)_2$, Et_2O	36
9	**5**	20 mol% $Cu(OTf)_2$, Et_2O	36[c]
10	**5**	20 mol% $Zn(OTf)_2$, CH_2Cl_2	97
11	**5**	20 mol% $Zn(OTf)_2$, CH_2Cl_2	87[e]

[a] Reactions were performed on 0.10 mmol scale with 1.1 equiv of iodine precursor. [b] Isolated yield after purification by column chromatography. [c] Decomposition of N-methylindole (**8a**) was observed. [d] No conversion of **7** or **8a**. [e] Reaction performed on 10 mmol scale.

Free NH IndoleBX **9b** could be also synthesized in 78% yield starting from N-silylated indole (Figure 1). The hypervalent structure of this compound was confirmed by X-ray analysis.[18] Different alkyl groups on the nitrogen were well tolerated (**9c-e**). Reagent **9f** bearing a C2-substituted indole was also obtained in good yield, but no conversion was observed with C3-substitution. Arenes bearing ethers (**9g**), halogens (**9h-j**) and a sensitive boronic ester (**9k**) could also be used. Reagent **9l** derived from a less reactive azaindole was still isolated in 30% yield. PyrroleBX **9m-q** were also successfully synthesized. When starting from *N*-silylated pyrrole, a complete C3 regioselectivity was achieved (**9m**). When methyl-and benzyl-pyrrole where used as substrates, mixtures of separable C2:C3 functionalized reagents were obtained. The availability of both isomers in pure form opened the way for the selective synthesis of C2- or C3- functionalized pyrroles by reaction with nucleophiles. The synthesis of new pyrrole and indole electrophilic synthons is especially important, as none of the currently available reagents can be used in C-H functionalization reactions, in contrast to other classes of heterocycles. Nevertheless, the use of other electron-rich aromatic compounds could also be envisaged. Indeed, carbazole-BX **9r**, thiophene-BX **9s** and furan-BX **9t** were also obtained in low to moderate yields without further optimization.

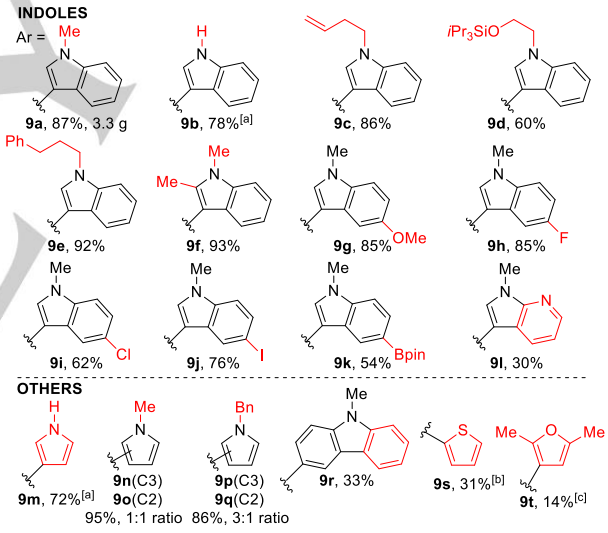


Figure 1. Scope of heteroaromatic benziodoxole reagents. Reaction conditions: 1.00 mmol heterocycle, 1.10 mmol **5**, 0.200 mmol $Zn(OTf)_2$, 0.05 M in DCM, RT, open air. Isolated yields. [a] $Sc(OTf)_3$ was used starting from N-TBS heterocycle [b] $Sc(OTf)_3$ was used. [c] $In(OTf)_3$ was used.

Preliminary investigations showed that the reactivity of indole-BX **9a** differed from the one of both aryliodonium salts and EBX reagents (Scheme 2). The reaction of EBX reagents and aryliodonium salts with thiols, alcohols and stabilized carbon nucleophiles in presence of base is well established,[19] but no reaction occurred with **9a**. In the case of thiol **10**, a moderate yield of thiol indolation product **11** could be obtained in presence of a copper catalyst (Scheme 2A). Palladium-catalyzed C-H bond arylation,[6a,20] was also unsuccessful. In contrast, highly efficient C-H functionalizations could be developed using either rhodium-

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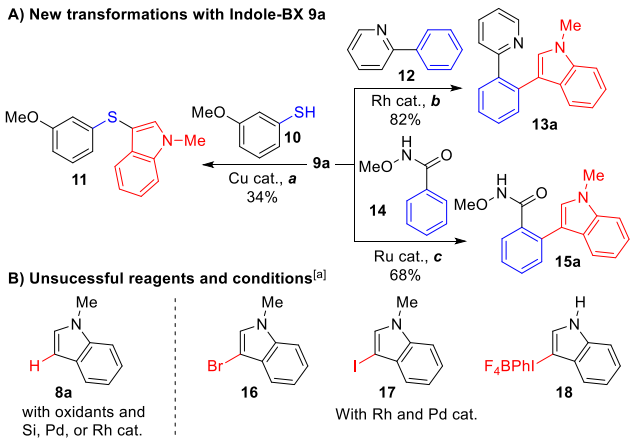
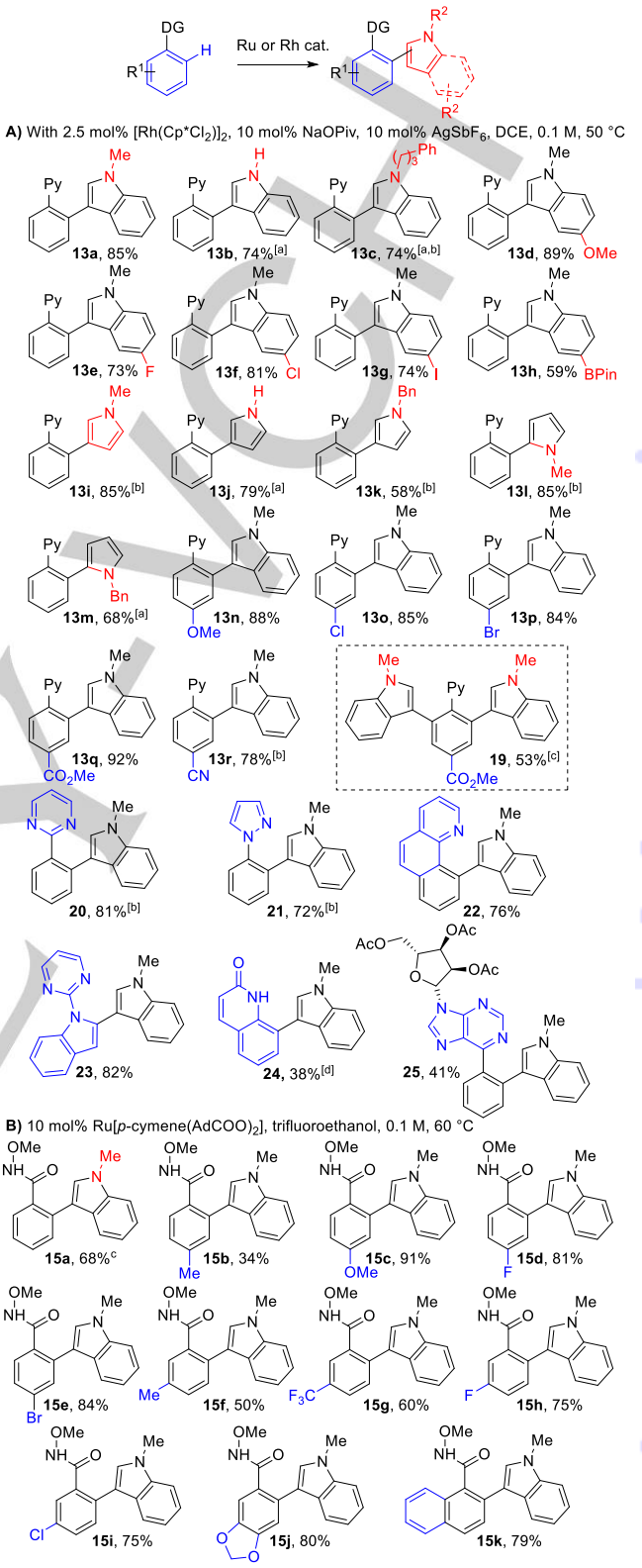
or ruthenium catalysts.[21] Importantly, complete and selective transfer of the indole was obtained to give **13a** and **15a**, with no coupling of benzoic acid.



Scheme 2. Preliminary studies of the reactivity of Indole-BX **9a**. Reaction conditions: a) **10**, 20 mol% CuOTf•C_6H_6, CH_2Cl_2, RT; b) **12**, 2.5 mol% $[Rh(Cp^*Cl_2)]_2$, 10 mol% NaOPiv, 10 mol% $AgSbF_6$, DCE, 0.1 M, 50 °C; c) **14**, 10 mol% Ru[*p*-cymene(AdCOO)$_2$],[22] trifluoroethanol, 0.1 M, 60 °C. [a] See supporting Information for detailed reaction conditions.

The latter results are especially interesting, as the introduction of an indole on a benzene C-H bond in *ortho* position to a pyridine or a benzamide has never been reported. This is surprising, as ortho C-H bond functionalization in arenes is now considered as a mature field.[23] When considering the high importance of indole and pyrrole heterocycles in synthetic and medicinal chemistry, realizing such a transformation would be an important breakthrough in the field. We wondered therefore if established methods for the introduction of indoles onto other types of C-H bonds could be used to access products **13a** and **15a**. However, when reported methods for C-H indolation based on oxidative C-H/C-H couplings[24-26] with indole **8a** or C-H functionalization with electrophilic indoles **16**, **17** and **18**,[18] were examined, compounds **13a** and **15a** could not be obtained (Scheme 2B). Therefore, the discovery of Indole-BX reagents allowed new C-H functionalizations which were not possible before.

The scope of the rhodium-catalyzed C-H functionalization was then examined (Scheme 3A). Indoles **13b** and **13c** bearing either a free NH group or an alkyl chain were obtained in good yield. Ethers, halogens and a sensitive boronic ester were well tolerated on the benzene ring of the indole reagent (**13d-h**). The regioselective synthesis of both C2 and C3 substituted pyrroles was possible (**13i-m**).[27] Methoxy, halogens, esters and cyanides functional groups could be present on the arene substrate (**13n-r**). Diarylation was also possible using an excess of reagent **8a** to give product **19**. Good results were also obtained with other heterocyclic directing groups such as pyrimidine (**20**) or pyrazole (**21**). Benzoquinoline **22** and pyrimidine-substituted indole **23** were also formed in good yield. When quinoline *N*-oxide was used as the starting material, quinolone **24** was obtained in 38% yield. The developed C-H arylation could also be applied to a purine-based nucleoside to give product **25**.



Scheme 3. Scope of the Rh- and Ru- catalyzed C-H Functionalizations. Reactions were performed on 0.30 mmol scale. [a] 0.1 M in DCE:MeOH (1:1 ratio). [b] at 80 °C. [c] Using 0.660 mmol **8a**. [d] at 100 °C.

The thermal stability of the developed reagents was essential to achieve a broad scope, as several substrates required higher temperature to reach useful conversion (80 °C for products **13c,k,l,r**, **20** and **21**, and 100 °C for compound **24**). Preliminary investigations of the scope of the ruthenium-catalyzed C-H functionalization were then conducted (Scheme 3B). The benzamide directing group is attractive, as it can be easily modified or removed. Alkyl groups, ethers, trifluoromethyl groups and halogens were all well tolerated both in *para* and *meta* position to the amide (**15a-i**). Tetrasubstituted arene **15j** and naphthyl derivatives **15k** were also obtained in good yields.

In conclusion, we have reported the first synthesis of indole- and pyrrole substituted benziodoxolone reagents. Indole- and Pyrrole-BX were synthesized in one-step from the heterocycles under mild Lewis acid catalyzed conditions and are thermally stable up to 150 °C. These new reagents can be used for the Rh- and Ru-ortho C-H functionalization of arenes using heterocyclic and benzamide directing groups, a transformation that could not be realized using previously reported methods. Many of the obtained products are new combinations of privileged (hetero)arenes, covering interesting chemical space for medicinal chemistry. The availability of stable electrophilic indole and pyrrole synthons is expected to lead to broad applications in synthetic and medicinal chemistry.

Acknowledgements

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Keywords: Indoles • Hypervalent Iodine • Umpolung • C-H Functionalization • Heterocycles

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[27] The rhodium-catalyzed C-H functionalization was not successful with reagents **9r-t**.

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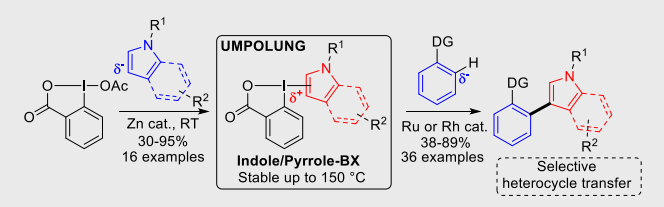

Electrophilic Indoles/Pyrroles: The first synthesis of indole and pyrrole-derived benziodoxole reagents in one step from the heterocycles is reported. The new Indole- and Pyrrole- BX reagents are stable up to 150 °C and can be used for selective heterocycle transfer onto the C-H bonds of arenes *ortho* to directing groups by using rhodium or ruthenium catalysts.

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