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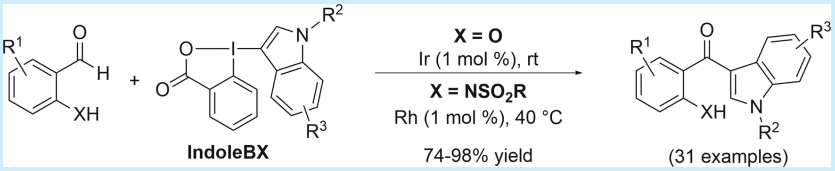
Iridium- and Rhodium-Catalyzed Directed C−H Heteroarylation of Benzaldehydes with Benziodoxolone Hypervalent Iodine Reagents

Erwann Grenet and Jérôme Waser*

Laboratory of Catalysis and Organic Synthesis, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fedérale de Lausanne, EPFL SB ISIC LCSO, BCH 4306, 1015 Lausanne, Switzerland

Supporting Information



ABSTRACT: The C−H heteroarylation of benzaldehydes with indoles and pyrroles was realized using the benziodoxolone hypervalent iodine reagents indole- and pyrroleBX. Functionalization of the aldehyde C−H bond using either an *o*-hydroxy or amino directing group and catalyzed by an iridium or a rhodium complex allowed the synthesis of salicyloylindoles and (2-sulfonamino)benzoylindoles, respectively, with good to excellent yields (74−98%). This new transformation could be carried out under mild conditions (rt to 40 °C) and tolerated a broad range of functionalities, such as ethers, halogens, carbonyls, or nitro groups.

Indoles and pyrroles are ubiquitous in medicinal chemistry and natural products.[1] Aryl indolyl ketones have attracted strong interest due to their interesting biological activities, in particular, through interactions with the cannabinoid receptor.[2] Among them, the subclass in which the aryl moiety wears a hydroxy or an amino group in the *ortho* position to the carbonyl showed in addition diverse biological activities (Figure 1). Polymethoxylated indole derivatives **1** were cytotoxic

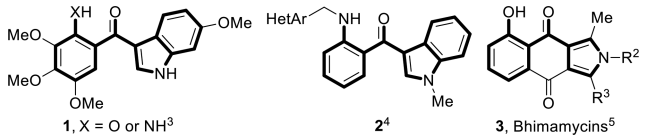
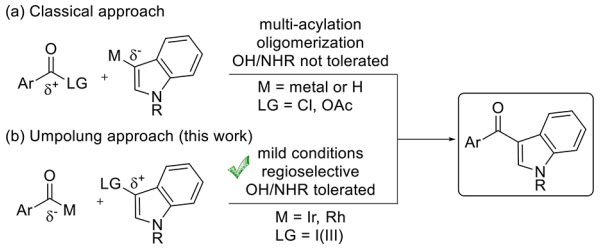


Figure 1. Synthetic and natural bioactive compounds with a 2-hydroxy or 2-amino benzoyl indole or pyrrole core.

against KB, MKN45, MCF-7, and colon HT-29 cells.[3] 3-(2-Aminobenzoyl)indole **2** led to VEGFR-2 inhibition.[4] Furthermore, the salicyloylpyrrole core is present in bhimamycins **3**, antibiotic natural products isolated from the bacteria *Streptomyces* sp.[5]

Due to their occurrence in biologically active compounds, the efficient synthesis of 3-benzoylindoles or -pyrroles is important. The most straightforward approach is based on the innate reactivity of the heterocycles as nucleophiles combined with an electrophilic acylation reagent (Scheme 1a). However, Friedel−Crafts acylation of indoles under standard conditions usually leads to a complex mixture of mono-, diacylated, and oligomerization products due to their high electron density.[1a] This issue can be partially resolved by the introduction of electron-withdrawing protecting groups, the use of milder

Scheme 1. Classical vs Umpolung Approaches for the Synthesis of 3-Arylcarbonyl Indoles



Lewis acids (Et_2AlCl,[6a,b] imidazolium chloroaluminate,[6c] or $ZrCl_4$[6d]), reaction with nitrilium salts,[7] or the use of hexafluoroisopropanol as solvent.[8] Furthermore, the nucleophilicity of the heterocycles can be enhanced by conversion into Grignard or other organometallic reagents, which can then be added directly to electrophiles or used in metal-catalyzed cross-couplings.[9] Recently, direct C−H acylation catalyzed by transition metals has also been reported.[10] The synthesis of 3-salicyloylindoles was either not reported in these works, or required the protection/deprotection of the hydroxy group. Therefore, developing a more direct access to these compounds would be highly desirable. In this respect, only limited success has been achieved by the ring-opening of chromones,[11,12] 1,3-dipolar cycloaddition, followed by decarboxylation,[13] and alkylation of indoles with nitroolefins, followed by oxidative C−C bond cleavage.[14]

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As an alternative strategy, we envisaged an Umpolung pathway involving a nucleophilic acyl metal intermediate generated via C_{sp2}–H activation of an aldehyde[15] and an electrophilic indole (Scheme 1b). Concerning the nucleophilic partners, benzaldehydes substituted with oxygen or nitrogen heteroatoms in the *ortho* position are privileged substrates, as the directing group is necessary for C–H activation under mild conditions.[15a] As electrophilic partners, we considered hypervalent iodine(III) reagents, which have been extensively used as Umpolung reagents in numerous transformations.[16] In fact, both aryl iodoniums and ethynylbenziodoxolones (EBX) have been used to introduce phenyl or alkyne derivatives via cross-coupling on salicylaldehydes.[17] However, there are only few methods for the synthesis of indole-and pyrrole-based iodonium salts.[18] Furthermore, due to their limited stability, these compounds have found only very limited use in transition-metal catalysis. Recently, our and Yoshikai's group reported the synthesis of bench-stable indole– and pyrrole–benziodoxolones (indoleBX and pyrroleBX).[19] We further demonstrated that the new indole- and pyrroleBX reagents could be used for directed C–H functionalization with rhodium or ruthenium catalysts, whereas iodonium salts were not successful.[19a] Herein, we report the C–H functionalization of 2-hydroxy and 2-amino benzaldehydes derivatives with indole- and pyrroleBX reagents using either iridium or rhodium catalysts to give access to important indole and pyrrole building blocks.

We initiated the studies on C–H indolation with the optimization of the reaction conditions for the coupling of salicylaldehyde **4a** with Me-indoleBX **5a** (Table 1). While

Table 1. Optimization Studies[a]

4a **5a** **6a**

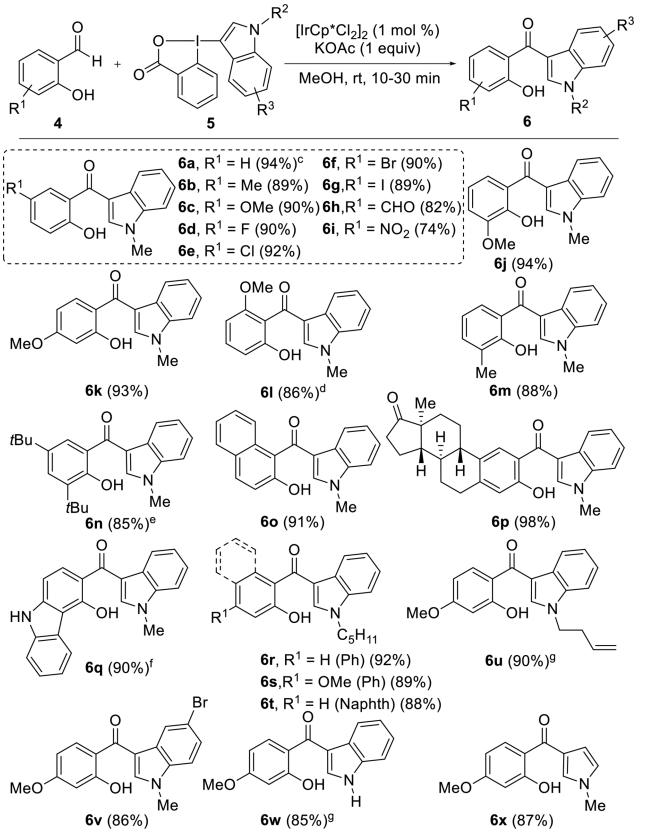
entry	catalyst	base (equiv)	yield[b] (%)
1	$[RhCp^*Cl_2]_2$	CsOAc (1.2)	traces[c]
2	$[IrCp^*Cl_2]_2$	CsOAc (1.2)	91
3	$[IrCp^*Cl_2]_2$	KOAc (1.2)	90
4	$[IrCp^*Cl_2]_2$	KOAc (1.0)	90
5	$[IrCp^*Cl_2]_2$	KOAc (0.5)	86
6	$[IrCp^*Cl_2]_2$	-	56
7	$[IrCp^*Cl_2]_2$	KOAc (1.0)	94[d]
8	$[IrCp^*Cl_2]_2$	KOAc (1.0)	93[e]

[a]Reactions conditions: **4a** (0.05 mmol), **5a** (0.05 mmol), $[IrCp^*Cl_2]_2$ (3 mol %), base, and methanol (0.5 mL) at rt for 10 min. [b]Isolated yield after column chromatography. [c]Reaction performed at 80 °C. [d]$[IrCp^*Cl_2]_2$ (1 mol %). [e]Yield at a 1.20 mmol scale with 0.5 mol % $[IrCp^*Cl_2]_2$.

$[RhCp^*Cl_2]_2$ as catalyst gave only traces of the desired product **6a** (Table 1, entry 1), we were pleased to see that the use of $[IrCp^*Cl_2]_2$ led to formation of **6a** in excellent 91% yield in the presence of cesium acetate at room temperature (Table 1, entry 2). This is the first example of the use of an iridium catalyst with indoleBX reagents. Furthermore, the reaction did not require any particular precautions concerning the presence of water or oxygen. Complete conversion was reached after 10 min at room temperature. Cheaper potassium acetate could also be used to give 90% yield of the ketone product **6a** (Table 1, entry 3). Variation of the amount of KOAc revealed that a superstoichiometric amount was not necessary (Table 1, entry 4). However, the yield decreased when the base was used in a substoichiometric quantity (Table 1, entry 5), and without base only 56% yield was obtained, even if full conversion was still observed (Table 1, entry 6). Finally, we were able to reduce the catalyst loading to 1 mol % without significant change in yield, demonstrating the robustness of the catalyst (Table 1, entry 7). A scale-up to 1.20 mmol allowed us to decrease the iridium catalyst loading to 0.5 mol %, giving 93% yield of **6a** in the same reaction time (Table 1, entry 8). Control experiments indicated that the transition-metal complex is essential for the reaction.[20] When 3-bromo-1-methylindole and 3-iodo-1-methylindole were used as reagents, the desired compounds were obtained in 59% and 53% yield, respectively, but only after heating overnight at 80 °C.[20] This result further highlights the exceptional reactivity of indoleBX reagents.

The scope of the reaction was then studied (Scheme 2). The effect of substituents in the *para* position to the hydroxy group

Scheme 2. Ir(III)-Catalyzed C–H Indolation of 2-Hydroxybenzaldehydes.[a,b]



[a]Reactions conditions: **4** (0.15 mmol), **5** (0.15 mmol), $[IrCp^*Cl_2]_2$ (1 mol %), KOAc (0.15 mmol), methanol (1.5 mL) at rt for 10 min. [b]Isolated yield after column chromatography. [c]93% yield for a reaction at 1.20 mmol scale. [d]30 min. [e]1 h. [f]Reaction performed at 50 °C for 2 h. [g]Reaction performed at 70 °C for 2 h.

was examined first (**6a–i**). In terms of electronic effect, both electron-donating alkyl and ether groups (**6b** and **6c**) and electron-withdrawing halogens, aldehyde, and nitro groups (**6d–i**) were well tolerated. The exclusive formation of product **6h** starting from a bis-formylated benzene confirmed the requirement of a directing group for C–H activation.[21] In term

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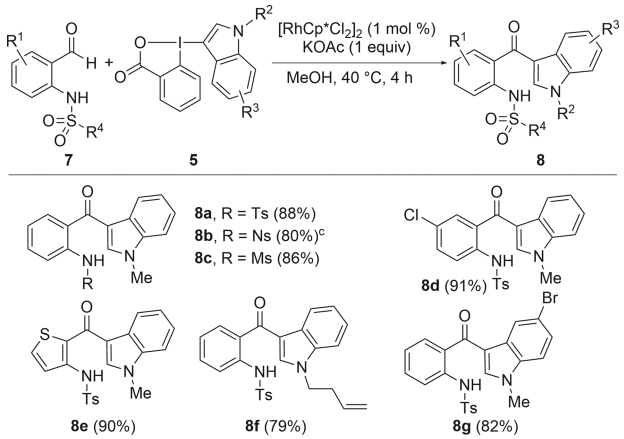
of substitution pattern of the benzene ring, a methoxy group was tolerated also in all other positions (**6j–l**).

A longer reaction time of 30 min was observed only in case of 2-hydroxy-6-methoxybenzaldehyde **4l** to give **6l** in 86% yield. Alkyl-substituted products **6m** and **6n** were also obtained in good yields. Naphthalene and estrone derivatives **6o** and **6p** were isolated in excellent 91% and 98% yields respectively. Pentacyclic compound **6q** wearing a carbazole heterocycle was obtained in 90% yield. Modification of the hypervalent iodine reagent was then investigated. Changing the *N*-substitution from methyl to pentyl or butenyl delivered indoles **6r–u**. The corresponding *O*-methylated compounds are reported synthetic cannabinoids.[22] A bromo substituent on the benzene ring was well tolerated (**6v**).The *N*-H free compound **6w** could be also obtained with complete regioselectivity in 85% yield. For products **6u** and **6w**, it was necessary to perform the reaction at 70 °C to reach full conversion. Importantly, the method could be extended to the synthesis of pyrrole **6x** using a pyrroleBX as reagent.

We then turned to the use of nitrogen-based directing groups for the activation of the aldehyde C–H bond. In the case of 2-aminobenzaldehyde **7a** bearing a *N*-tosyl directing group, a Rh(III) dimer catalyst proved to be as effective as the Ir(III) catalyst (Scheme 3), in contrast to what had been observed

Scheme 3. Rh(III)-Catalyzed C–H Indolation of 2-Sulfonylaminobenzaldehydes[a,b]

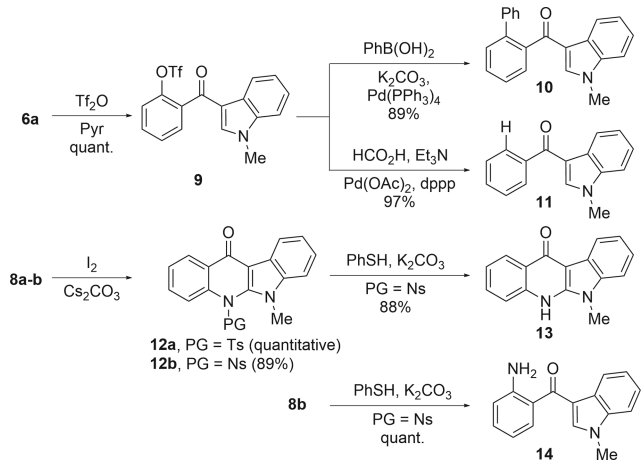


[a]Reaction conditions: **7** (0.15 mmol), **5** (0.15 mmol), $[RhCp^*Cl_2]_2$ (1 mol %), KOAc (0.15 mmol), methanol (1.5 mL) at 40 °C for 4 h. [b]Isolated yield after column chromatography. [c]80% yield for a reaction at 0.80 mmol scale.

with salicylaldehyde **4a** (Table 1). The reaction was best run in MeOH at 40 °C during 4 h.[20] Several *N*-sulfonyl groups (tosyl, *p*-nosyl, and mesyl) could be used to direct the C–H functionalization, giving products **8a–c** in 80–88% yield. In contrast, a *N*-Boc directing group was inefficient for this transformation (result not shown). The reaction could be perform in the presence of a chlorine atom on the phenyl ring affording the product **8d** with 91% yield. The thiophene-derived compound **8e** was isolated in an excellent 90% yield. This rhodium-catalyzed reaction also tolerated a *N*-butenyl substituent or a bromo group on the indole benzene ring, giving the desired products **8f** and **8g** in 79% and 82% yields, respectively.

The directing groups not only were useful for allowing C–H functionalization under mild conditions (see the Supporting Information for a mechanism proposal)[15a,17c] but also served as handles for further modifications (Scheme 4). For example,

Scheme 4. Product Modifications



phenol **6a** was quantitatively transformed into the corresponding triflate **9** by reaction with triflic anhydride. Suzuki–Miyaura cross-coupling with phenyl boronic acid gave then biphenyl derivative **10** in 89% yield over two steps. Alternatively, the directing group could be fully removed by a palladium-catalyzed reduction of the triflate to furnish 3-benzoylindole **11**. From *N*-sulfonylphenyl substituted ketones **8a** and **8b**, an iodine-mediated oxidative C-2 amination generated tetracyclic indolo-[2,3*b*]quinolinone **12a** and **12b** in quantitative yield for tosyl **8a** and 89% yield for nosyl **8b**.[23] The nosyl protecting group was synthetically especially useful, as it could be removed in the presence of thiophenol, either on the cyclized product **12b** or the indolation product **8b** to give the *N*-H free heterocycles **13** and **14**.

In summary, we have reported the first example of aldehyde C–H heteroarylation giving highly useful indole and pyrrole building blocks. The reaction proceeded under mild, neutral conditions using either an alcohol or a sulfonylamide directing group with an iridium or a rhodium catalyst, respectively, and the cyclic hypervalent iodine reagents indole- and pyrroleBX. This represented also the first use of an iridium catalyst with indole- and pyrroleBX as reagents. As the reaction tolerated a broad range of functional groups and the obtained versatile indole and pyrrole building blocks could be easily further modified, the method is expected to be highly useful in synthetic and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00337.

Experimental procedures, analytical data, optimization tables, and NMR spectra for all compounds (PDF)
NMR data (ZIP)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jerome.waser@epfl.ch.

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ORCID

Jérôme Waser: 0000-0002-4570-914X

Notes

The authors declare no competing financial interest.

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