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Synthesis of 4-Iodoisoquinolin-1(2*H*)-ones by a Dirhodium(II)-Catalyzed 1,4-Bisfunctionalization of Isoquinolinium Iodide Salts

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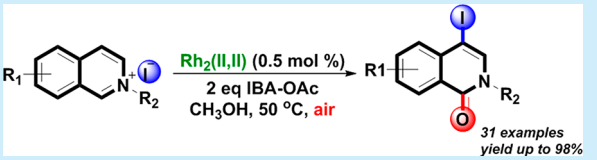
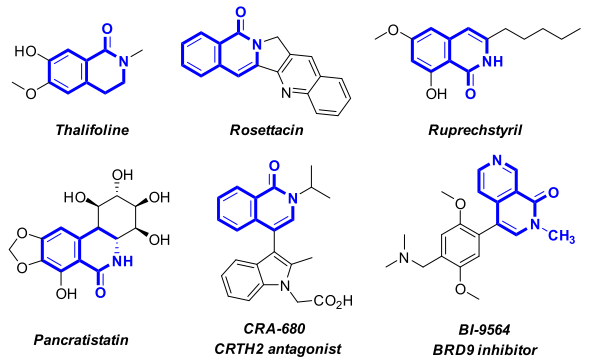
Supporting Information

ABSTRACT: An efficient $Rh_2(II,II)$-catalyzed reaction has been developed under mild conditions. This synthetic method proceeds through iodination/oxidation of readily available isoquinolinium iodide salts under aerobic conditions with good to excellent yields. 4-Iodoisoquinolin-1(2*H*)-ones are important building blocks for biologically and medicinally important compounds. The developed methodology was applied to the gram-scale synthesis of a key intermediate in the synthesis of the CRTH2 antagonist CRA-680.

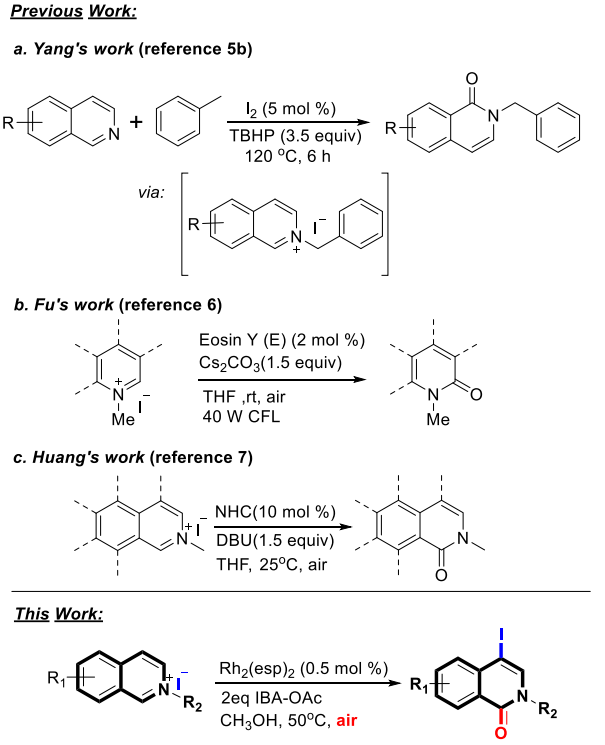


Isoquinolin-1-(2*H*)-ones are privileged structural motifs that are ubiquitous in natural and bioactive compounds, such as thalifoline, rosettacin, etc. (Scheme 1).[1] Owing to their important biological activities, including as antidepressant, antiulcer, and antihypertensive agents, the synthesis of isoquinolin-1(2*H*)-ones and their amide analogues has attracted considerable interest, and a number of synthetic methods have been developed over the past few years.[2] Among the many reported effective synthetic approaches, the direct oxidation of easily prepared isoquinolinium salts[3a,b] to isoquinolin-1-(2*H*)-ones is a convenient and efficient method.[3c,d] The traditional oxidation method requires excess $K_3Fe(CN)_6$ as the oxidant, resulting in a large amount of harmful $K_4Fe(CN)_6$ as waste.[4] Other approaches include copper-, iodine-, or phosphite-catalyzed oxidative functionalizations of isoquinolines leading to isoquinolones.[5] Recently, several elegant methods have been reported (Scheme 2). Fu and co-workers reported a visible-light-mediated radical catalyst and air as the sole oxidant (Scheme 2b).[6] Huang et al. described a carbene-catalyzed aerobic oxidation of isoquinolinium salts to isoquinolones (Scheme 2c).[7] Notably, isoquinolin-1(2*H*)-ones are also frequently used as scaffolds in medicinal chemistry (Scheme 1).[8] For example, lead compounds containing isoquinolin-1-(2*H*)-ones are used in the treatment of asthma and tumors as depicted in Scheme 1.[8a,b]

Scheme 1. Biologically Active Natural Products and Drug Candidates Containing the Isoquinolin-1-(2*H*)-one Motif



Scheme 2. Representative Recent Examples of the Direct Oxidation of Isoquinolinium Salts to Isoquinolin-1-(2*H*)-ones



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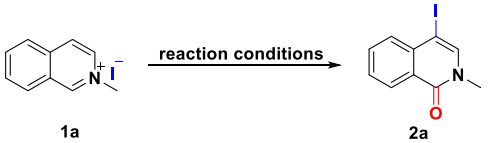
In the discovery and development of drugs or drug candidates, it is highly desirable to develop important synthetic blocks on which the pharmacophore can be efficiently constructed. Vinyl iodides are versatile synthons that are widely used in highly effective metal-catalyzed cross-coupling reactions because a weaker carbon−iodine bond is more reactive, facilitating the oxidative addition better than aryl bromides and aryl chlorides.[9]

Thus, iodine-functionalized isoquinolin-1-(2*H*)-one derivatives would be ideal building blocks in biomedical research as they are effective coupling partners. A typical example is the 4-iodoisoquinolin-1-(2*H*)-ones, which are used in the synthesis of a series of CRTH2 antagonists as key synthetic intermediates (Scheme 1).[8a] Herein, as part of our continuing studies of one-electron oxidation reactions catalyzed by Rh_2(II,II) complexes,[10] we report an efficient, one-step formation of 4-iodoisoquinolin-1-(2*H*)-ones from a readily available isoquinolinium iodide salt employing Rh_2(II,II) and acetoxybenziodoxolone (IBA-OAc)[11] with ambient air as the oxidant. During our studies on Rh_2(II,II)-catalyzed azidation reactions with azidobenziodoxolone (IBA-N_3) reagents,[11] small amounts of substituted isoquinolones were detected when *N*-alkylisoquinolin salts were used as substrates. This observation led to the discovery that the Rh_2(II,II) complex combined with IBA-OAc catalyzes the difunctionalization of isoquinolines[12] to form 4-iodoisoquinolin-1-(2*H*)-ones in one step. The studies to optimization this reaction began with a solvent screening using *N*-methylisoquinolin-2-ium iodide (**1a**) as the substrate. Initially, considering the water solubility of alkylisoquinolin salts, mixed solvents such as methanol (MeOH)/H_2O, DCE/H_2O, and dimethyl carbonate (DMC)/H_2O were used, and MeOH/H_2O gave better yields (Table 1, entries 1−4). Further investigations revealed that the yields of product **2a** were greatly improved to 85% when pure MeOH was applied as the solvent (Table 1, entry 5). Therefore, other alcohol solvents were also examined, and the results were inferior to that achieved with MeOH (Table 1, entries 6 and 7). It is worth mentioning that a large amount of iodine was observed to stick on the walls of the reaction tube when hexafluoroisopropanol (HFIP) was used as the solvent. We reason that the iodine was insoluble in the HFIP and precipitated on the tube wall, which led to the poor yield of **2a**. This observation suggested that iodine may be generated and be involved in this reaction system. It was noted the isoquinolinium bromide salt cannot give the desired product **2a**. Next, the screening of the reaction temperature indicated that 50 °C was optimal (Table 1, entries 8 and 9). Other hypervalent iodine reagents were also investigated, and 1-hydroxy-3-oxobenziodoxole (IBA-OH),[11] which is structurally similar to IBA-OAc, resulted in 73% yield of **2a**, while PhI$(OAc)_2$ gave poor results (Table 1, entries 10 and 11). Decreasing the amount of IBA-OAc to 0.8 mmol lowered the yield of **2a** to 49%, while increasing the amount of IBA-OAc had little effect on the yield of **2a** (Table 1, entries 12 and 13). For comparison, other Rh_2(II,II) complexes were evaluated in the reaction. By replacing $Rh_2(esp)_2$ with common $Rh_2(OAc)_4$, the reaction occurred with only 14% yield of **2a** (Table 1, entry 15). The catalytic effect of $Rh_2(OPiv)_4$ is similar to that of $Rh_2(esp)_2$ at 1 mol % catalyst loading, which leads to 86% yield of **2a** (Table 1, entry 16). However, when the catalyst loading was reduced, the efficiency of $Rh_2(OPiv)_4$ gradually became lower than that of $Rh_2(esp)_2$. When the loading of $Rh_2(OPiv)_4$ was reduced to 0.3 mol %, the yield of the reaction dropped significantly (Table 1, entry 20). As described in previous reports, the performance of Rh_2(II,II) complexes in the oxidation reaction was related to its structural stability. $Rh_2(esp)_2$, with its characteristic chelating structure, shows high stability and resists degradation during reactions.[10,13] Other metal catalysts, such as $Cu(acac)_2$ and $Co(OAc)_2$, were less efficient and gave inferior yields (Table 1, entries 21 and 22). The Rh(III) catalyst only gave a trace amount of desired compound **2a** (Table 1, entry 23). Thus, 0.5 mol % of $Rh_2(esp)_2$ was selected as the optimal catalyst loading.

Table 1. Optimization of Conditions for Oxidation and Iodination of *N*-Methylisoquinolinium Salts[a]



entry	solvent	catalyst	yield[b] (%)
1	MeOH/H_2O (v/v = 3/1)	$Rh_2(esp)_2$	52
2	DCE/H_2O (v/v = 3/1)	$Rh_2(esp)_2$	46
3	DMC/H_2O (v/v = 3/1)	$Rh_2(esp)_2$	48
4	THF/H_2O (v/v = 3/1)	$Rh_2(esp)_2$	26
5	MeOH	$Rh_2(esp)_2$	85
6	EtOH	$Rh_2(esp)_2$	72
7	HFIP	$Rh_2(esp)_2$	trace
8[c]	MeOH	$Rh_2(esp)_2$	61
9[d]	MeOH	$Rh_2(esp)_2$	82
10[e]	MeOH	$Rh_2(esp)_2$	8
11[f]	MeOH	$Rh_2(esp)_2$	73
12[g]	MeOH	$Rh_2(esp)_2$	49
13[h]	MeOH	$Rh_2(esp)_2$	82
14	MeOH	none	complex
15	MeOH	$Rh_2(OAc)_4$	14
16	MeOH	$Rh_2(OPiv)_4$	86
17[i]	MeOH	$Rh_2(esp)_2$	86
18[i]	MeOH	$Rh_2(OPiv)_4$	82
19[j]	MeOH	$Rh_2(esp)_2$	78
20[j]	MeOH	$Rh_2(OPiv)_4$	51
21[k]	MeOH	$Cu(acac)_2$	49
22[k]	MeOH	$Co(OAc)_2$	43
23	MeOH	$Rh(Cp^*)Cl_2$	trace

[a]Reactions were performed by using **1a** (0.53 mmol), IBA-OAc (1.06 mmol), solvent (2 mL), and catalyst (1.0 mol %) at 50 °C. [b]Yield after column chromatography. [c]The reaction temperature was 25 °C. [d]The reaction temperature was 40 °C. [e]PhI$(OAc)_2$ (1.06 mmol) was used instead. [f]IBA-OH (1.06 mmol) was used instead. [g]IBA-OAc (0.8 mmol) was used. [h]IBA-OAc (1.33 mmol) was used. [i]0.5 mol % of catalyst was used. [j]0.3 mol % of catalyst was used. [k]5 mol % of catalyst was used. esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropanoate

Next, with the optimized conditions in hand, we extensively expanded the scope of substrates **1**. The various *N*-methylisoquinolinium salts bearing different substituents on the aromatic ring were applied in the reaction (Scheme 3). It was found that the substrates **1** with electron-donating and electron-withdrawing groups at the C-6 and C-7 positions all gave moderate to high yields of desired products **2b−f**. Functionalities including amide, ester, halogen, and aromatic groups were well tolerated. However, the efficiency of the reaction was significantly affected by the position of the substituents on **1**. Substrates **1** with electron-withdrawing substituents gave higher yields than those with electron-donating groups. For example, with a methyl ester group on

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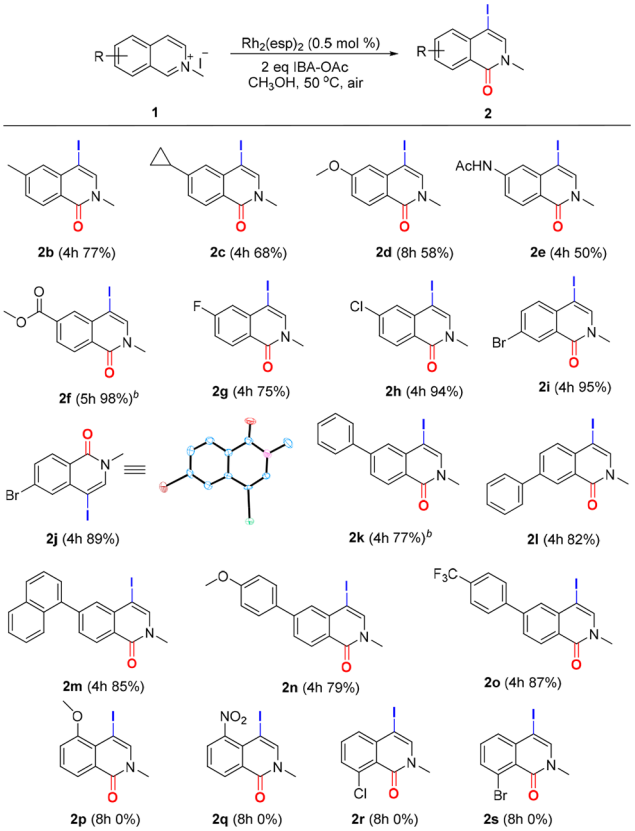
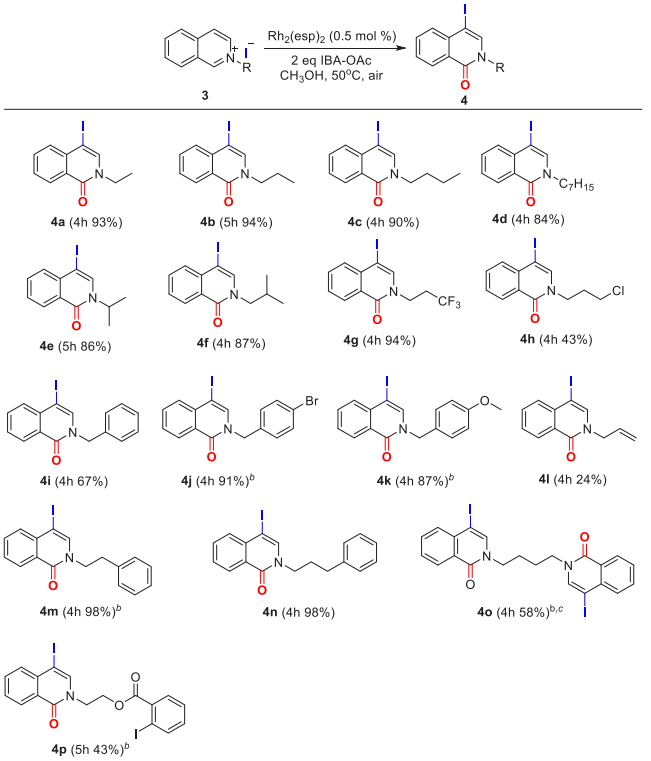
Scheme 3. Substrate Scope for the Oxidation and Iodine of *N*-Methylisoquinolinium Salts[a]



[a]Reactions were performed by using **1** (0.8 mmol), IBA-OAc (1.6 mmol), CH_3OH (3 mL), and $Rh_2(esp)_2$ (0.5 mol %) at 50 °C. Yield after column chromatography. [b]$Rh_2(esp)_2$ (1.0 mol %) was used.

Scheme 4. Substrate Scope for Oxidation and Iodination of *N*-Alkylisoquinolinium Salts[a]



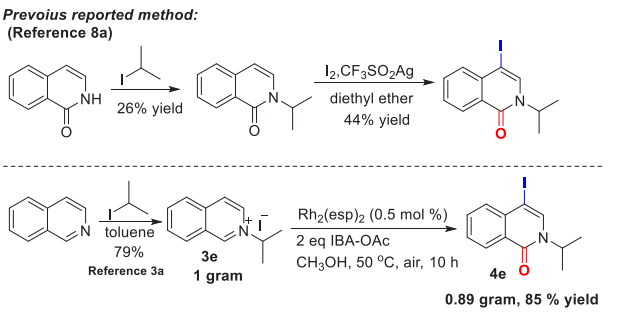
[a]Reactions were performed by using **3** (0.8 mmol), IBA-OAc (1.6 mmol), CH_3OH (3 mL), and $Rh_2(esp)_2$ (0.5 mol %) at 50 °C. Yield after column chromatography. [b]$Rh_2(esp)_2$ (1.0 mol %) was used. [c]IBA-OAc (3.2 mmol) was used.

the C-6 position, the yield of product **2f** reached 98%, while acetylamino (NHAc) group substituted **1e** gave product **2e** in only 50% yield. Products **2g–o** were obtained in good yields when various halogenated substrates **1g–j** as well as aryl substituted substrates **1k–o** were applied. Notably, products **2g–j** with halogen substituents are attractive for further synthetic elaboration. It is worth mentioning that substrates **1p–s** with substituents on the C-5 and C-8 positions resulted in complex reaction mixtures. We reason that steric effects may have caused the reaction to fail. Next, isoquinoline salts with different N-substituents were synthesized to extend the scope of the procedure (Scheme 4). Substrates with linear and branched aliphatic substituents (**3a–f**) gave **4a–f** in good yields of 84–94%. Product **4h**, in which the *N*-substituent contained a chloride, can be further derivatized regardless of the moderate yield. Substrates **3i–k** and **3m–n**, which were highly susceptible to benzylic oxidation under standard conditions due to the presence of benzyl groups, still gave desired products **4i–k** and **4m–n** in satisfactory yields when the catalyst loading was increased to 1.0 mol %. *N*-Allyl-substituted substrate **3l** resulted in a complicated mixture at the end of the reaction, and only a 24% yield of **4l** was obtained after silica gel chromatography. The low yield of **4l** was attributed to the high reactivity of the double bond, which allowed it to readily form unidentified byproducts. When two *N*-substituted isoquinoline derivatives were connected by an alkyl linker, dimeric 4-iodoisoquinolin-1-(2*H*)-one (**4o**) was obtained successfully. It is interesting to note that when 1-hydroxyiodoethane-substituted **3p** is used as the substrate, the *o*-iodobenzoic acid generated in the reaction from IBA-OAc undergoes an esterification reaction with the hydroxyl group to give **4p** in 43% yield.

To explore the synthetic practicality of this transformation, a gram-scale reaction was conducted to prepare **4e**, which is a key intermediate for the synthesis of the CRTH2 antagonist CRA-680 (Scheme 5).[8a] The reaction showed good performance, smoothly giving 85% yield of **4e** from **3e**.

Next, we conducted a number of experiments to elucidate the reaction mechanism (Scheme 6). Dioxygen is the co-oxidant in the reaction, and this was confirmed by the nitrogen-protected experiment (Scheme 6, eqs 1 and 2). Under a nitrogen atmosphere, **1a** gave a trace amount of product **2a** and was primarily transformed into 4-iodoisoquinoline **5**. After

Scheme 5. Gram-Scale Experiment



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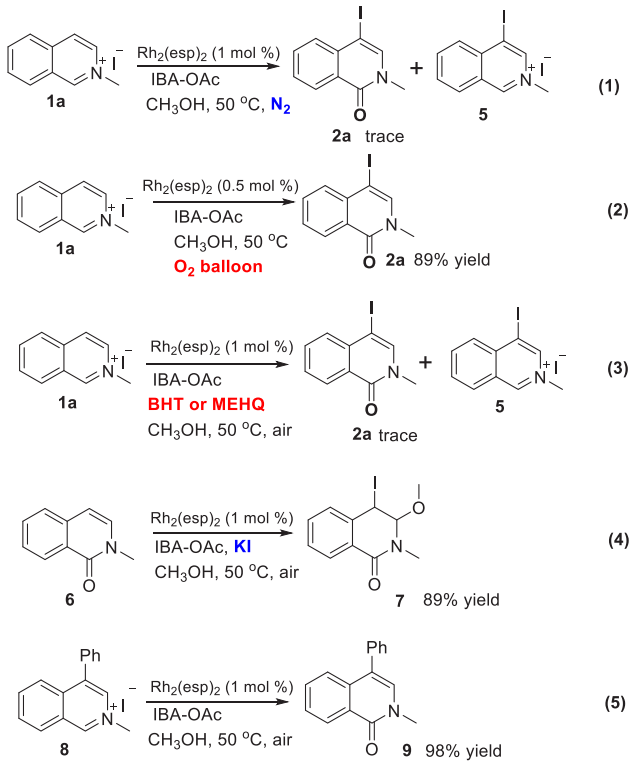
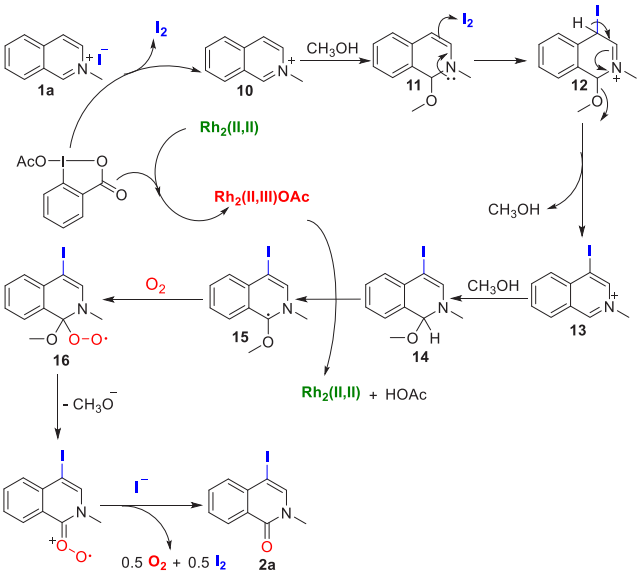
Scheme 6. Control Experiments



the addition of the free-radical inhibitors 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 4-methoxyphenol (MEHQ) under the standard reaction conditions, only a trace of **2a** was detected, which indicated a free-radical reaction mechanism is active (Scheme 6, eq 3). In addition, the reaction still gave **5** as the main product. As mentioned above, molecular iodine was generated in the reaction. Therefore, the formation of **5** indicated that the substrate may be more susceptible to substitution with iodine. Further studies revealed that the reaction rate of the iodination was faster than that of the oxidation. If the oxidation occurred first, bifunctional alkene product **7** was obtained rather than product **2a** (Scheme 6, eq 4). 4-Phenyl-substituted substrate **8** readily gave oxidized isoquinoline product **9** under standard conditions without interference from the iodide ion (Scheme 6, eq 5), suggesting the iodination and oxidation are two independent processes occurring in the reaction system.

On the basis of the results of these experiments and previous reports of the oxidation of isoquinoline,[5−7] a plausible mechanism is proposed (Scheme 7). IBA-OAc first reacts with iodide ions of **1a** to produce molecular iodine through redox reactions[14] and isoquinolinium cation **10**. After that, the nucleophilic addition of MeOH to **10** generates enamine intermediate **11**. Then, the **11** rapidly reacts with iodine to form 4-iodo-substituted isoquinolinium **12**, which undergoes 1, 4-elimination to form **13**.[15] The liberation of the bound anion to generate isoquinolinium cation **10** is key to the reaction since I_2 reacted with isoquinolinium iodide or bromide salt under reaction conditions cannot give the iodine product **5**. At the same time, $Rh_2(esp)_2$ undergoes one-electron oxidation by IBA-OAc to give $Rh_2(esp)_2OAc$.[10a] Subsequently, the nucleophilic addition of MeOH to **13** lead to hemiaminal-type intermediate **14**. $Rh_2(esp)_2OAc$ then abstracts a hydrogen atom from **14** to form radical **15**, which is captured by the

Scheme 7. Proposed Mechanism



dioxygen in air to form peroxide **16**. After the methoxy group leaves and cleavage of the O−O bond, product **2a** is obtained with the help of the iodide accompanying dioxygen and iodine formation.[6]

In summary, we have developed a Rh_2(II,II)-catalyzed one-pot reaction starting from readily accessible isoquinoline iodide salts to efficiently prepare 4-iodoisoquinolones, which are important building blocks in the synthesis of lead compounds in drug discovery. Mechanistic investigations revealed that this methodology proceeds through an iodine substitution with molecular iodine generated in situ and a radical-mediated aerobic oxidation. Further mechanistic studies and application of various hypervalent iodine reagents in other Rh_2(II,II)-catalyzed reaction systems are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03614.

Additional experimental procedures and spectroscopic data for all new compounds are supplied (PDF)

Accession Codes

CCDC 1870347 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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