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A Highly Efficient Friedel–Crafts Reaction of 3-Hydroxyoxindoles and Aromatic Compounds to 3,3-Diaryl and 3-Alkyl-3-aryloxindoles Catalyzed by $Hg(ClO_4)_2 \cdot 3H_2O$

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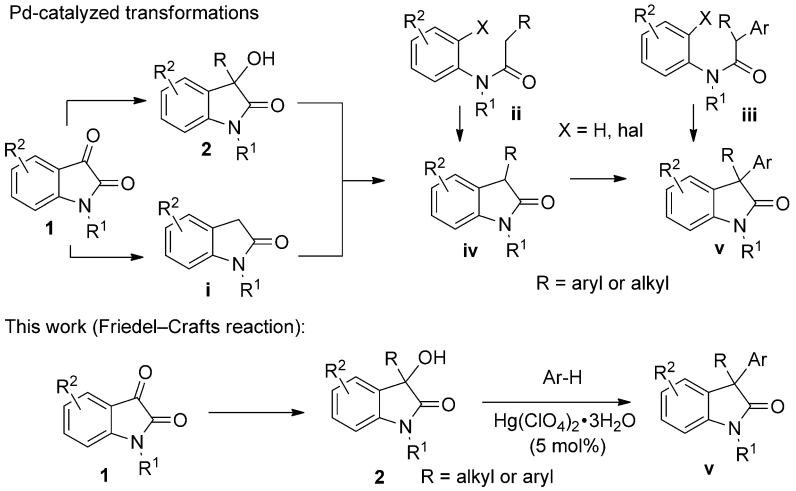
Abstract: We report a highly efficient Friedel–Crafts reaction of 3-alkyl or 3-aryl 3-hydroxyoxindoles with a variety of aromatic and heteroaromatic compounds to unsymmetrical 3,3-diaryloxindoles or 3-alkyl-3-aryloxindoles, which are interesting medicinal targets and useful building blocks for the synthesis of natural products. $Hg(ClO_4)_2 \cdot 3H_2O$ was identified as a powerful catalyst for this reaction, and is significantly more efficient than other screened metal perchlorate hydrates and Brønsted acids such as HOTf and $HClO_4$. The high catalytic property of $Hg(ClO_4)_2 \cdot 3H_2O$ originates from the unprecedented dual activation effects of aromatic mercuration, which could generate a strong protic acid to facilitate the generation of a carbocation at the C3-position of oxindoles and simultaneously form the more reactive nucleophilic reaction partner.

Keywords: atom economy · carbocations · Friedel–Crafts reaction · mercury · natural products

Introduction

The 3,3-disubstituted oxindole framework is present in many biologically active natural products and medicinal targets.[1] Of particular interest are 3,3-diaryloxindoles and 3-alkyl-3-aryloxindoles. Both subclasses are useful building blocks for the total synthesis of bioactive natural products,[2] and have been studied as pharmaceutically active compounds.[3] Surprisingly, methods for the synthesis of unsymmetrical 3,3-diaryloxindoles are rare.[4] Most recently, Sammakia et al. reported the first example of a palladium-catalyzed α-arylation of 3-aryloxindoles for the catalytic synthesis of unsymmetrical 3,3-diaryloxindoles,[4e] thereby demonstrating the versatility of palladium-catalyzed coupling reactions to prepare both frameworks from 3-substituted oxindole **iv**[5a–g] or amide **iii**[5h–l] (Scheme 1). However, as Pd^0 species are involved, the preparation of products with substituents sensitive to oxidative addition—bromo groups, for example—has not been reported by means of these coupling reactions.[5] Furthermore, the introduction of hetereoaromatics to the C3-position of oxindoles to increase the structural diversity is less studied. Accordingly, it is highly desirable to develop new methods that allow the efficient synthesis of both structural motifs, with hindered all-carbon quaternary centers, in high structural diversity for biological evaluation and studies on the structure–activity relationship.



Scheme 1. Methods to synthesize 3,3-diaryl and 3-alkyl-3-aryloxindoles.

The catalytic Friedel–Crafts reaction[6] of 3-hydroxyoxindoles **2** and aromatic compounds would be an atom-efficient

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procedure[7] to construct both structural motifs, as it only produces water as waste. In addition, compound **2** can be prepared in a single step from isatins, whereas precursor **iii** or **iv** for coupling reactions are usually obtained by two steps from isatins or anilines.[8] The synthesis of symmetrical 3,3-diaryloxindoles from isatins and arenes in the presence of a large excess amount of strong acids or superacids was known.[4a,b] The reaction of 3-hydroxy-3-aryloxindoles and L-tyrosine derivatives promoted by 5.0 equivalents of trifluoromethanesulfonic acid (TfOH) was developed by Nicolaou et al. during the synthesis of diazonamide A.[2a] They also found that the use of 20 mol% of TfOH or some metal triflates led to the decomposition of starting materials.[2b] Despite their achievements, the catalytic versions of this reaction were very limited, possibly because the formation of the carbocationic intermediate was difficult due to the electron-withdrawing effect of the amide group of 3-hydroxyoxindole **2**. By now, only Lewis acid catalyzed arylation of isatins with indoles or *N*,*N*-dimethylaniline to symmetric 3,3-diaryl oxindoles, and the arylation of 3-indolyl-3-hydroxyoxindoles by using indoles or pyrroles have been reported,[3d,9a–e] which involved the formation of reactive vinylogous iminium intermediates.[9f,g] To increase the structural diversity for structure–activity relationship studies, the catalytic synthesis of unsymmetrical 3,3-diaryl oxindoles by means of Friedel–Crafts arylation of 3-aryl-3-hydroxyloxindoles that cannot form vinylogous iminium intermediates is highly desirable but is unprecedented.

Recently, much effort has been devoted to the exploration of new catalytic properties of inexpensive and easily available metal salts such as iron, bismuth, and copper salts in organic synthesis.[10] Mercury, as an "element of mystery,"[11] however, has received very limited attention, mainly due to the concern about its toxicity.[12a,b] This is to some extent perplexing because mercury still has numerous applications in many areas nowadays.[12] In industrial applications, mercury could be used for barometers, manometers, gauges, high-intensity discharge (HID) lamps, and as an electrode in the electrolytic production of chlorine and caustic soda from saline, and in electrical switches widely used in automobiles. The application of mercury to extract gold and silver from their respective ores continues to this day. Furthermore, mercury and its chemical compounds still have medical applications nowadays. For example, mercury amalgam principally with silver is widely used as a tooth filling, and there is no convincing evidence that dental amalgam leads to adverse health effects.[12a] Thimerosal is still used in vaccines in many countries, and the current scientific consensus is that no convincing scientific evidence to support the thimerosal controversy that mercury-containing vaccines lead to the development of autism and brain development disorders.[12a,b]

In view of the aforementioned facts, academic research that aims toward the discovery of new catalytic properties of mercury compounds is still needed, although unnecessary usage of mercury compounds in organic synthesis should be avoided. In particular, recent studies have shown that mercury compounds had interesting properties worthy of exploration. For example, Barron et al. reported that the formation of stabilized arene–mercury complexes significantly increased the acidity of the aromatic protons of the coordinated arenes. The thus-obtained stable arene–mercury complexes could serve as highly efficient catalysts for the H/D exchange reaction of C_6D_6 with arenes in which the coordinated arene protonated C_6D_6.[13] Nishizawa and co-workers identified $Hg(OTf)_2$ as a highly efficient catalyst for a number of transformations, including hydration of alkynes, C–C bond-forming cyclizations initiated from alkynes or allylic alcohols, and heterocycle synthesis.[14b–l] Deslongchamps et al. also contributed greatly to mercury catalysis.[14m] The high catalytic efficiency and mild reaction conditions made these transformations very useful, particularly when applied to natural product synthesis.[15]

Although aromatic mercuration has been extensively studied and Olah et al. have suggested that mercury–arene complexes might be the intermediates by NMR spectroscopic studies,[16] most of these studies focused on the use of a stoichiometric amount of mercury salts to convert aromatic compounds to arylmercurials, which were used as versatile synthons in transition-metal-catalyzed coupling reactions.[17] Whereas Barron et al. reported a highly efficient H/D exchange reaction of C_6D_6 with arenes catalyzed by a stabilized arene–mercury complex that resulted from aromatic mercuration,[13] the highly efficient catalytic C–C bond-forming reactions initiated by aromatic mercuration have not been reported as far as we know.[17] Here we wish to report the unprecedented dual activation effects of aromatic mercuration, which could generate a strong protic acid to facilitate the generation of a carbocationic intermediate and simultaneously activate the aromatics to form more nucleophilic aryl mercurials. This would contribute to a highly efficient Friedel–Crafts reaction of 3-hydroxyoxindoles and a variety of aromatic compounds to furnish the congested quaternary carbon center at the C3-position of oxindole.

Results and Discussion

In our efforts to synthesize 3,3-disubstituted oxindoles for biological evaluation,[18] we speculated that the formation of a reactive carbocation at the C3-position from oxindole **2** might be difficult owing to the electron-withdrawing amide group, therefore we tried to develop a catalytic arylation of 3-hydroxyindoles **2** by using Lewis acids with weak-coordinating counteranions that might enhance the catalytic property of Lewis acids.[19] Given that inexpensive and easy-to-handle metal perchlorate hydrates with a weak-coordinating anion had been identified as powerful Lewis acids for a number of reactions,[20] we first examined a series of metal perchlorate hydrates in the reaction of 3-hydroxyoxindole **2b** and *N*-methylindole **3a** by using tetrahydrofuran (THF) as the solvent in the presence of 10 mol% catalyst. Some typical results are shown in Table 1.

It was found that In^{III}-, Al^{III}-, Cr^{III}-, Cu^{II}-, Zn^{II}-, Co^{II}-, Ni^{II}-, and Ag^{I}-derived metal perchlorate hydrates all failed to

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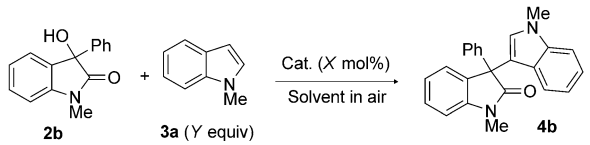
Table 1. Optimization of the reaction conditions.



Entry[a]	Catalyst	X	Y	Solvent	T [°C]	t [h]	Conv. [%][b]
1[c]	$Hg(ClO_4)_2 \cdot 3H_2O$	10	2	THF	50	120	90
2[c]	$Fe(ClO_4)_3 \cdot xH_2O$	10	2	THF	50	120	25
3[c]	$Fe(ClO_4)_3 \cdot xH_2O$	10	2	CH_3CN	50	120	<12
4[c]	$Hg(ClO_4)_2 \cdot 3H_2O$	10	2	CH_3CN	50	120	100
5[d]	$Hg(ClO_4)_2 \cdot 3H_2O$	10	2	CH_3CN	80	4	100
6[d]	$Hg(ClO_4)_2 \cdot 3H_2O$	5	1.5	CH_3CN	80	8	100 (95)[e]
7[d]	$Hg(ClO_4)_2 \cdot 3H_2O$	2	1.5	CH_3CN	80	72	100 (82)[e]
8[d]	$Hg(ClO_4)_2 \cdot 3H_2O$	5	1.2	CH_3CN	80	8	100 (95)[e]

[a] On a 0.1 mmol scale. [b] Determined by ^1H NMR spectroscopic analysis of the crude mixture. [c] The concentration of **2b** was 0.2 M. [d] The concentration of **2b** was 0.5 M. [e] On a 0.3 mmol scale, with isolated yield.

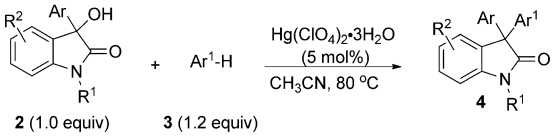
catalyze the reaction. Only $Hg(ClO_4)_2 \cdot 3H_2O$ and $Fe(ClO_4)_3 \cdot xH_2O$ could catalyze the desired reaction to some extent by ^1H NMR spectroscopic analysis (Table 1, entries 1 and 2). Some typical Brønsted acids were also employed, but only TfOH and $HClO_4$ could slightly catalyze the reaction (around 10% conversion; see the Supporting Information for details). The counteranion effect of mercury salts was also evaluated, and $HgCl_2$ and $HgSO_4$ both failed to catalyze the reaction. We then compared the potency of $Hg(ClO_4)_2 \cdot 3H_2O$ and $Fe(ClO_4)_3 \cdot xH_2O$ in different solvents, and $Hg(ClO_4)_2 \cdot 3H_2O$ turned out to be much more effective. $Fe(ClO_4)_3 \cdot xH_2O$ could only catalyze the reaction in THF and CH_3CN with low activity (Table 1, entries 2 and 3). In light of this, we further optimized the reaction conditions by using $Hg(ClO_4)_2 \cdot 3H_2O$ as the catalyst. It was found that when the reaction was carried out at 80 °C with the substrate concentration increased from 0.2 to 0.5 M, the reaction rate could be greatly improved, and the reaction could finish within four hours (Table 1, entry 4 and 5). By lowering the catalyst loading to 5 mol% and the amount of *N*-methylindole **3a** to 1.5 equivalents, the reaction could still be completed after eight hours to afford product **4b** in 95% yield (Table 1, entry 6). Further lowering of the catalyst loading to 2 mol% greatly slowed down the reaction rate (Table 1, entry 7). With 5 mol% of catalyst, the amount of indole **3a** could be reduced down to 1.2 equivalents without obvious influence on the reactivity to afford product **4b** in 95% yield (Table 1, entry 8).

Next, the substrate scope with respect to both the electrophile and nucleophile was investigated under the optimal conditions to run the reaction in air at 80 °C and by using CH_3CN as the solvent in the presence of 5 mol% of $Hg(ClO_4)_2 \cdot 3H_2O$ as the catalyst. A number of unsymmetrical 3,3-diaryloxindoles with enough diversity could be readily obtained by this method (the right aryl group of the C3-position was from the nucleophilic reaction partner **3**), as shown in Table 2. As the indole framework is a "privileged" structure or pharmacaphore, together with the fact that few methods allowed the generation of a full-carbon quaternary center adjacent to the C3-position of indole,[21] a number of substituted indoles were first tried. The reaction of unprotected 3-phenyl-3-hydroxyoxindole **2a** and *N*-methyl indole afforded product **4a** in 86% yield. As the unprotected 3-substituted hydroxyoxindoles dissolved poorly in CH_3CN, the *N*-methyl-protected ones were used subsequently. By comparison, product **4b** was indeed obtained at a much faster rate. All the differently substituted indoles, even with electron-withdrawing groups, worked well to afford the desired products in good to excellent yield (**4c–i**). The structure of product **4i** was also confirmed by X-ray analysis (see the Supporting Information).[22] It should be noted that this protocol allowed the retention of the bromo group, which might be difficult in the palladium-catalyzed coupling reactions shown in Scheme 1. The halogenated indole adducts **4g–k** might be valuable synthons for use in conjunction with organometallic technologies (e.g., Buchwald–Hartwig and Stille couplings).[23] The substituent effect on the oxindole framework was also examined, and the corresponding products **4j–q** could also be obtained in good to excellent yield. A variety of (hetero)aromatic compounds were then tried, and 2-methyl-substituted furan or thiophene, *para-tert*-butylphenol, and 1,3-dimethoxybenzene worked well to afford the corresponding products (**4r**, **4s**, **4u**, **4w–y**) in high yield. However, *N*-methylpyrrole and *N*-acetylindoline were less reactive, and the desired products **4t** and **4v** were obtained in diminished yield.

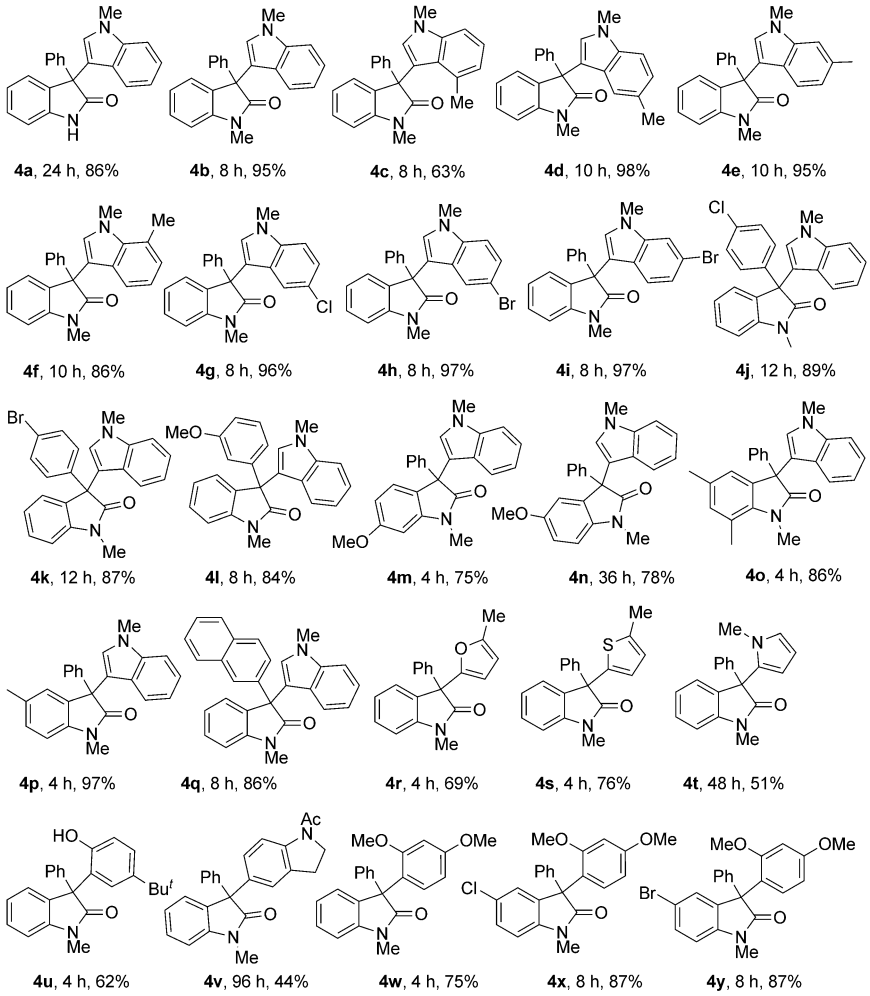
To demonstrate the generality of this method, we further tried 3-hydroxyl-3-alkyloxindoles (Table 3). Previously, only Padwa et al. reported that 3-hydroxy-3-methyloxindole could react with anisole, furan, or thiophene in the presence of 20 mol% of *p*-TsOH (TsOH = toluenesulfonic acid), which was carried out in toluene heated to reflux temperature, by using 5.0 to 20.0 equivalents of aromatic compounds.[5p] We found to our delight that both 3-methyl- and 3-allyl-substituted 3-hydroxyoxindoles could react with a series of (hetero)aromatic compounds. Because of their low boiling point, furan and anisole were used in three equivalents to ensure a good yield of product **5a**,**b**. 3-Allyl-3-hydroxyoxindoles were less reactive than 3-methyl ones, but the corresponding products **5m–t** were very useful for the synthesis of a fused indoline ring system present in a multitude of bioactive compounds according to literature methods.[2e,5m]

The broad substrate scope of this reaction was very impressive: not only 3-alkyl and 3-aryl 3-hydroxyoxindoles worked well as the electrophilic reaction partner, but also a variety of aromatic and heteroaromatic compounds (including halogenatedindoles) could serve as the nucleophilic reaction partner. In addition, this reaction was carried out in air by using an inexpensive and easy-to-handle $Hg(ClO_4)_2 \cdot 3H_2O$ catalyst. These facts made this method very efficient for the synthesis of unsymmetrical 3,3-diaryloxindoles and 3-alkyl-3-aryloxindoles in sufficient diversity. When benzene derivatives such as bromobenzene, benzene, and toluene were used as the nucleophiles, only complex

Table 2. Synthesis of unsymmetrical 3,3-diaryloxindoles.



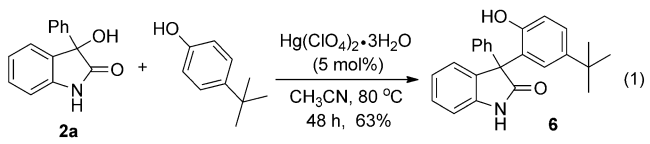
Product 3,3-diaryloxindoles **4**[a–c]



[a] On a 0.3 mmol scale. [b] Isolated yield. [c] The right aryl group at the C3-position of product **4** was from nucleophile **3**.

mixtures were obtained with the full conversion of 3-hydroxyoxindoles, which was a limitation for this transformation. This limitation might be to some extent compensated in the synthesis of unsymmetrical 3,3-diaryloxindoles by using 3-hydroxyoxindoles with different substituted phenyl groups to react with electron-rich arenes, as shown in Table 2.

We also applied our method for the synthesis of Ca^{2+}-depleting translation initiation inhibitor **6**,[3a] which was obtained in 63% yield from hydroxyoxindole **2a** [Eq. (1)]. Compound **6** was more potent than 3,3-diphenyloxindole in inducing eIF2α phosphorylation and four times more potent in inhibiting cancer-cell growth, which further demonstrated the importance of the preparation of 3,3-diaryloxindoles and 3-alkyl-3-aryloxindoles in great diversity.



Strong electronic effects were observed in this reaction. For example, the methoxy group at the C6-position of the oxindole framework greatly accelerated the reaction, so product **4m** was obtained at a much faster reaction rate than **4n**. The bromo group at the C5-position of oxindole slowed down the reaction rate, and product **5r** was obtained in much lower yield than **5p**. When enantioenriched 3-hydroxyoxindole **7**[24] reacted with **3a** under the standard conditions, product **8** was isolated in racemic form [Eq. (2)]. These results provided strong evidence that prochiral carbocationic intermediates were involved in the reaction.

To understand the high catalytic efficiency of $Hg(ClO_4)_2•3H_2O$, we next conducted some experiments to investigate if the high reactivity realized by $Hg(ClO_4)_2•3H_2O$ in this reaction was related to aromatic mercuration.[16] NMR spectroscopic studies were first employed. As shown in Figure 1, after adding $Hg(ClO_4)_2•3H_2O$ (10 mol%) to a solution of *N*-methylindole **3a** in CD_3CN, the interaction could be immediately monitored. Even in the presence of only 10 mol% of $Hg(ClO_4)_2•3H_2O$, the characteristic peaks of the protons at the C2-, C3-positions, and the *N*-methyl group were completely shifted from $\delta = 7.12$, 6.42, and 3.73 ppm to $\delta = 7.29$, 6.34, and 3.77 ppm by ^{1}H NMR spectroscopic analysis, respectively. Obvious changes were also observed by ^{13}C NMR spectroscopic studies. The aromatic mercuration of *N*-methylindole **3a** might arrive at a state of equilibrium after one hour, as revealed by NMR spectroscopic analysis. The aromatic mercuration of other typical aromatics used in this reaction was

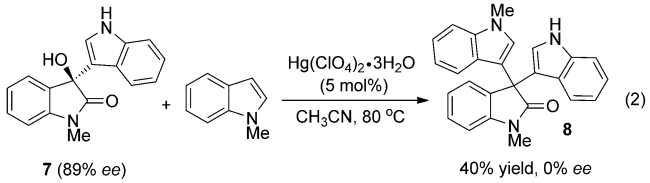


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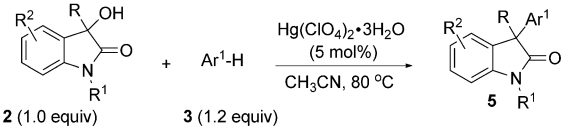
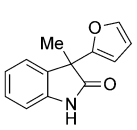
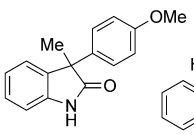
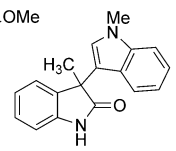
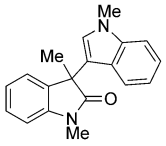
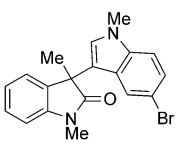
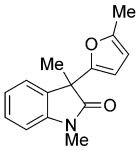
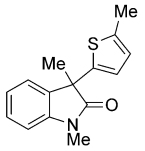
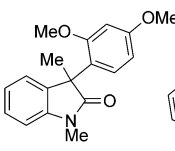
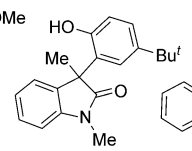
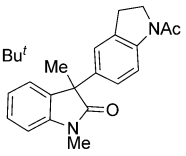
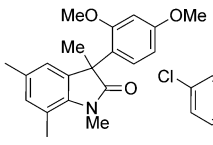
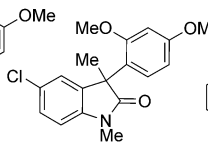
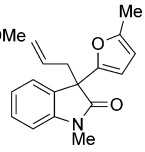
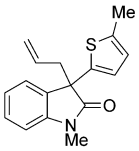
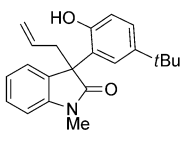
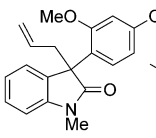
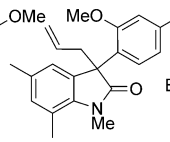
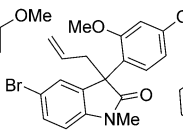
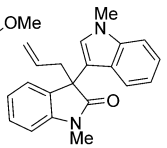
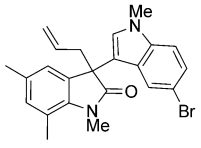
Table 3. Synthesis of 3-alkyl-3-aryloxindoles.



Product 3-alkyl-3-aryloxindoles **5**[a,b]				
 **5a**, 48h, 72% (3.0 equiv furan)	 **5b**, 48h, 63% (3.0 equiv anisole)	 **5c**, 48 h, 57%	 **5d**, 12 h, 88%	 **5e**, 12 h, 86%
 **5f**, 4 h, 81%	 **5g**, 4 h, 85%	 **5h**, 4 h, 90%	 **5i**, 4 h, 60%	 **5j**, 96 h, 25%
 **5k**, 4 h, 70%	 **5l**, 4 h, 56%	 **5m**, 96 h, 72%	 **5n**, 96 h, 73%	 **5o**, 96 h, 63%
 **5p**, 96 h, 95%	 **5q**, 6 h, 77%	 **5r**, 96 h, 38%	 **5s**, 96 h, 56%	 **5t**, 12 h, 94%

[a] On a 0.3 mmol scale. [b] Isolated yield.

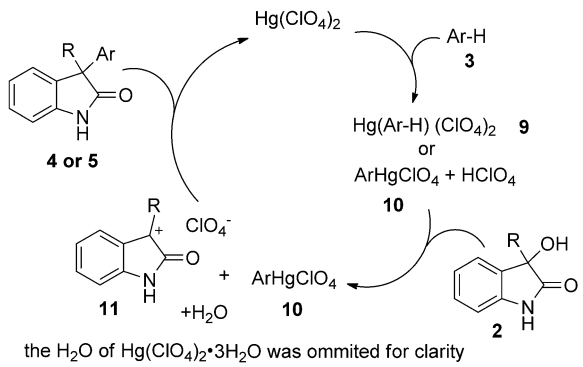
also confirmed by NMR spectroscopic analysis (see the Supporting Information). On the other hand, the coordination of the hydroxy group of *N*-methyl-3-phenyl-3-hydroxyoxindole **2b** to Hg^{II} was not clear, although the characteristic peak of hydroxy group shifted from $\delta = 4.46$ to 3.53 ppm by ^{1}H NMR spectroscopic analysis.

Because the use of a stoichiometric amount of $Hg(ClO_4)_2 \cdot 3H_2O$ to interact with *N*-methylindole resulted in insoluble complexes unable to be characterized, we next tried UV/Vis titration experiments to get more information about the complex. The spectral changes of *N*-methylindole **3a** upon addition of $Hg(ClO_4)_2 \cdot 3H_2O$ at 298 K are shown in Figure 2. With the addition of Hg^{2+}, the absorbance at 308 nm gradually developed and increased. A Job plot indicated the formation of the 1:1 complex between *N*-methylindole and Hg^{2+}.

To further understand the role of aromatic mercuration in the course of the reaction, we monitored the reaction of highly reactive oxindole **2p** with *N*-methylindole **3a** by ^{1}H NMR spectroscopic studies, which proceeded smoothly at 25 °C in CD_3CN by using 10 mol % of $Hg(ClO_4)_2 \cdot 3H_2O$. The aromatic mercuration of *N*-methylindole **3a** indeed took place the moment $Hg(ClO_4)_2 \cdot 3H_2O$ was added to the reaction mixtures, as the characteristic peak of indole **3a** immediately shifted from $\delta = 6.43$ to 6.30 ppm (c versus d–e in Figure 3). However, the high reactivity of $Hg(ClO_4)_2 \cdot 3H_2O$ in this reaction could not merely be explained by the formation of arene–mercury complex as strong protic acids, because even $HClO_4$ alone catalyzed the reaction at a much slower rate. As shown in Figure 3, whereas $Hg(ClO_4)_2 \cdot 3H_2O$ could promote the reaction to finish within 4 hours (Figure 3d–f), only 83 % conversion was obtained after 40 hours when using $HClO_4$ as the catalyst (Figure 3g–i).

Based on the above information, especially the fact that $Hg(ClO_4)_2 \cdot 3H_2O$ was able to catalyze the reaction at a much faster rate than $HClO_4$, the high efficiency that $Hg(ClO_4)_2 \cdot 3H_2O$ exhibited in this reaction was thought to be related to the dual activation effects that resulted from the aromatic mercuration of the electron-rich arene during the course of the reaction, which could generate a strong acid to facilitate the dehydration of 3-substituted 3-hydroxyoxindole and simultaneously generate the aryl mercury compound as the more reactive nucleophilic reaction partner.

As shown in Scheme 2, the aromatic mercuration of aromatic compounds **3** with $Hg(ClO_4)_2 \cdot 3H_2O$ led to the formation of arene–mercury complexes **9**, which could serve as a strong protic acid, as Barron et al. proposed,[13] to react with 3-hydroxyoxindole **2** to produce the carbocationic intermediate **11**, and simultaneously generate aryl mercury compound **10**. The reaction of **10** and **11** readily gave the desired product **4** or **5**, and regenerated the catalyst. Alternatively, the aromatic mercuration might directly afford the aryl mer-



Scheme 2. Proposed reaction mechanism.

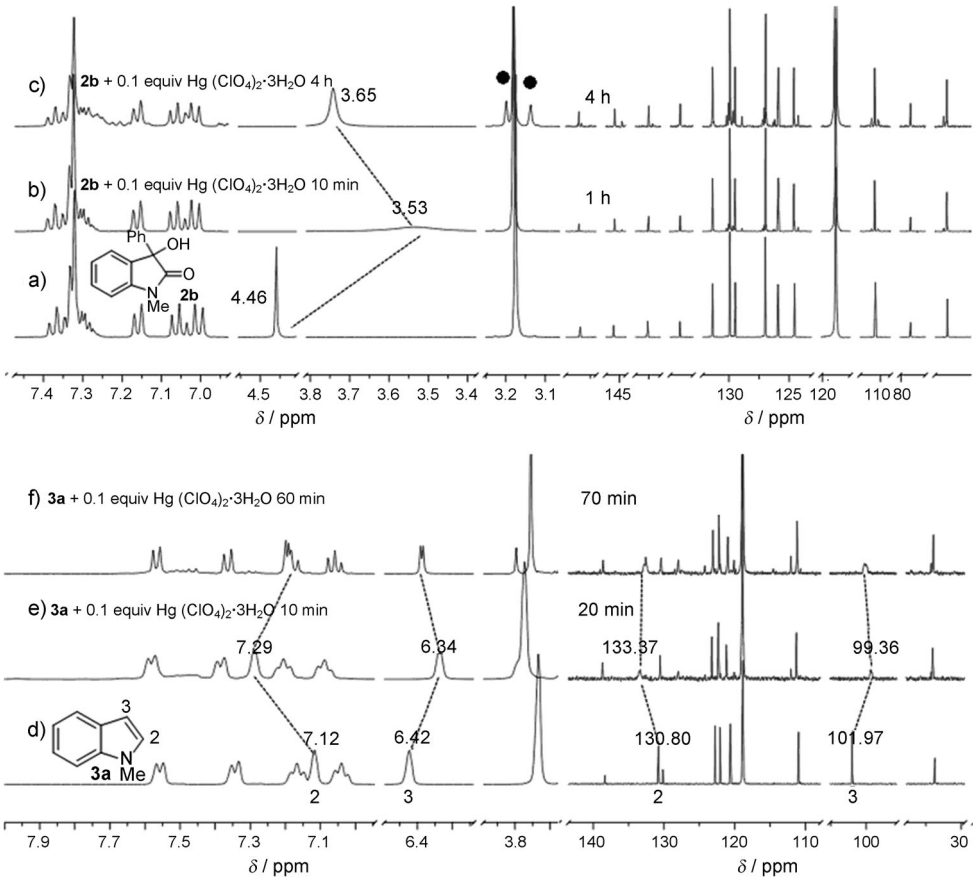


Figure 1. ^{1}H NMR (400 MHz, CD_3CN, 298 K) spectra of a) oxindole **2b**; b), c) the mixture of **2b** and 10 mol% of $Hg(ClO_4)_2{\cdot}3H_2O$, the time as indicated; d) *N*-methylindole **3a**; e), f) the mixture of **3a** and 10 mol% of $Hg(ClO_4)_2{\cdot}3H_2O$, the time as indicated.

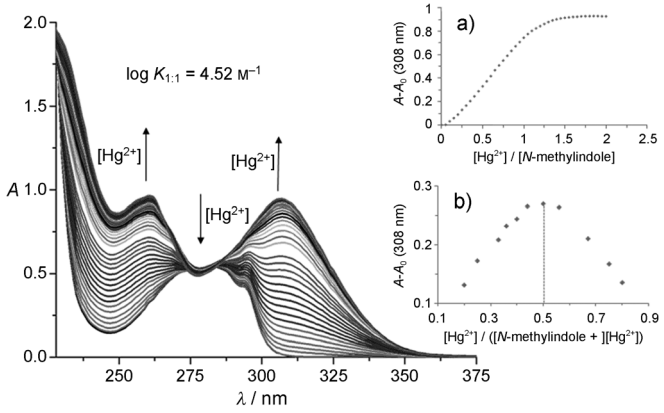


Figure 2. UV/Vis spectral changes of *N*-methylindole **3a** (1.0×10^{-4} M in CH_3CN) in response to the addition of Hg^{2+} ion at 298 K (0–2.0 equiv). Inset: a) variation of absorbance at 308 nm of *N*-methylindole **3a** using a 1:1 complexation model. b) Job plot showing a 1:1 complex of **3a** and Hg^{2+} ion (*N*-methylindole+Hg^{2+} = 1.0×10^{-4} M in CH_3CN).

cury compound **10** and $HClO_4$, similar to the mechanism that Toste et al. proposed for the Cu^{II}-catalyzed cycloisomerization-indole addition reaction.[25] The $HClO_4$ facilitated the dehydration of hydroxyoxindole **2** to form a reactive benzylic cation that would then readily react with the activated nucleophile **10** to give product **4** or **5**.

The formation of a strong protic acid in the course of the reaction was also supported by the fact that basic *N*-methylindoline failed to react with 3-hydroxyoxindoles under our reaction conditions, although NMR spectroscopic studies undoubtedly showed the occurrence of aromatic mercuration. On the contrary, the less electron-rich *N*-acetyl indoline could react with 3-hydroxyloxindoles to give the desired product **4v** and **5j**. As aromatic mercuration happened both in the case of *N*-methylindoline and *N*-acetyl indoline (see the Supporting Information), the failure of *N*-methylindoline to work with hydroxyoxindoles was possibly due to the fact that the in situ-generated protic acid was caught by the basic moiety of *N*-methylindoline, which prevented the formation of carbocation.

Noticeably, aromatic mercuration in this reaction took place under mild conditions to form stable mercury–arene complexes, possibly on account of the high Lewis acidity of $Hg(ClO_4)_2{\cdot}3H_2O$ and the electron-rich nature of the aromatics involved. This observation was interesting, because Barron et al. used $AlCl_3$ or $GaCl_3$ to increase the Lewis acidity of $HgCl_2$ to form stabilized arene–mercury complexes that were sensitive to moisture or coordinating solvents.[13]

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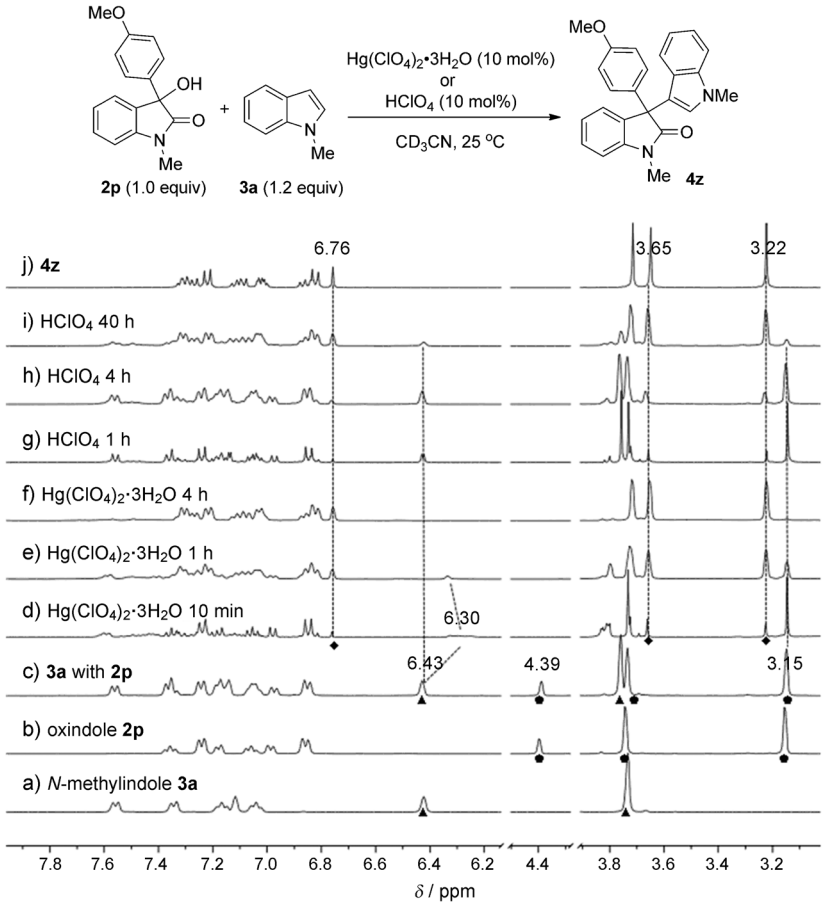

Figure 3. ^{1}H NMR (400 MHz, CD_3CN, 298 K) spectra of a) *N*-methylindole **3a**; b) oxindole **2p**; c) the mixture of **3a** and **2p**; d)–f) the reaction of **3a** and **2p** catalyzed by 10 mol% of $Hg(ClO_4)_2{\cdot}3H_2O$, the reaction time as indicated; g)–i) the reaction of **3a**- and **2p**-catalyzed by 10 mol% of $HClO_4$, the reaction time as indicated; j) product **4z**.

Conclusion

In conclusion, we report for the first time that aromatic mercuration had dual activation effects, which allowed us to use the inexpensive and easy-to-handle $Hg(ClO_4)_2{\cdot}3H_2O$ as a powerful catalyst for the catalytic Friedel–Crafts reaction of 3-substituted 3-hydroxyoxindoles with a variety of aromatics and heteroarenes. This reaction could serve as a complementary method to palladium-catalyzed coupling reactions for the synthesis of unsymmetrical 3,3-diaryloxindoles and 3-alkyl-3-aryloxindoles in sufficient structural diversity. The use of easily available starting materials and catalyst, as well as broad substrate scope make our method very useful.

The finding that aromatic mercuration of $Hg(ClO_4)_2{\cdot}3H_2O$ and aromatic compounds takes place at room temperature is very interesting, as it can be potentially applied to the development of C–H functionalization reactions because the thus-formed aryl mercury compounds would be useful intermediates in palladium-catalyzed coupling reactions.

The high catalytic property of $Hg(ClO_4)_2{\cdot}3H_2O$ in this reaction suggested that safe mercury compounds, other than toxic organomercury compounds such as MeHgCl, have some interesting catalytic properties that are worthy of exploration.[14b] Experiments are now underway in our lab to develop an asymmetric version of this reaction and to explore the catalytic properties of $Hg(ClO_4)_2{\cdot}3H_2O$ in other carbon–carbon and carbon–heteroatom bond-forming reactions.

Experimental Section

$Hg(ClO_4)_2{\cdot}3H_2O$ (6.8 mg, 0.015 mmol), oxindole **2** (0.30 mmol), and anhydrous CH_3CN (0.6 mL) were added to a 5 mL vial, and then the aromatic compounds **3** (0.36 mmol) were quickly added. The resulting mixture was stirred at 80 °C until almost full conversion of **2** by TLC analysis. After evaporating the solvent under vacuum, the reaction mixture was directly subjected to column chromatography (10–20% EtOAc in petroleum ether) to afford the desired product **4** or **5**.

Acknowledgements

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