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Rongalite-induced transition-metal and hydride-free reductive aldol reaction: a rapid access to 3,3′-disubstituted oxindoles and its mechanistic studies†

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A transition-metal and hydride-free reductive aldol reaction has been developed for the synthesis of biologically active 3,3′-disubstituted oxindoles from isatin derivatives using rongalite. In this protocol, rongalite plays a dual role as a hydride-free reducing agent and a C1 unit donor. This transition metal-free method enables the synthesis of a wide range of 3-hydroxy-3-hydroxymethyloxindoles and 3-amino-3-hydroxymethyloxindoles with 79–96% yields. One-pot reductive hydroxymethylation, inexpensive rongalite (*ca.* $0.03/1 g), mild reaction conditions and short reaction time are some of the key features of this synthetic method. This protocol is also applicable to gram scale synthesis.

Introduction

Oxindole is a privileged building block in many natural products and biologically active compounds.[1] Among these, 3,3′-disubstituted oxindoles have captivated chemists due to the wide spectrum of biological activities.[2,3] In the realm of oxindoles, the skeleton with a hydroxy and amine-bearing quaternary centre at C3 (3-hydroxy-2-oxindole and 3-amino-2-oxindole) has significantly intersected the biological space through its three-dimensional spatial arrangement.[2b] Notably, these are the core structures of many pharmaceutical lead compounds such as convolutamydines A and B,[4a,b] TMC-95A-B,[4c] YK-4-279[4d] and AG-041R[4e] (Fig. 1). Although there are wide-ranging methods to treat cancer, it is the second major cause of mortality in the world.[4f] Recently, 3-amino-3-hydroxymethyloxindoles have been reported as an anti-cancer agents and show anti-proliferating effect against SJSA-1, HCT-116 and Jurkat cancer cell lines *via in vitro* screening.[4g]

The biological significance of 3,3′-disubstituted oxindoles is that it provides impetus to the development of new synthetic strategies.[5] Limited methods are available for the synthesis of 3-hydroxy-3-hydroxymethyloxindoles and 3-amino-3-hydroxymethyloxindoles despite their biological activity.

The most common synthetic routes to 3-hydroxy(amino)-3-hydroxymethyloxindoles are (i) the C3-functionalization of activated oxindoles and (ii) the direct functionalization at the C3-position of isatins. The first relies on catalyst-induced ring opening of spiro-epoxyoxindoles[6] or the $Rh_2(OAc)_4$-catalyzed

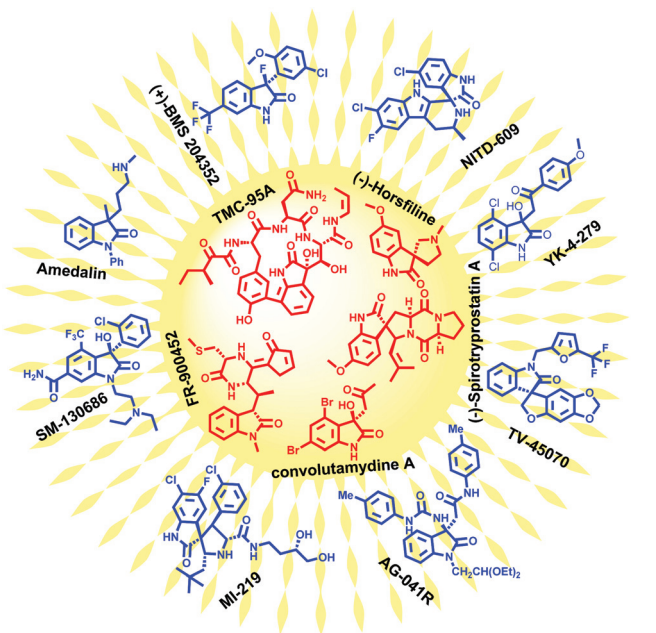

Fig. 1 Representation of natural (red) and synthetic (blue) bioactive 3,3′-disubstituted oxindoles.

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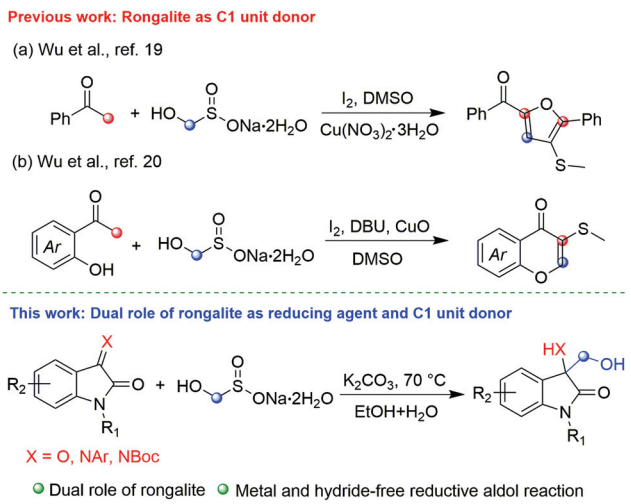
MCR reaction of 3-diazooxindoles to afford 3-hydroxy(amino)-3-hydroxymethyloxindoles.[7,4g]

This approach suffers from the use of expensive catalysts and starting materials (requires multiple steps). The second strategy relies on the direct C3-functionalization of isatin using the C1 source.[8] Recently, Zhang and co-workers employed microwave-assisted sequential Cannizzaro and aldol reactions of isatins and its derivatives in an excess of paraformaldehyde under microwave irradiation to obtain 3-hydroxy-3-hydroxymethyloxindoles and 3-amino-3-hydroxymethyloxindoles. Although this approach is easy to employ, it has its own limitations such as excessive use of formaldehyde, which is a potential carcinogenic agent,[9] harsh reaction conditions and limited substrate scope.

In this context, we are developing a transition metal-free commercially viable method using a green reagent "rongalite" in the presence of a mild base.

Sodium hydroxymethanesulfinate dihydrate (SHM), also called rongalite, is an industrial product and found to be a green reagent which can replace the use of toxic formaldehyde.[9] Kotha and co-workers extensively used rongalite in organic synthesis and named it as a green reagent.[10,11] It acts as a super electron donor in the synthesis of pyrazoles[12] and in transition-metal free arylation.[13] It is a potential source of both formaldehyde and sulfoxylate dianion (SO_2^{2-}) but the latter is utilized more in organic synthesis.[14–18]

To the best of our knowledge, only Wu and co-workers have utilized the *in situ* generated CH_2O from rongalite as a C1 unit donor in the synthesis of 2,4,5-trisubstituted furans and chromones (Scheme 1a and b).[19,20] Moreover, within the aldol-type reactions, the reductive aldol reaction (RAR) is one of the most important reactions to form the C–C bond.[21] Although there are several variations of the RAR, metal and hydride-free RAR has been capturing the imagination of chemists the world over in recent years.[22] In continuation of our efforts in exploring the synthetic utility of rongalite,[23] herein we report a transition-metal and hydride-free reductive aldol reaction to synthesize 3,3′-disubstituted oxindoles using multifaceted rongalite as a reducing agent and a C1 unit donor.



Scheme 1 Synthetic application of the *in situ* generated C-1 unit donor using rongalite.

Results and discussion

In our initial studies, isatin **1a** was allowed to react with rongalite **2** in the presence of K_2CO_3 in a suitable solvent and at a suitable temperature to obtain 3-hydroxy-3-(hydroxymethyl) indolin-2-one **3a** and only the key facts are reported (Table 1).

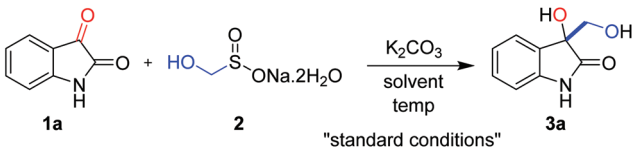
The reaction of isatin **1a** (1 mmol) with rongalite **2** (2 mmol) and K_2CO_3 (2 mmol) in CH_3CN + H_2O at ambient temperature resulted in the formation of **3a** in 10% yield (Table 1, entry 1). The structure of **3a** was identified using ^1H, ^{13}C NMR and HRMS spectral data. To our delight, the yield of **3a** was dramatically improved to 70% when the temperature was increased to 70 °C (Table 1, entry 2). Inspired by these preliminary results, further screenings were carried out with different solvent systems and bases to improve the product yield. Reactions were conducted in polar aprotic solvents, *i.e.* acetone, THF, DMF, and DMSO, and **3a** was obtained in 35–75% yields (Table 1, entries 4–7).

Among the tested polar protic solvents, ethanol was found to be superior and gave the target compound in 92% yield (Table 1, entries 8–10). Then, we screened the reaction using different organic and inorganic bases and obtained inferior results (Table 1, entries 11–15). Additionally, changing the loadings of rongalite, base and temperature did not improve the yields of the product (Table 1, entries 16–18). Surprisingly, formaldehyde sources such as formalin and paraformaldehyde did not form the desired product (Table 1, entries 19 and 20). Thus, the optimized reaction conditions are 1.0 mmol of isatin **1a**, 2.0 mmol of rongalite **2** and 2.0 mmol of K_2CO_3 in 2 mL of EtOH + H_2O (8 : 2) at 70 °C for 20 min as shown in Table 1, entry 9.

With the optimized reaction conditions in hand, we turned our attention to evaluate the scope and limitations of the reaction with various isatin substrates (Table 2). The electron-donating groups on the benzene ring such as methyl and methoxy isatins underwent the reaction smoothly with rongalite to furnish **3b** and **3c** in 80% and 79% yields, respectively (Table 2). This method also can tolerate various isatin halogen derivatives (F, Cl, Br, and I) and afforded dihydroxylated products **3d–3i** in 82–92% yields (Table 2).

5-Nitroisatin **1j** did not offer the dihydroxylated product even at high temperatures for long durations. We observed that *N*-substituted isatins are superior to *N*-unsubstituted isatins in terms of product yields and reaction time. *N*-alkyl, *N*-allyl, *N*-propargyl, *N*-benzyl and *N*-arylated isatins readily reacted with rongalite to form vicinal diols in 86–95% yields (Table 2, **3k–3v**). Interestingly, rongalite is more chemoselectively added to the carbonyl group of isatin when compared to the carbonyl group of the ester to give 3-hydroxy-3-(hydroxymethyl)indolin-2-one in 92% yield (Table 2, **3w**). The dimers of isatins linked by the alkyl chain (1,4- and 1,6-) through nitro-

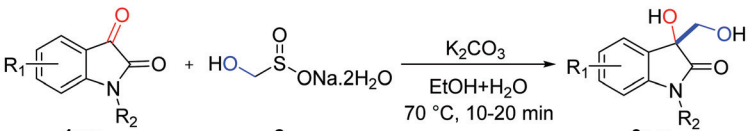
Table 1 Optimization of the reaction conditions[a]

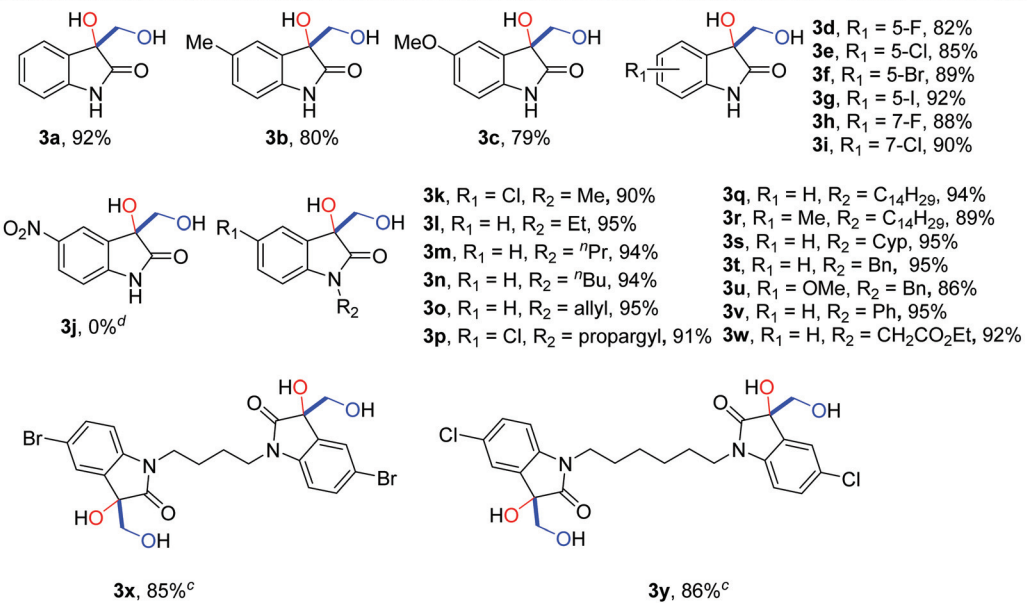


Entry	Solvent (8 : 2 v/v)	Variation from the standard conditions (equiv.), *i.e.* rongalite (**2**) and K_2CO_3 (**2**)	Temp (°C)	Time (h)	Yield[b] (%)
1.	$CH_3CN + H_2O$	None	rt	15	10
2.	$CH_3CN + H_2O$	None	70	0.5	70
3.	H_2O + β-CD	None	70	1	50
4.	Acetone + H_2O	None	50	1	35
5.	THF + H_2O	None	70	1	40
6.	DMF + H_2O	None	70	0.5	70
7.	DMSO + H_2O	None	70	0.3	75
8.	MeOH + H_2O	None	60	0.5	75
9.	**EtOH + H_2O**	**None**	**70**	**0.3**	**92**
10.	*i*-PrOH + H_2O	None	70	0.5	70
11.	EtOH + H_2O	Na_2CO_3 instead of K_2CO_3	70	0.5	78
12.	EtOH + H_2O	KOH instead of K_2CO_3	70	0.5	65
13.	EtOH + H_2O	NaOH instead of K_2CO_3	70	0.5	68
14.	EtOH + H_2O	DBU instead of K_2CO_3	70	0.5	70
15.	EtOH + H_2O	NEt_3 instead of K_2CO_3	70	0.5	66
16.	EtOH + H_2O	None	60	1	85
17.	EtOH + H_2O	Rongalite (1.5) instead of (**2**)	70	2	50
18.	EtOH + H_2O	K_2CO_3 (1.5) instead of (**2**)	70	1	75
19.	EtOH + H_2O	Paraformaldehyde (**3**) instead of rongalite	70	5	n.d.
20.	EtOH + H_2O	Formalin (**5**) instead of rongalite	70	5	n.d.

[a] Reaction conditions: isatin **1a** (1 mmol), reagent and base in different solvent mixtures at different temperatures. [b] Yield of the isolated product. rt = room temperature. n.d. = not detected.

Table 2 Scope of isatins[a,b,c,d]





[a] Reaction conditions: isatin **1** (1 mmol), rongalite **2** (2 mmol) and K_2CO_3 (2 mmol) in 2 mL of EtOH + H_2O at 70 °C. [b] Yield of the isolated product. [c] 4 equiv. of rongalite and K_2CO_3 are used. [d] No reaction.

gen atoms are also efficiently involved in the reaction to produce the corresponding products **3x** and **3y** with 85–86% yields, respectively (Table 2).

To demonstrate the generality of this methodology, we also explored the substrate scope of isatin Schiff bases so as to obtain the desired products, *i.e.* 3-(hydroxymethyl)-3-(phenylamino)indolin-2-ones, which show potential anti-cancer activity.[4g] The isatin Schiff bases are prepared from isatins and anilines by the reported method.[24] We tested the scope of the optimized conditions and the results are presented in Table 3.

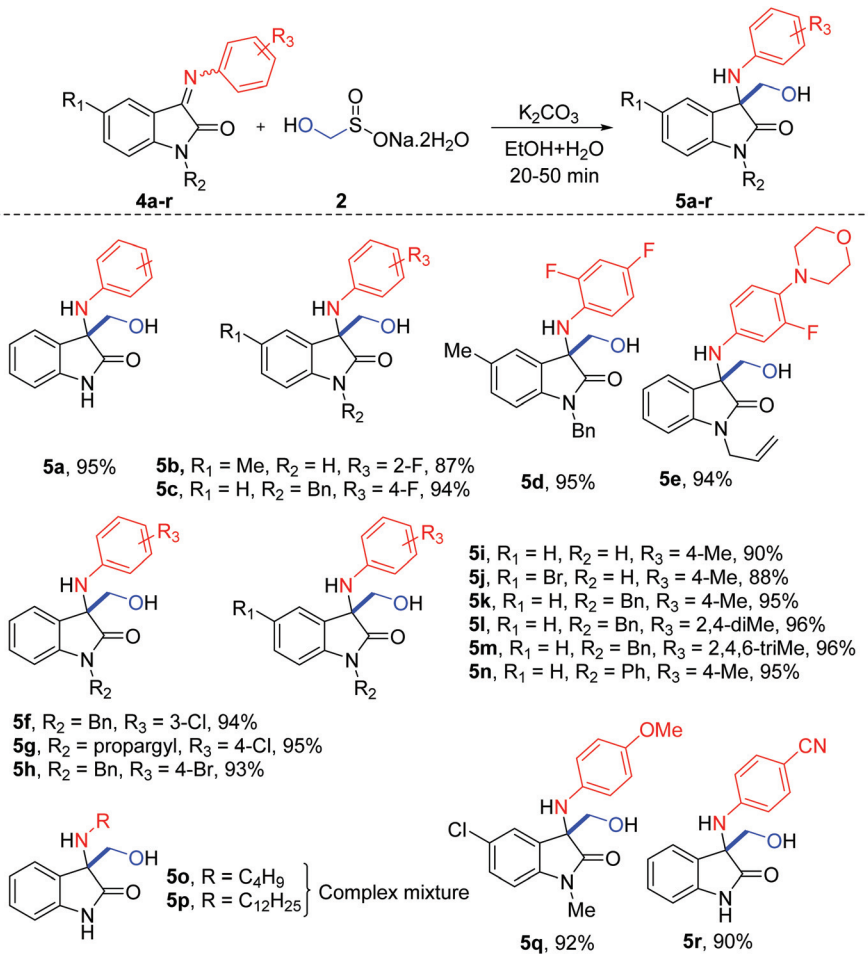
All the synthesized isatin Schiff bases **4a–4r** readily reacted with rongalite to form the corresponding 3-(hydroxymethyl)-3-(phenylamino)indolin-2-ones **5a–5r** in good to excellent yields within 50 min. During the course of the study, we observed that isatins are more reactive with rongalite than with isatin Schiff bases. Notably, isatin Schiff bases containing both electron-donating groups and electron-withdrawing groups on the aniline moiety did not affect the product yields (Table 3, **5i–5m**, **5q** and **5r**). The *N*-phenyl isatin Schiff base also afforded the corresponding oxindole with 95% yield (Table 3, **5n**).

Next, we extended our methodology to isatin-derived ketimines and the results are shown in Table 4. To our delight, unprotected isatin-derived ketimines reacted smoothly under the optimized conditions to furnish *tert*-butyl (3-(hydroxymethyl)-2-oxoindolin-3-yl)carbamates **7a** and **7b** in 86–88% yields, which is not possible with other reported methods.[8] Similarly, the *N*-protected substrates, *i.e.* *N*-benzyl and *N*-methyl isatin-derived ketimines, readily participated in the reaction under the optimized reaction conditions to form the corresponding products **7c–7e** with 91–95% yields (Table 4).

Finally, we evaluated the synthetic potential of our method on a gram scale reaction using 1-benzylindoline-2,3-dione **1t** (3 g, 13 mmol), rongalite **2** (4 g, 26 mmol) and K_2CO_3 (3.6 g, 26 mmol) in EtOH + H_2O (20 mL) at 70 °C, which gave 1-benzyl-3-hydroxy-3-(hydroxymethyl)indolin-2-one **3t** in 88% yield within 10 min (Scheme 2a). We also synthesized the biologically active compound **5d** with IC_{50} = 3.14 μM against the SJSA-1 cell line on a gram scale with 84% yield (Scheme 2b).

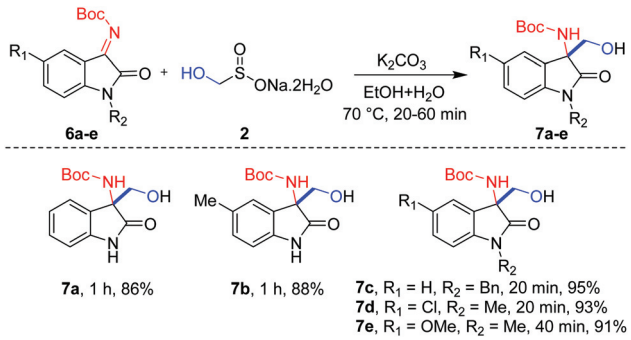
In order to unveil the reaction mechanism, we carried out several control experiments to determine the role of rongalite

Table 3 Scope of isatin Schiff bases[a,b]

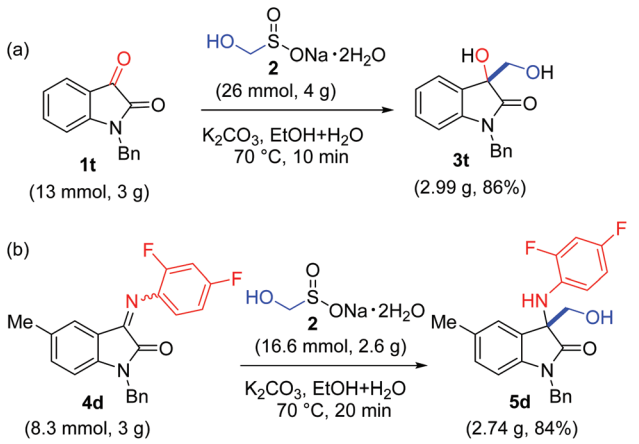


[a] Reaction conditions: isatin Schiff base **4** (1 mmol), rongalite **2** (2 mmol) and K_2CO_3 (2 mmol) in 2 mL of EtOH + H_2O at 70 °C. [b] Yield of the isolated product.

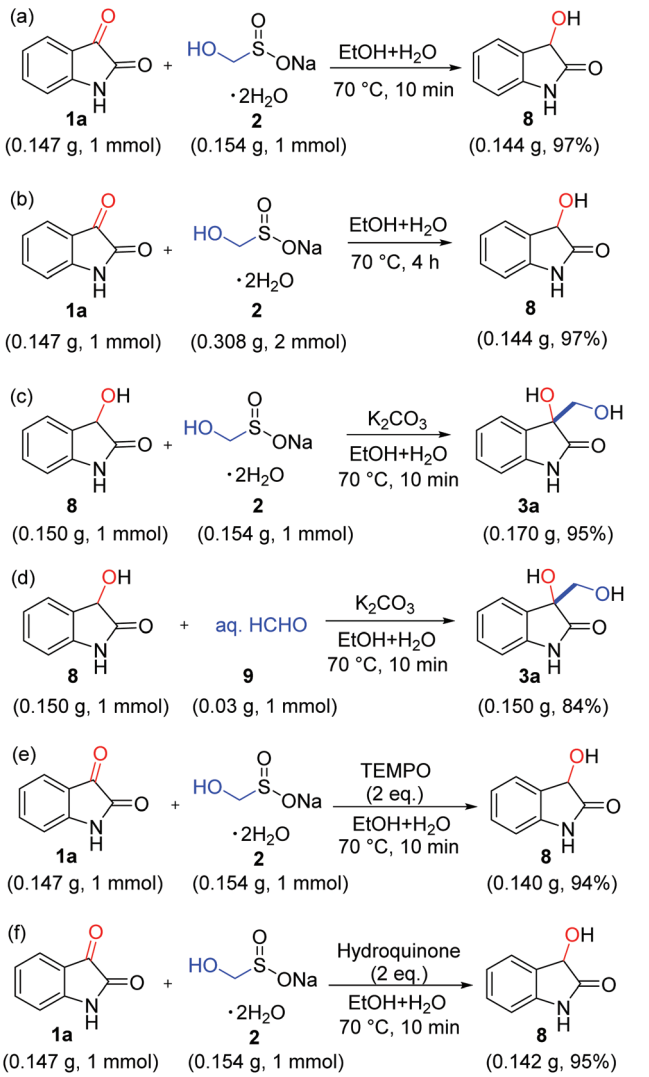
Table 4 Scope of isatin-derived ketimines[a,b]



[a] Reaction conditions: isatin-derived ketimines **6** (1 mmol), rongalite **2** (2 mmol) and K_2CO_3 (2 mmol) in 2 mL of EtOH + H_2O at 70 °C. [b] Yield of the isolated product.



Scheme 2 Gram-scale reactions: (a) on isatins and (b) isatin Schiff bases.



Scheme 3 Control experiments.

and the base (Scheme 3). A reaction between isatin **1a** (1.0 mmol) and rongalite **2** (1.0 mmol) in EtOH + H_2O at 70 °C in the absence of a base resulted in the formation of 3-hydroxyindolin-2-one **8** with 97% yield within 10 min (Scheme 3a). This intermediate is stable even after increasing the quantity of rongalite and the reaction time (Scheme 3b) and was isolated and characterized by ^{1}H and ^{13}C NMR. Later, the intermediate product 3-hydroxyindolin-2-one **8** was treated again with rongalite **2** (1.0 mmol) in the presence of K_2CO_3 at 70 °C and the product **3a** was obtained within 10 min with 95% yield (Scheme 3c). Furthermore, 3-hydroxyindolin-2-one **8** was treated with aq. formaldehyde **9** instead of rongalite in the presence of K_2CO_3 at 70 °C and the formation of product **3a** was observed in 84% yield (Scheme 3d), which revealed that rongalite plays a dual role as a reducing agent and an *in situ* formaldehyde source. Finally, we conducted a few more control experiments with radical scavengers such as TEMPO and hydroquinone to determine the reaction pathway and found no impact on the reaction outcome. These results eliminate the possibility of the radical pathway (Scheme 3e and f). Notably, reductive dimerization of isatins was observed during the photoredox-catalysis *via* the radical mechanism, but we did not observe any reductive dimerization products.[25]

These results revealed that initially, rongalite converts isatin to 3-hydroxy oxindole **8** *via* hydride-free reduction, which further reacts with another mole of rongalite to obtain aldol product **3a** with the help of K_2CO_3.

Furthermore, to gain more insights into the mechanism of the reductive aldol reaction, we performed some ^{1}H NMR experiments. Isatin **1a** (50 mg, 0.35 mmol) was treated with rongalite **2** (2 equiv.) in 1 mL of DMSO-d_6 at 70 °C and after 5 min K_2CO_3 (2 equiv.) was added. A 10 μL aliquot of the reaction mixture was transferred to an NMR tube and diluted with DMSO-d_6 (0.5 mL) and the ^{1}H NMR spectrum was recorded. The ^{1}H NMR spectra of all the aliquots are shown in Fig. 2.

Characterization data of the identified compounds are as follows. When the reaction mixture was analyzed at 5 min, peaks at δ 10.23, 6.17 and 4.83 ppm were observed, which

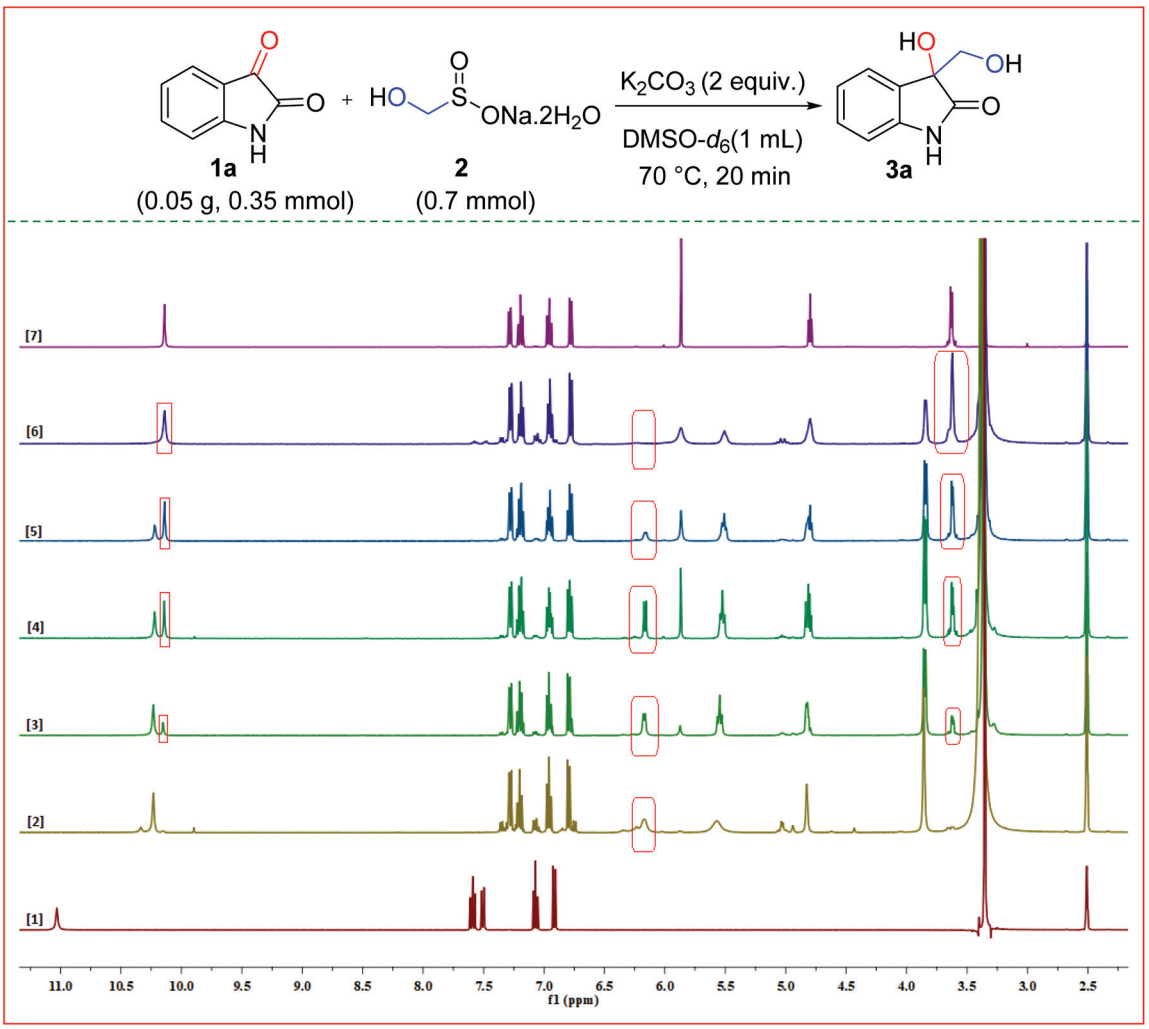
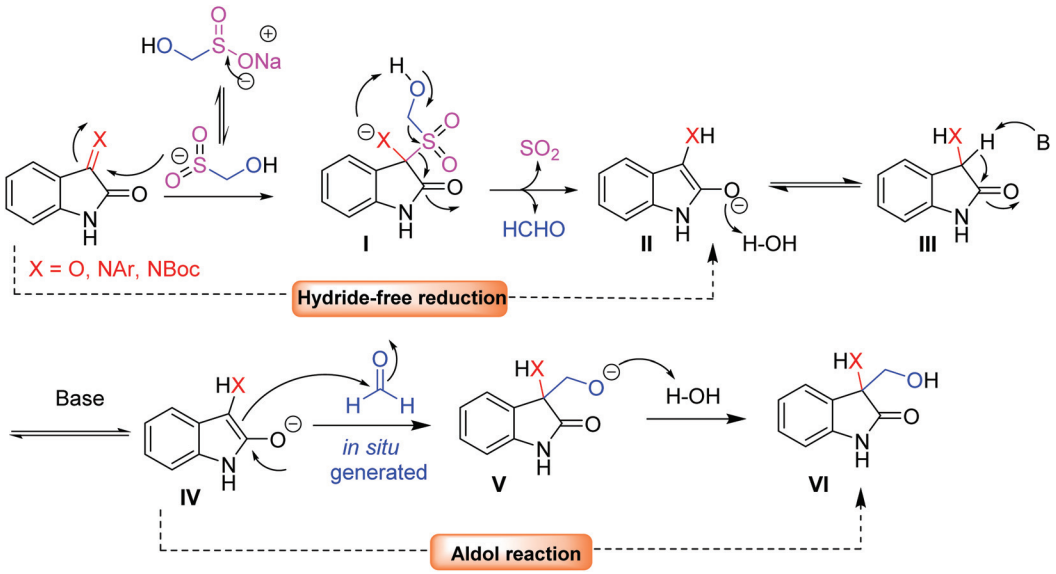


Fig. 2 400 MHz ^{1}H NMR spectra of aliquots taken at different times. All spectra were recorded by diluting an aliquot of the reaction mixture in DMSO-d_6. Panel 1: Isatin; panel 2: isatin and rongalite; panel 3: 5 min after the addition of K_2CO_3; panel 4: after 10 min; panel 5: after 15 min; panel 6: after 20 min; and panel 7: purified compound **3a**.

correspond to the intermediate, *i.e.* 3-hydroxyindolin-2-one **8**. The ^{1}H NMR spectrum of the aliquot (10 min) showed peaks at δ 10.14 ppm representing the NH proton, 5.87 ppm representing the OH proton (C3, quaternary carbon) and 3.62 ppm representing the CH_2 protons of the final product, *i.e.* 3-hydroxy-3-(hydroxymethyl)indolin-2-one **3a**. Notably, a decrease in the intensity of the peak at δ 10.23 ppm and an increase in the intensity of the peak at δ 10.14 were observed during the course of the reaction. Finally, the peak at 10.23 ppm disappeared after 20 min. Similarly, the intensity of the peak at δ 6.17 ppm initially increased (5–10 min) and later decreased (from 10–20 min). Also, the intensity of the peak at δ 3.62 ppm increased between 5 and 20 min. Continuous monitoring of this reaction by ^{1}H NMR showed that the reaction was completed and finally no trace of isatin was detected after 20 min. Also, ^{1}H NMR experiments were conducted on the isatin Schiff base and a similar pattern was observed (Fig. S1 in the ESI†). To gain more insights into the reduction steps, deuterium labelling experiments were conducted with deuterated rongalite and it was observed that 35% of deuterium was incorporated into the product **3a** (Fig. S2 and S3 in the ESI†).

Based on the existing literature,[26] control experiments and collective mechanistic insights from the ^{1}H NMR studies, a full mechanistic proposal is presented in Scheme 4. Initially, rongalite chemoselectively reacts with the carbonyl group of isatin in a nucleophilic addition manner to form intermediate sulfone (I), which liberates formaldehyde and sulfur dioxide to form the intermediate (II). Later, proton abstraction from water forms the intermediate (III), which was identified during the reaction progress on TLC, and isolated and characterized by ^{1}H and ^{13}C NMR. Furthermore, the base abstracts the proton from the intermediate (III) to form an enolate which further undergoes the aldol reaction with the *in situ* generated formaldehyde to form the intermediate (V) with subsequent abstraction of the proton from water to form the final product (VI).



Scheme 4 Plausible reaction mechanism.

Conclusions

We have developed a transition-metal and hydride-free reductive aldol reaction for the synthesis of biologically active 3-hydroxy-3-(hydroxymethyl)indolin-2-ones and 3-amino-3-(hydroxymethyl)indolin-2-ones from isatin derivatives. Rongalite, a commercially available inexpensive reagent (1 g, 0.03$), plays a vital role as a reducing agent and a source of the C1 unit. This transition metal-free reductive aldol reaction provides rapid access to various 3,3′-disubstituted oxindoles with 79–96% yields. Also, this method enables the gram scale synthesis of the potential anti-cancer agent 1-benzyl-3-((2,4-difluorophenyl)amino)-3-(hydroxymethyl)-5-ethylindolin-2-one (**5d**) in 84% yield.

Experimental section

General experimental considerations

Isatins, anilines, sodium hydroxymethanesulfinate dihydrate, all other reagents and organic solvents were purchased from a commercial source and used as received. The reactions were monitored by analytical TLC on 200 μm aluminium-foil-backed silica gel plates. Column chromatography was performed using 100–200 mesh silica gel. NMR (^{1}H and ^{13}C) spectra were recorded on a 300/400/500 MHz spectrometer using $CDCl_3$, DMSO-d_6 and MeOD as solvents and TMS as an internal standard. Chemical shifts were reported in parts per million (ppm) and coupling constants (J) were reported in hertz (Hz). Standard abbreviations were used to designate resonance multiplicities. FT-IR spectra were recorded on a PerkinElmer spectrometer. Melting points were determined on a Stuart SMP30 apparatus and are uncorrected. HRMS spectra were recorded using an Agilent Q-TOF 6230 instrument.

General procedures

General procedure (A) for the synthesis of 3-hydroxy-3-(hydroxymethyl)indolin-2-one derivatives (3a–y). An oven dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with the appropriate isatin derivative (1 mmol), rongalite (2 mmol), K_2CO_3 (2 mmol) and EtOH + H_2O (2 mL, 8 : 2 v/v). The mixture was stirred at 70 °C for an appropriate time (10–20 min). The progress of the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion of the reaction, EtOH was evaporated under vacuum and extracted with ethyl acetate (3 × 10 mL). The organic layers were separated, dried (Na_2SO_4) and evaporated to give a residue that was purified on a short pad of silica gel by column chromatography using hexanes and ethyl acetate as an eluent.

General procedure (B) for the synthesis of 3-(hydroxymethyl)-3-(phenylamino)indolin-2-one derivatives (5a–r). An oven dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with the appropriate isatin Schiff base/*N*-protected isatin Schiff base (1 mmol), rongalite (2 mmol), K_2CO_3 (2 mmol) and EtOH + H_2O (2 mL, 8 : 2 v/v). The mixture was stirred at 70 °C for an appropriate time (20–50 min). The progress of the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion of the reaction, EtOH was evaporated under vacuum and extracted with ethyl acetate (3 × 10 mL). The organic layers were separated, dried (Na_2SO_4) and evaporated to give a residue that was purified on a short pad of silica gel by column chromatography using hexanes and ethyl acetate as an eluent.

General procedure (C) for the synthesis of *tert*-butyl (3-(hydroxymethyl)-2-oxoindolin-3-yl)carbamate derivatives (7a–e). An oven dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with the appropriate isatin-derived ketimine (0.5 mmol), rongalite (1 mmol), K_2CO_3

(1 mmol) and EtOH + H_2O (2 mL, 8 : 2 v/v). The mixture was stirred at 70 °C for an appropriate time (20–60 min). The progress of the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion of the reaction, EtOH was evaporated under vacuum and extracted with ethyl acetate (3 × 10 mL). The organic layers were separated, dried (Na_2SO_4) and evaporated to give a residue that was purified on a short pad of silica gel by column chromatography using hexanes and ethyl acetate as an eluent.

Experimental procedure (D) for the synthesis of 3-hydroxyindolin-2-one (8). An oven dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with isatin **1a** (1 mmol), rongalite **2** (1 mmol) and EtOH + H_2O (2 mL, 8 : 2 v/v). The mixture was stirred at 70 °C for 10 min. The progress of the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion of the reaction, EtOH was evaporated under vacuum and extracted with ethyl acetate (3 × 10 mL). The organic layers were separated, dried (Na_2SO_4) and evaporated to give a residue that was purified on a short pad of silica gel by column chromatography using hexanes and ethyl acetate as an eluent.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

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