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# Transition metal-free functionalization of 2-oxindoles *via* sequential aldol and reductive aldol reactions using rongalite as a C1 reagent†

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A sequential one-pot classical aldol, transition-metal and hydride-free reductive aldol reaction is reported here for C(sp3)- H functionalization of 2-oxindoles using the multifaceted reagent rongalite. Here, rongalite functions as a hydride-free reducing agent and double C1 unit donor. This protocol enables the synthesis of a wide range of 3-methylindoline-2-ones and 3-(hydroxymethyl)-3-methylindolin-2-ones from 2-oxindoles (65–95% yields), which are the synthetic precursors for many natural products. Some of the important aspects of this synthetic approach include one-pot methylation and hydroxymethylation, low-cost rongalite (*ca.* $0.03 per 1 g), mild reaction conditions and applicability to gram-scale synthesis.

## Introduction

Oxindoles are ubiquitous motifs in bioactive natural products and pharmaceutical lead compounds,[1] and have captivated the synthetic community to develop novel 2-oxindole scaffolds with pharmacological properties.[2,3] Among 2-oxindoles, 3-methyl-2-oxindoles are versatile reactants in organic and natural product synthesis,[4] leading to the development of new protocols. Traditionally, 3-methylindoline-2-ones are prepared from 2-oxindoles using *n*-BuLi with MeI.[5] After that, many procedures have been established to accomplish 3-methyl-2-oxindoles *viz*., olefin hydrocarbamoylation[6] and Friedel–Crafts alkylation,[7] but these methods each suffer from their own set of limitations such as the formation of side products, poor regioselectivity and cryogenic conditions.

In addition, 3-methyl-2-oxindoles are also accessed by various reducing[8] and oxidizing[9] protocols. Recently, a borrowing hydrogen approach has been explored by Morrill *et al.*[10] and Venkatasubbaiah *et al.*[11] to prepare 3-methyl-2-oxindoles using transition metal catalysts with methanol as a methylating agent. Parallelly, Pulis *et al.* also employed pempidine as a C1 unit source with $B(C_6F_5)_3$ as a catalyst.[12] Although a borrowing hydrogen strategy gives better results, it requires high temperatures and long reaction periods. Overall, the methods developed for 3-methyl-2-oxindoles require expensive chemicals, transition metal catalysts, long reaction times and limited substrate scope.

In addition to 3-methyl-2-oxindoles, 3-hydroxymethyl-3-methyl-2-oxindoles are key intermediates in the total synthesis of (−)-physostigmine and (−)-esermethole,[13] albeit limited methods are available for the synthesis of 3-(hydroxymethyl)-3-methylindolin-2-ones. In 2010, Feng *et al.* reported 1,3-bis(hydroxymethyl)-2-oxindoles from 3-methyl oxindoles, but the high reactivity of formalin limits the selectivity towards C-aldol products even when 1 equiv. of formalin is used.[14] In 2016, Wang *et al.* developed the oxidative rearrangement of pre-functionalized indoles (Scheme 1b).[15] Also, some strategies include domino Heck/borylation (Scheme 1a)[16] and aminooxyarylation of *N*-arylacrylamides (Scheme 1a),[17] which give intermediates that require one more step and a longer reaction time to obtain the desired products. Recently, He *et al.* reported oxone-mediated arylhydroxylation of *N*-arylacrylamides (Scheme 1a),[18] but it suffers from regioselectivity. In this context, we are developing commercially viable and transition metal-free protocols using a green reagent "rongalite" in the presence of a mild base.

Sodium hydroxymethanesulfinate dihydrate (SHM), commonly known as rongalite, is an industrial product that is a potential substitute for toxic formaldehyde.[19] Kotha and co-workers widely used rongalite in the organic synthesis and named it as a green reagent.[20,21] It acts as a super electron donor,[22,23] and a source of the C1 unit and sulfoxylate dianion ($SO_2^{2-}$).[24–31] Recently, the reductive aldol reaction, which is one of the modified versions of the aldol reaction, has become a promising method for organic synthesis.[32]

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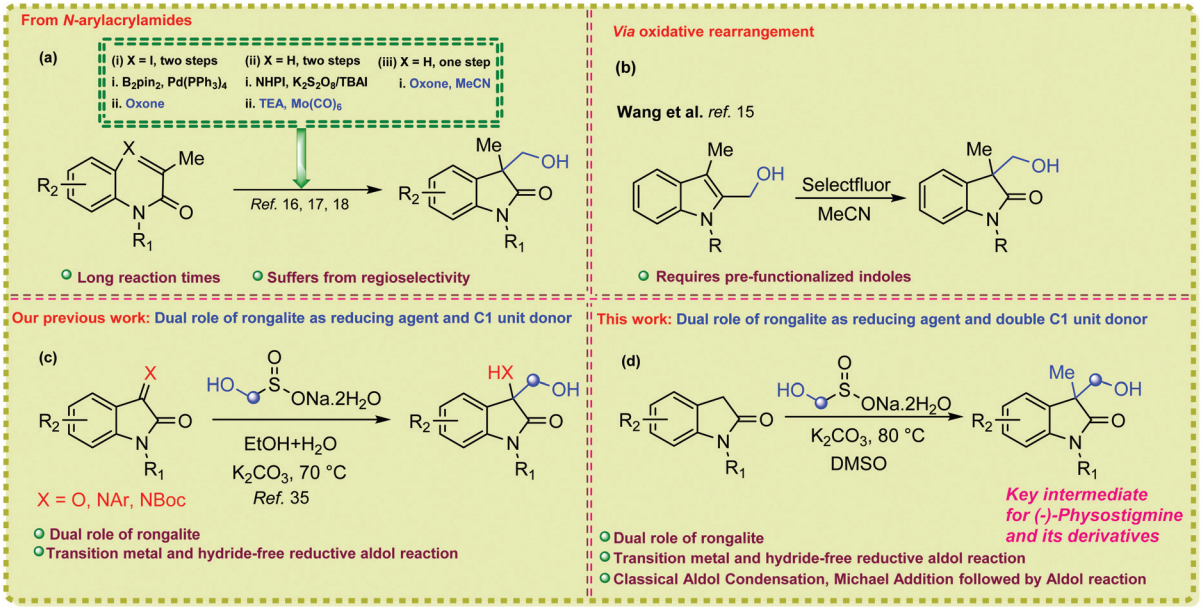



**Scheme 1** The synthesis of 3,3′-disubstituted oxindoles.

Although there are several variations of RAR, metal and hydride-free RARs have been attracting chemists from all over the world in recent years.[33] In continuation of our efforts on exploring the synthetic utility of rongalite[34] and reductive aldol reactions (Scheme 1c),[35] herein, we report a domino aldol condensation reaction followed by the transition metal and hydride-free reductive aldol reaction to synthesize 3-(hydroxymethyl)-3-methylindolin-2-ones using multifaceted rongalite as the reducing agent and double C1 unit donor.

## Results and discussion

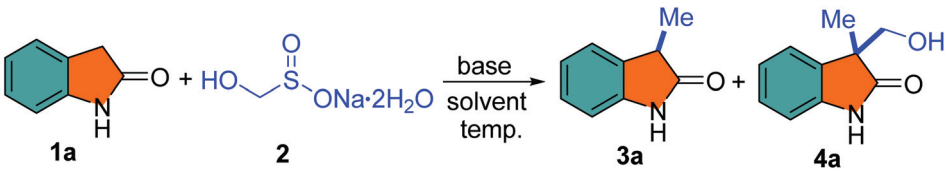
To test our hypothesis, the reaction of indolin-2-one **1a** (1 mmol) was attempted with rongalite **2** (2 mmol) and $K_2CO_3$ (2 mmol) in EtOH + $H_2O$ (8 : 2 v/v) at room temperature and it was observed that there was no progress in the reaction even after 24 h (Table 1, entry 1). Later, the same reaction was carried out at 80 °C, which interestingly resulted in a mixture of two products *i.e.*, 3-methylindolin-2-one **3a** and 3-(hydroxymethyl)-3-methylindolin-2-one **4a** in 40% and 20% yields, respectively (Table 1, entry 2), which were later confirmed by $^1$H, $^{13}$C NMR and HRMS data.

Inspired by this preliminary result, further screening was carried out using polar protic solvents such as aq. MeOH and aq. *i*-PrOH and resulted in a mixture of products **3a** and **4a** (Table 1, entries 3 and 4). Furthermore, we tested the reaction in chlorinated solvents such as aq. $CHCl_3$ and aq. 1,2-DCE and **3a** was obtained predominantly, albeit in low yields (Table 1, entries 5 and 6). These results prompted us to test the effects of non-polar solvents on product selectivity. Thus, the same reaction was conducted in non-polar solvents such as aq. benzene, aq. *p*-xylene and aq. toluene. To our delight, as we go from aq. benzene to aq. *p*-xylene, the yield of **3a** was increased while that of **4a** was decreased (Table 1, entries 7 and 8). When aq. toluene was used, 3-methylindolin-2-one **3a** was obtained predominantly in 81% yield within 1 h without the formation of any trace amounts of **4a** (Table 1, entry 9). Furthermore, an increase in the temperature led to improved yields (Table 1, entries 10–12). Notably, prolonging the reaction time and increasing the equiv. of rongalite did not affect the product yield of **3a** (Table 1, entries 13 and 14).

Later, we shifted our attention towards the synthesis of **4a** selectively. In this regard, screening was done in polar aprotic solvents such as aq. acetone, aq. THF, aq. $CH_3CN$, DMF and DMSO (Table 1, entries 15–19). Among all, a good amount of **4a** was observed in DMSO (Table 1, entry 19). With this promising result, next, we screened the equiv. of rongalite and base and acquired **4a** predominantly (Table 1, entries 20 and 21). Furthermore, varying the temperature and loadings of rongalite was not useful (Table 1, entries 22 and 23). Moreover, we tested the reaction with organic and inorganic bases and obtained inferior results (Table 1 entries 24–27). Also, to identify the source of C1 unit in **4a**, a test reaction was conducted on 3-methylindolin-2-one **3a** with $K_2CO_3$ and DMSO at 80 °C in the absence of rongalite but they were found to be unreactive (Table 1, entry 28). This result clearly indicates that the C1 unit is coming from rongalite and not from the DMSO solvent. Therefore, the optimized reaction conditions are entry 11 and entry 21 for obtaining 3-methylindolin-2-one **3a** and 3-(hydroxymethyl)-3-methylindolin-2-one **4a**, respectively.

With the optimized reaction conditions in hand for compound **3a** (Table 1, entry 11), we commenced evaluating the scope of the reaction with various 2-oxindoles (Table 2). Electron-donating groups on the benzene ring of 2-oxindole,

**Table 1** Optimization of the reaction conditions[a]

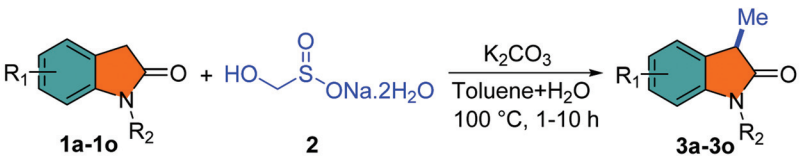



1a 2 3a 4a

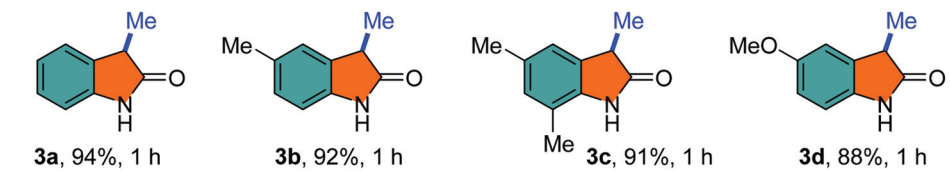
| Entry | Solvent (8 : 2 v/v) | Rongalite (equiv.) | Base (equiv.) | Temp. (°C) | Time (h) | Yield[b] (%) 3a | 4a |
|---|---|---|---|---|---|---|---|
| 1 | EtOH + $H_2O$ | 2 | $K_2CO_3$ (2) | rt | 24 | n.r. | n.r. |
| 2 | EtOH + $H_2O$ | 2 | $K_2CO_3$ (2) | 80 | 6 | 40 | 20 |
| 3 | MeOH + $H_2O$ | 2 | $K_2CO_3$ (2) | 65 | 6 | 49 | 16 |
| 4 | *i*-PrOH + $H_2O$ | 2 | $K_2CO_3$ (2) | 80 | 6 | 40 | 17 |
| 5 | $CHCl_3$ + $H_2O$ | 2 | $K_2CO_3$ (2) | 60 | 6 | 45 | n.d. |
| 6 | 1,2-DCE + $H_2O$ | 2 | $K_2CO_3$ (2) | 80 | 6 | 60 | n.d. |
| 7 | Benzene + $H_2O$ | 2 | $K_2CO_3$ (2) | 80 | 6 | 55 | 10 |
| 8 | *p*-Xylene + $H_2O$ | 2 | $K_2CO_3$ (2) | 80 | 1 | 70 | 5 |
| 9 | Toluene + $H_2O$ | 2 | $K_2CO_3$ (2) | 80 | 1 | 81 | n.d. |
| 10 | Toluene + $H_2O$ | 2 | $K_2CO_3$ (2) | 90 | 1 | 85 | n.d. |
| **11** | **Toluene + $H_2O$** | **2** | **$K_2CO_3$ (2)** | **100** | **1** | **94** | **n.d.** |
| 12 | Toluene + $H_2O$ | 2 | $K_2CO_3$ (2) | 110 | 1 | 94 | n.d. |
| 13 | Toluene + $H_2O$ | 2 | $K_2CO_3$ (2) | 100 | 6 | 94 | n.d. |
| 14 | Toluene + $H_2O$ | 3 | $K_2CO_3$ (2) | 100 | 1 | 94 | n.d. |
| 15 | Acetone + $H_2O$ | 2 | $K_2CO_3$ (2) | 55 | 6 | 30 | 10 |
| 16 | THF + $H_2O$ | 2 | $K_2CO_3$ (2) | 60 | 6 | 5 | n.d. |
| 17 | $CH_3CN$ + $H_2O$ | 2 | $K_2CO_3$ (2) | 80 | 6 | 40 | 15 |
| 18 | DMF | 2 | $K_2CO_3$ (2) | 80 | 6 | 35 | 43 |
| 19 | DMSO | 2 | $K_2CO_3$ (2) | 80 | 6 | 35 | 59 |
| 20 | DMSO | 2.5 | $K_2CO_3$ (2.5) | 80 | 6 | 14 | 81 |
| **21** | **DMSO** | **3** | **$K_2CO_3$ (2.5)** | **80** | **5** | **n.d.** | **91** |
| 22 | DMSO | 3 | $K_2CO_3$ (2.5) | 70 | 6 | trace | 85 |
| 23 | DMSO | 3.5 | $K_2CO_3$ (2.5) | 80 | 5 | n.d. | 91 |
| 24 | DMSO | 3 | DBU (2.5) | 80 | 6 | n.d. | 79 |
| 25 | DMSO | 3 | 4-DMAP (2.5) | 80 | 6 | n.d. | 51 |
| 26 | DMSO | 3 | $Cs_2CO_3$ (2.5) | 80 | 6 | n.d. | 80 |
| 27 | DMSO | 3 | KOH (2.5) | 80 | 6 | n.d. | 85 |
| 28[c] | DMSO | — | $K_2CO_3$ (2) | 80 | 6 | — | n.d. |

[a] Reaction conditions: indolin-2-one **1a** (1 mmol), rongalite **2** and base in different reaction media at different temperatures. [b] Yields of isolated products. [c] 3-Methylindolin-2-one **3a** (1 mmol) and $K_2CO_3$ (2 equiv.) in DMSO at 80 °C. rt = room temperature. n.r. = no reaction. n.d. = not detected.

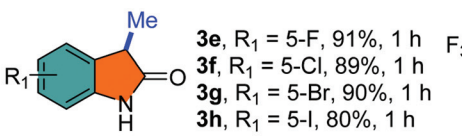
**Table 2** Substrate scope of rongalite mediated 3-methylation of indolin-2-ones[a,b,c]



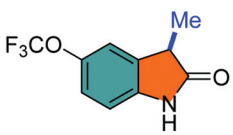

1a-1o 2 3a-3o



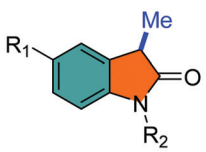

**3a**, 94%, 1 h **3b**, 92%, 1 h **3c**, 91%, 1 h **3d**, 88%, 1 h




**3e**, $R_1$ = 5-F, 91%, 1 h
**3f**, $R_1$ = 5-Cl, 89%, 1 h
**3g**, $R_1$ = 5-Br, 90%, 1 h
**3h**, $R_1$ = 5-I, 80%, 1 h
**3i**, $R_1$ = 6-Cl, 90%, 1 h
**3j**, $R_1$ = 6-Br, 89%, 1 h
**3k**, $R_1$ = 7-F, 90%, 1 h
**3l**, $R_1$ = 7-Cl, 89%, 1 h



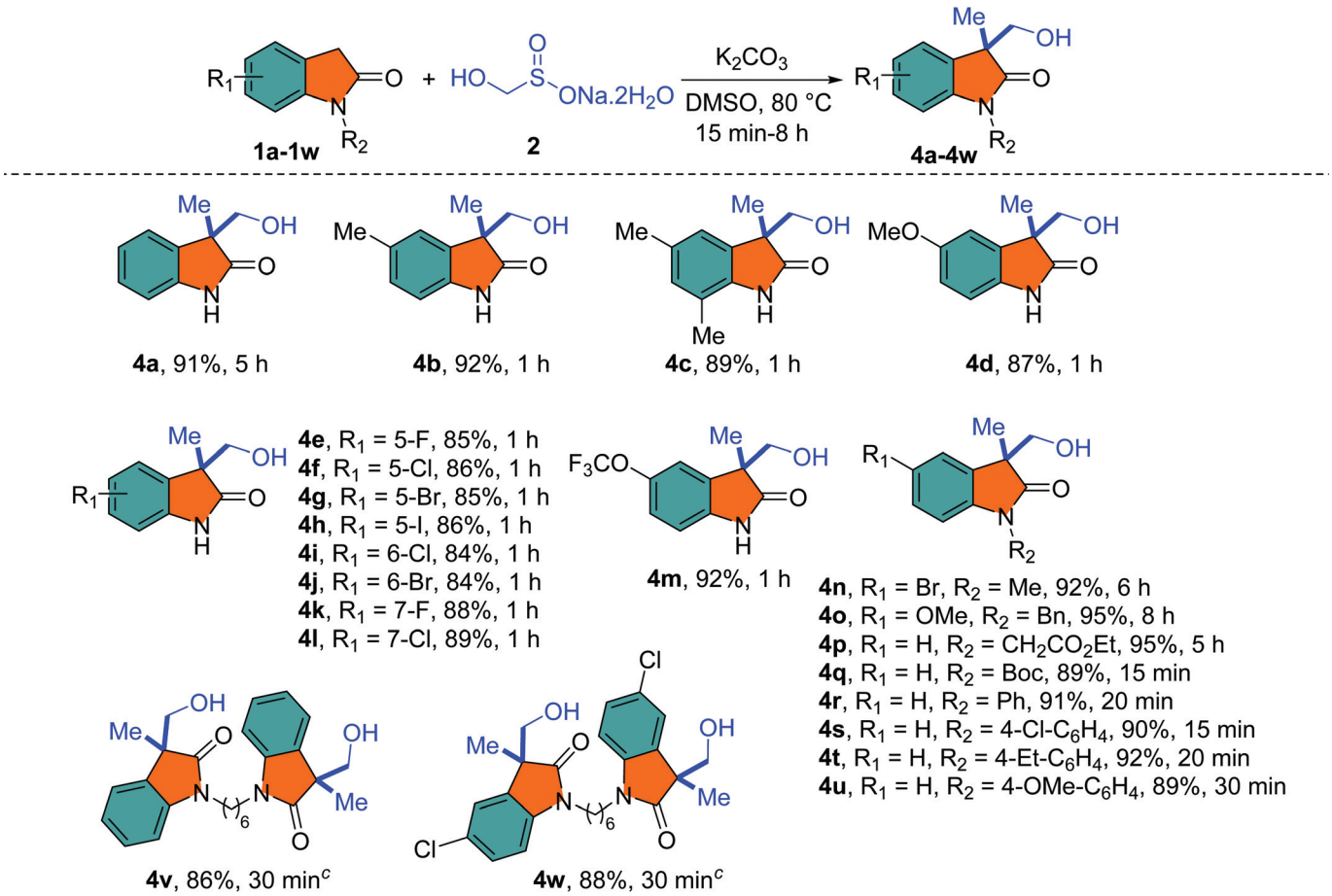

**3m**, 75%, 1 h




**3n**, $R_1$ = Br, $R_2$ = Me, 71%, 5 h[c]
**3o**, $R_1$ = OMe, $R_2$ = Bn, 65%, 10 h[c]

[a] Reaction conditions: indolin-2-one **1** (1 mmol), rongalite **2** (2 mmol) and $K_2CO_3$ (2 mmol) in 2 mL of toluene + $H_2O$ (8 : 2 v/v) at 100 °C. [b] Yields of isolated products. [c] KOH (2 mmol) was used instead of $K_2CO_3$.

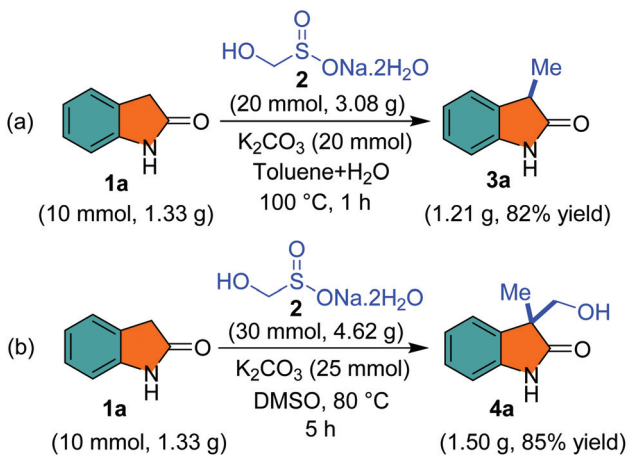
Table 3 Substrate scope of rongalite mediated 3,3′-methylation and hydroxymethylation of indolin-2-ones[a,b,c]




[a] Reaction conditions: indolin-2-one **1** (1 mmol), rongalite **2** (3 mmol) and $K_2CO_3$ (2.5 mmol) in 2 mL of DMSO at 80 °C. [b] Yields of isolated products. [c] Rongalite (6 mmol) and $K_2CO_3$ (5 mmol) were used.

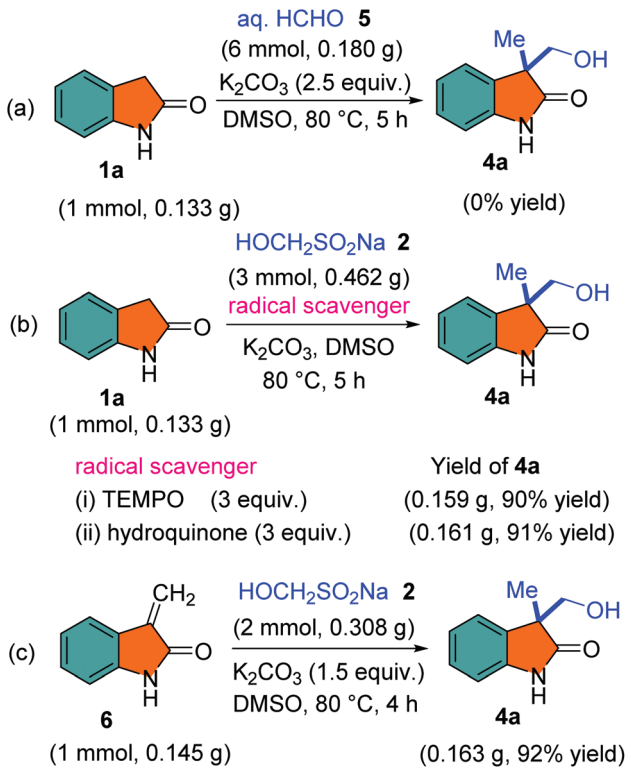
such as methyl and methoxy, underwent the reaction smoothly with rongalite to furnish **3b–3d** in 88–92% yields (Table 2). Halogens (F, Cl, Br and I) present at various positions of the benzene ring of oxindoles readily participated in the reaction to produce **3e–3l** in 80–91% yields (Table 2). An electron-withdrawing group on the benzene ring, *i.e.*, trifluoromethoxy-substituted oxindole, is also efficiently involved in the reaction to afford **3m** in 75% yield (Table 2). Also, *N*-alkylated oxindoles offered the respective 3-methyl oxindoles **3n** and **3o** in 5–10 h (Table 2).

Next, we paid attention to the synthesis of diversely substituted 3-(hydroxymethyl)-3-methylindolin-2-ones **4** under optimized conditions (Table 1, entry 21). Electron-donating groups present on the benzene ring, such as methyl and methoxy substituted oxindoles, reacted smoothly with rongalite to furnish **4b–4d** in 87–92% yields (Table 3). This method can also tolerate various halogen derivatives (F, Cl, Br, and I) and afforded hydroxymethylated products **4e–4l** in 84–89% yields (Table 3). The electron-withdrawing group *i.e.*, trifluoromethoxy substituted oxindole, was also efficiently involved in the reaction to deliver **4m** in 92% yield (Table 3). Both *N*-alkylated and *N*-arylated oxindoles effortlessly reacted with rongalite and offered the respective products **4n and 4o** and **4r–4u** in 89–95% yields and, moreover, we observed that *N*-arylated oxindoles were more reactive with rongalite compared to




Scheme 2 Gram-scale synthesis.

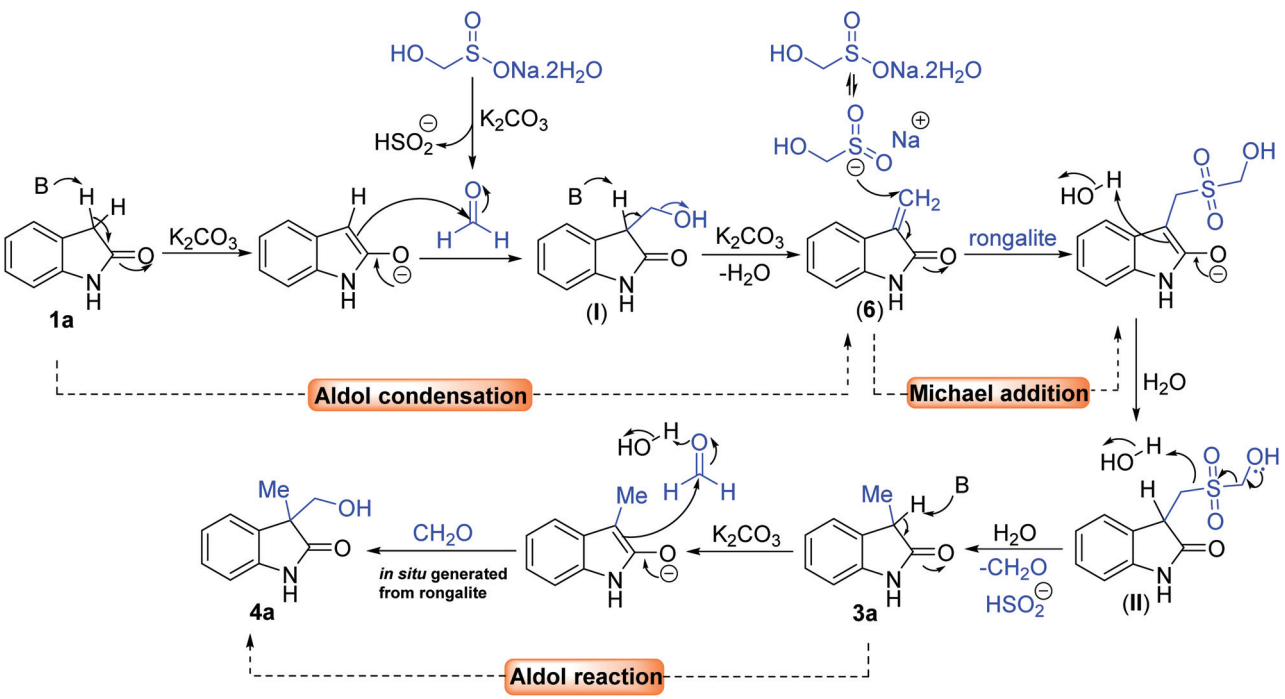
*N*-alkylated oxindoles. Ester and Boc protecting groups were also stable with rongalite and delivered **4p and 4q** in 95% and 89% yields (Table 3). This protocol is also applicable to bis-oxindoles and products **4v and 4w** were obtained in 86% and 88% yields (Table 3).




**Scheme 3** Control experiments.

Finally, we evaluated the gram-scale synthesis of the developed protocols by employing indolin-2-one **1a** (10 mmol), rongalite **2** (20 mmol) and $K_2CO_3$ (20 mmol) in 15 mL of toluene + $H_2O$ (8 : 2 v/v) at 100 °C for 1 h, which afforded the 3-methylindolin-2-one **3a** in 82% yield (Scheme 2a). Also, 3-(hydroxymethyl)-3-methylindolin-2-one **4a** was synthesized in 85% yield on a gram scale using indolin-2-one **1a** (10 mmol), rongalite **2** (30 mmol) and $K_2CO_3$ (25 mmol) in 15 mL of DMSO at 80 °C for 5 h (Scheme 2b).

In order to unveil the reaction mechanism and to understand the role of rongalite, we conducted some control experiments (Scheme 3). Firstly, we conducted a reaction between indolin-2-one **1a** (1 mmol), aq. formaldehyde **5** (6 mmol) and $K_2CO_3$ (2.5 mmol) in DMSO at 80 °C for 5 h, and the formation of product **4a** *i.e.*, 3-(hydroxymethyl)-3-methylindolin-2-one, was not observed. This control experiment indicates that rongalite is not only acting as a source of the C1 unit but also working as a reducing agent (Scheme 3a). Furthermore, we performed two more control experiments using radical scavengers, such as TEMPO and hydroquinone, to reveal the reaction pathway but observed no significant change in the product **4a** yield (Scheme 3b). In addition, we conducted another reaction between 3-methyleneindolin-2-one **6** (1 mmol) and rongalite **2** (2 mmol) in the presence of $K_2CO_3$ (1.5 mmol) in DMSO at 80 °C. To our delight, the product *i.e.*, 3-(hydroxymethyl)-3-methylindolin-2-one **4a**, was formed in 92% yield within 4 h supporting our hypothesis (Scheme 3c). Based on this control experiment, we are assuming that 3-methyleneindolin-2-one **6** could be a possible reac-




**Scheme 4** Plausible reaction mechanism.

tion intermediate. There is mounting evidence that 3-methylindolin-2-one **3a** is an intermediate for the final product **4a** (see Fig. S1†) and it was also observed from the control experiment that 3-methyleneindolin-2-one **6** is another intermediate.

Based on the existing literature[31,35,36] and collected information, a full mechanistic proposal is summarized in Scheme 4. Firstly, 2-oxindole reacts with *in situ* generated formaldehyde from rongalite under basic conditions to form intermediate (**I**), which further undergoes dehydration to yield intermediate **6**. Later, rongalite undergoes Michael addition with intermediate **6** to form intermediate (**II**). Furthermore, the decomposition of (**II**) leads to the formation of 3-methylindolin-2-one **3a** *via* loss of formaldehyde and sulfur dioxide. Finally, **3a** undergoes the second aldol reaction with *in situ* generated formaldehyde to form the desired product **4a** under basic conditions.

## Conclusions

We have developed an efficient sequential one-pot methylation and hydroxymethylation strategy, which involves a classical aldol condensation reaction followed by a reductive aldol reaction using rongalite. In this method, rongalite is an industrial product with low cost (1 g, $0.03), which plays a vital role as a hydride-free reducing agent and double C1 unit donor. This transition metal and hydride-free reductive aldol protocol allows rapid access to 3-methylindoline-2-ones and 3-(hydroxymethyl)-3-methylindolin-2-ones, which are the key building blocks of many natural products such as (−)-physostigmine and its derivatives. This one-pot method is also applicable to gram-scale synthesis for industrial applications.

## Conflicts of interest

There are no conflicts to declare.

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