

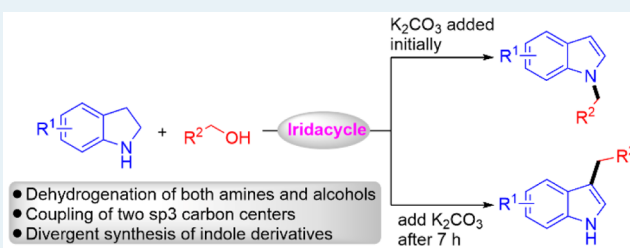
Divergent Dehydrogenative Coupling of Indolines with Alcohols

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Supporting Information

ABSTRACT: The dehydrogenative coupling of indolines with alcohols catalyzed by an iridium complex has been achieved to afford both N- and C3-alkylated indoles selectively, by simply changing the addition time of a base additive. The iridacycle catalyst plays multiple roles in these reactions, which dehydrogenates both amines and alcohols and catalyzes the coupling reactions. Mechanistic studies reveal that a borrowing hydrogen-dehydrogenation process and a dehydrogenation-borrowing hydrogen process are involved in N-alkylation and C3-alkylation reactions, respectively. The C3-alkylation reaction involves the direct coupling of two sp³ carbon centers.

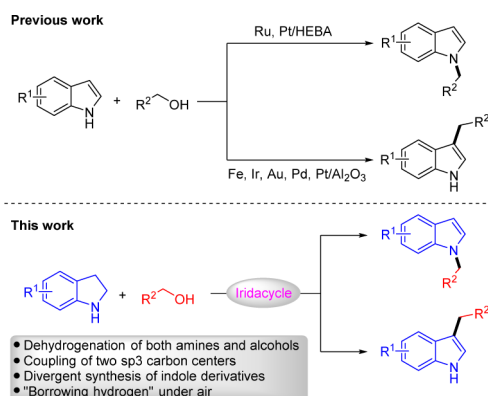
KEYWORDS: dehydrogenation, indole, alcohol, iridium, cross coupling



Indole moieties are found in many natural products, pharmaceuticals, and dyes, as well as fine chemicals.¹ The selective functionalization of indoles has attracted great attention.² The use of alcohol as alkylating reagents for indole alkylation is appealing, with water as the only byproduct. However, control of the N-alkylation³ or C3-alkylation⁴ selectivity is not easy, with most systems preferring C3-alkylation (see Scheme 1). To the best of our knowledge, the regioselective access to both N- and C3-alkylated indoles with a single catalyst has not been reported yet.

Dehydrogenation as a substrate activating strategy has found broad application in organic synthesis.⁵ The dehydrogenation of amines and alcohols to imines/enamines and carbonyl compounds has been utilized in many green transformations, e.g., alkylation with alcohols^{5e,6} via a borrowing hydrogen strategy,^{5b,7} and amide formation from amines and alcohols.^{5d}

Scheme 1. Divergent Synthesis of N- and C3-Alkylated Indoles



In most of the examples reported, the catalyst dehydrogenates either the amine or the alcohol substrates. For example, a Ru catalyst was able to dehydrogenate cyclic amines, allowing for C3-alkylation of amines with aldehydes;⁸ and catalysts were reported to catalyze the functionalization of indoles with alcohols via dehydrogenation.^{4c,f-h} A catalyst capable of dehydrogenating both amines and alcohols is desirable, because it would allow for more diverse coupling patterns. However, such catalysts are rare,⁹ and, to the best of our knowledge, the catalytic dehydrogenation of both amines and alcohols in a single dehydrogenative coupling reaction is still elusive. Herein, we present a catalyst capable of dehydrogenating both amines and alcohols, allowing for the divergent dehydrogenative coupling of indolines with alcohols (see Scheme 1). Mechanistic studies suggest that a borrowing hydrogen-dehydrogenation process for N-alkylation and a dehydrogenation-borrowing hydrogen process for C3-alkylation under aerobic conditions are involved.

Recently, we disclosed that cyclometalated iridium catalysts (iridacycles)¹⁰ were able to dehydrogenate both alcohols and amines under the same mild conditions, allowing for N-alkylation of amines with both alcohols and amines.¹¹ We envisioned that mixing alcohols or amines that are capable of dehydrogenation in one pot, novel coupling patterns might be expected. In our previous work,¹¹ the reaction of indolines with benzyl alcohol afforded N-benzylindole (**5a**) with 1 mol % of catalyst **1** in 2,2,2-trifluoroethanol (TFE) under argon at 100 °C in the presence of K₂CO₃ for 12 h. By lowering the catalyst loading to 0.5 mol %, a mixture of **4a**, **5a**, and **6a** were observed

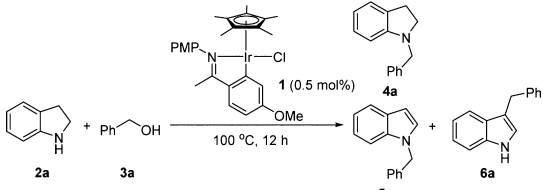
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(Table 1, entry 1). Performing the reaction under air, **5a** was formed preferentially within 12 h with 0.5 mol % of **1** (Table 1,

Table 1. Dehydrogenative Coupling of Indoline with Benzyl Alcohol^a



entry	air/argon	Yield (%)		
		4a	5a	6a
1	argon	56	37	trace
2	air	trace	82	5
3 ^b	air	n.d. ^c	trace	90
4 ^d	air	n.d. ^c	n.d. ^c	n.d. ^c

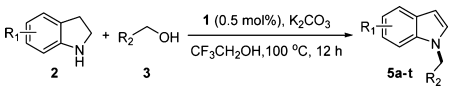
^aReaction conditions: **2a** (1 mmol), **3a** (1 mmol), **1** (0.005 mmol), K₂CO₃ (0.75 mmol), CF₃CH₂OH (2 mL), 100 °C, 12 h, isolated yield; PMP = para-methoxyphenyl. ^bK₂CO₃ was added after 7 h and further reacted for 12 h. ^cn.d. = not detected. ^dWithout **1**.

entry 2). Interestingly, when the base (K₂CO₃) was added after 7 h, and the reaction mixture was allowed to react for an additional 12 h under air, C3-alkylated product **6a** was isolated in 90% yield (Table 1, entry 3). The catalyst is essential for these reactions. None of the products were detected and the starting materials remained unreacted in its absence (Table 1, entry 4). Other metal complexes showed little or no activity for the coupling reactions under the standard conditions (see Table S1 in the Supporting Information (SI)). For example, [Cp*IrCl₂]₂, which is an effective catalyst for dehydrogenative C3-alkylation of indoles with alcohols, has low activity for the coupling of indolines with alcohols under our conditions.^{4c}

Various indolines and alcohols were then tested to examine the versatility of the divergent synthetic protocols. Initially, the generality of dehydrogenative N-alkylation protocol was investigated (Table 2). Aromatic alcohols with electron-donating substituents on their phenyl rings reacted well with indolines, affording yields ranging from 76% to 93% within 12 h (see Table 2, **5a–5e**). However, the reaction of electron-deficient aromatic alcohols had a tendency to produce a mixture of **4** and **5**. The very electron-deficient alcohol, 4-nitrobenzyl alcohol gave the N-alkylated indolines product **4b** in 73% yield. Aliphatic alcohols are suitable substrates as well, affording moderate to good yields for alcohols with varying chain length (see Table 2, **5e–5j**). Notably, methanol could be used, allowing for N-methylation of indolines (**5e**). The cyclopropyl group was tolerated under the reaction conditions (**5k**). The steric hindrance of substrates seems to affect their activity. Thus, while 71% yield was obtained for 1-isopentyl-1H-indole (**5m**), only 46% yield was observed for 1-isobutyl-1H-indole (**5l**). When two hydroxy groups were presented, only one could be alkylated, which allowed for further functionalization of the free hydroxy group (**5n–5p**). Satisfactory yields were obtained for substituted indolines with ethanol as the alkylating reagent (**5q–5t**).

The substrate scope for the dehydrogenative C3-alkylation of indolines with alcohols was then studied (Table 3). Differing from N-alkylation, both electron-rich and electron-deficient benzyl alcohols reacted well to afford the C3-alkylated indoles

Table 2. Substrate Scope for Dehydrogenative N-Alkylation of Indolines with Alcohols^a



5a , 82% yield	5b , 93% yield	5c , 93% yield	5d , 86% yield
5e ^b , 76% yield	5e ^b , 65% yield	5f ^b , 86% yield	5g ^c , 76% yield
5h ^c , 74% yield	5i ^c , 77% yield	5j , 76% yield	5k ^c , 86% yield
5l ^c , 46% yield	5m ^c , 71% yield	5n ^b , 60% yield	5o ^b , 61% yield
5p ^c , 62% yield	5q ^c , 73% yield	5r ^c , 83% yield	5s ^c , 98% yield 5t ^c , 82% yield

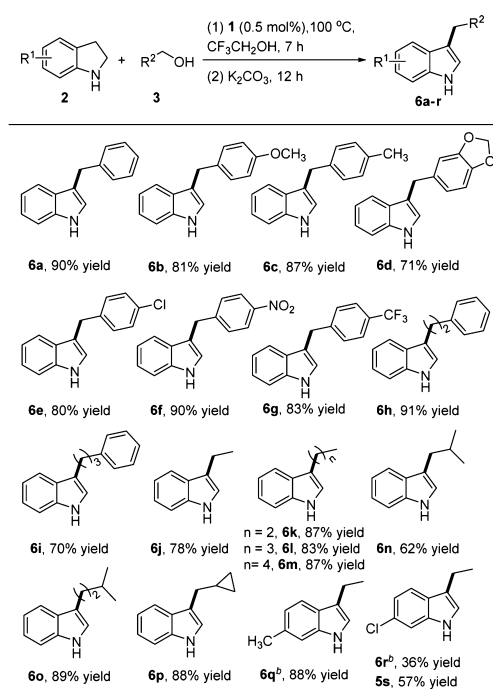
R = Cl, **5s**^c, 98% yield
R = CH₃, **5t**^c, 82% yield

^aReaction conditions: **2** (1 mmol), **3** (1 mmol), **1** (0.005 mmol), K₂CO₃ (0.75 mmol), CF₃CH₂OH (2 mL), 100 °C, 12 h, under air, isolated yield. ^bWith 1.5 mmol alcohol. ^cWith 2 mmol alcohol.

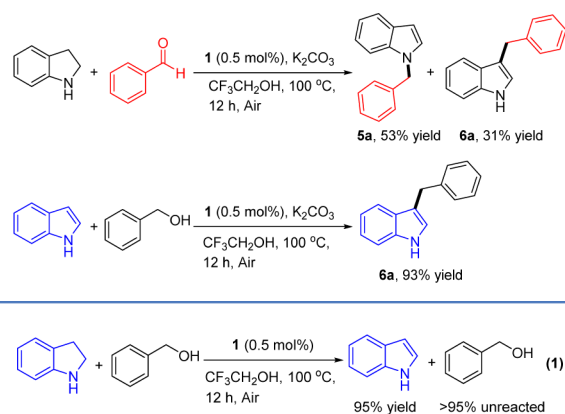
with good yields (**6a–6g**). Aliphatic alcohols, with differing chain length and steric hindrance, are viable substrates as well (**6h–6p**). Similarly, relative low yield was obtained for the steric bulky isobutanol (**6n**). While indoline bearing electron-donating group at the 6-position afforded C3-alkylated product (**6q**) in good yield with ethanol, the electron-withdrawing group at that position lead to a mixture of C3- and N-alkylated products (**6r** and **5s**).

The mechanism of these coupling reactions was then considered. Aldehydes were believed to be intermediates for alkylation reactions via borrowing hydrogen.^{5b,7} Reacting indoline with benzaldehyde under standard reaction conditions, both N-alkylated product (**5a**) and C3-alkylated product (**6a**) were obtained (Scheme 2), suggesting that aldehydes might serve as intermediates for these coupling reactions. Furthermore, the reaction of indole with benzyl alcohol afforded the C3-alkylated product exclusively, suggesting indole as an intermediate for the C3-alkylation reaction but not for the N-alkylation reaction.

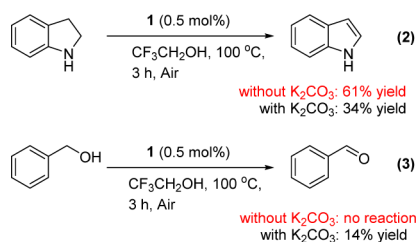
An interesting question is how the addition time of the base, K₂CO₃, switched the coupling reaction from N-alkylation to C3-alkylation. Removing K₂CO₃ from the standard reaction conditions for N-alkylation of indoline with benzyl alcohol, none of the coupling product was observed. Instead, indole was isolated in 95% yield and benzyl alcohol remained unreacted (see eq 1). This result suggests that, in the absence of K₂CO₃, the iridacycle catalyst dehydrogenates indolines to indoles preferentially, even in the presence of alcohols. Further experiments by subjecting benzyl alcohol or indoline alone to

Table 3. Substrate Scope for Dehydrogenative C3-Alkylation of Indoline with Alcohols^a

^aReaction conditions: **2** (1 mmol), **3** (1 mmol), **1** (0.005 mmol), and $\text{CF}_3\text{CH}_2\text{OH}$ (2 mL) were stirred at 100 °C for 7 h under air; after cooling to room temperature (rt), K_2CO_3 was added and further stirred for 12 h, isolated yield. See the SI for more details. ^bWith 2 mmol alcohol.

Scheme 2. Mechanistic Studies for Possible Intermediates

the standard conditions with or without K_2CO_3 revealed that K_2CO_3 promoted the oxidation of benzyl alcohol to aldehyde but decreased the rate for dehydrogenation of indoline to indole (eqs 2 and 3). In the catalytic reaction, in the presence of



K_2CO_3 , the produced aldehyde might rapidly react with indoline to form an iminium intermediate, which further accelerates the alcohol dehydrogenation reaction and decreases the rate of indoline dehydrogenation, leading to the formation of N-alkylated indoles as the major product. If K_2CO_3 was not added initially, the catalyst only dehydrogenated indoline to indole. Moreover, when K_2CO_3 was introduced, the alcohol dehydrogenation began and the resulting aldehyde reacted with indole to give the C3-alkylated product.

Another question is posed: What is the role of the iridacycle catalyst in these transformations, and how are the products formed? Control experiments showed that, in the absence of **1**, neither indolines nor benzyl alcohols underwent dehydrogenation, indicating that **1** catalyzed the dehydrogenation of both amines and alcohols. The N-alkylated product **5a** could not be formed from indoline and benzaldehyde under standard conditions without **1**, suggesting the involvement of **1** in the steps leading to **5a**. Kinetic profile of the reaction between **2a** and **3a** in the presence of K_2CO_3 indicate that **4a** is an intermediate during the reaction (Figure 1). Subjecting **4a** to

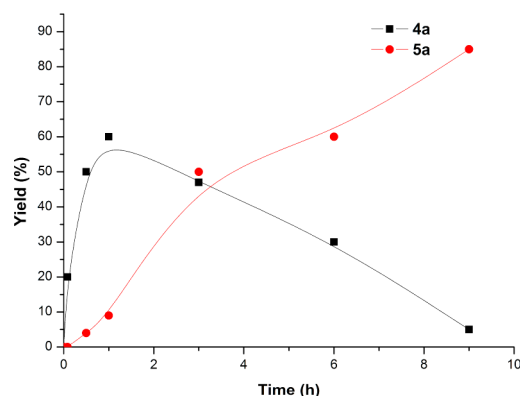
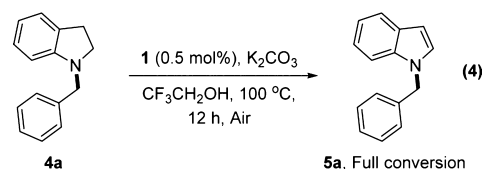
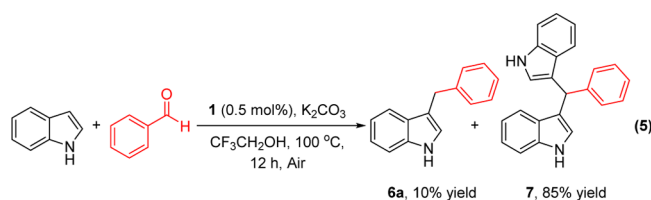


Figure 1. Kinetic profile for the reaction of **2a** and **3a** in the presence of K_2CO_3 . Reaction conditions: **2a** (1 mmol), **3a** (1 mmol), **1** (0.005 mmol), K_2CO_3 (0.75 mmol), $\text{CF}_3\text{CH}_2\text{OH}$ (2 mL), 100 °C, under air. Yields were determined by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard.

the standard conditions of N-alkylation, full conversion of **4a** to **5a** was observed (see eq 4). These observations suggest that the reaction first produces **4a** via a borrowing hydrogen process, which was then dehydrogenated to form **5a**.

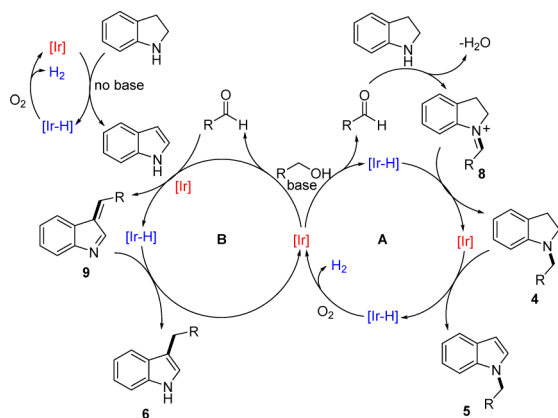


Experiments were also designed to probe the role of **1** in the C3-alkylation reaction. **6a** was believed to be formed via indole and benzaldehyde.^{4c} No reaction occurred between indole and benzaldehyde in the absence of **1** under the C3-alkylation conditions, suggesting that **1** is again essential for the C–C coupling event, probably acting as a Lewis acid to activate the aldehyde. Interestingly, the reaction of indole and benzaldehyde under the standard C3-alkylation conditions afforded only a small amount **6a** and a major new product **7** (eq 5). The formation of **7** was also observed by Grigg and co-workers^{4c} and Beller and co-workers.¹²



Based on the above analysis and literature,^{3,4} catalytic cycles for both N- and C3-alkylation were proposed (see Scheme 3).

Scheme 3. Proposed Mechanism for the Divergent Formation of Indoles



Cycle A in Scheme 3 describes the formation of 5 from indoline and alcohol via aldehyde and iminium intermediates. In this cycle, the iridium hydride, which is formed from the dehydrogenation of alcohol in the presence of a base, could reduce the iminium intermediate 8, which is generated from indolines and aldehyde, to afford 4, which is then dehydrogenated by the iridium catalyst to give 5. Cycle B in Scheme 3 depicts the formation of 6 via the intermediacy of indole and aldehyde. In the absence of a base, indoline is dehydrogenated to indole; and with the addition of base, alcohol dehydrogenation occurs to give aldehyde. Indole then reacts with the aldehyde by iridium catalysis to afford intermediate 9, which is then transformed to 6 by the iridium hydride. The switch of selectivity from 6a to 7 in the reaction of eq 5 could be due to the lack of hydrogen source to reduce the intermediate 9, which, instead, is attacked by indole. The N-alkylation reaction could also proceed under an argon atmosphere (Table 1), and experiments showed that the C3-alkylation reaction proceeded equally well under both argon and air (see Table S2 in the SI). These results suggest that the iridium hydride could either react with oxygen or be protonated to release hydrogen gas to regenerate the active catalyst. Indeed, hydrogen gas could be detected in the head gas of both reactions under air (see section 8 in the SI). It is interesting to note that cycle A involves a borrowing hydrogen–dehydrogenation process and cycle B involves a dehydrogenation–borrowing hydrogen process. In addition, this iridacycle catalyst allowed the borrowing hydrogen process to be performed in an air atmosphere.

In conclusion, through the use of an iridacycle catalyst, the divergent synthesis of indoles through the selective coupling of indolines and alcohols has been developed. The iridacycle catalyst plays multiple roles in these transformations, which catalyzed the dehydrogenation of both amines and alcohols and

the subsequent coupling reactions. The C3-alkylation reaction realized the coupling of two sp³ carbon centers with air as an oxidant or under oxidant-free conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b03667.

Additional optimization studies, experimental procedures and characterization data, ¹H and ¹³C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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