Letter

Divergent Dehydrogenative Coupling of Indolines with Alcohols

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Divergent Dehydrogenative Coupling of Indolines with Alcohols

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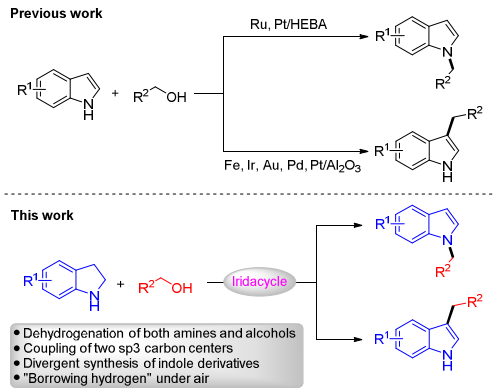
ABSTRACT: The dehydrogenative coupling of indolines with alcohols catalyzed by an iridium complex has been achieved to afford both *N*- and *C*3-alkylated indoles selectively, by simply changing the addition time of a base additive. The iridacycle catalyst plays multiple roles in these reactions, which 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 *C*3-alkylation reactions, respectively. The *C*3-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, 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 by-product. However, the control of the *N*-[3] or *C*3-alkylation[4] selectivity is not easy, with most system preferring *C*3-alkylation (Scheme 1). To the best of our knowledge, the regioselective access to both *N*- and *C*3-alkylated indoles with a single catalyst has not been reported yet.

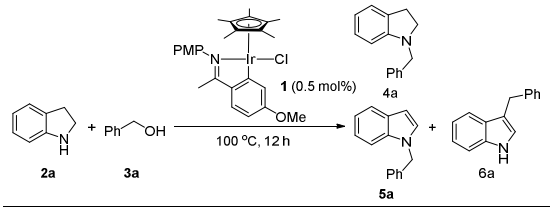
Dehydrogenation as a substrate activating strategy has found broad application in organic synthesis.[5] The dehydrogenation of amines and alcohols to imines/enamines and carbonyl compounds has been utilized in a number of green transformations, e.g. alkylation with alcohols[5e,6] via a borrowing hydrogen strategy,[5b,7] and amide formation from amines and alcohols.[5d] 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 catalyse the functionalization of indoles with alcohols via dehydrogenation.[4c,4f-h] A catalyst capable of dehydrogenating both amines and alcohols is desirable, as it would allow for a 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 (Scheme 1). Mechanistic studies suggest that a borrowing hydrogen-dehydrogenation process for *N*-alkylation and a dehydrogenation-borrowing hydrogen process for *C*3-alkylation under aerobic conditions are involved.

Scheme 1. Divergent synthesis of *N*- and *C*3- alkylated indoles



Recently, we disclosed that cyclometalated iridium catalysts (iridacyles)[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

Table 1. Dehydrogenative coupling of indoline with benzyl alcohol[a]



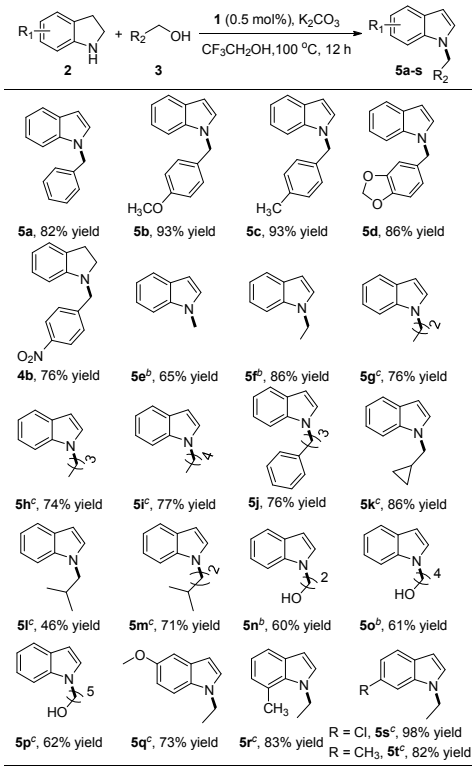
Entry	Air/Argon	Yield (%)		
		4a	5a	6a
1	Argon	56	37	trace
2	Air	trace	82	5
3[b]	Air	n.d.	trace	90
4[c]	Air	n.d.	n.d.	n.d.

[a]Reaction conditions: **2a** (1 mmol), **3a** (1 mmol), **1** (0.005 mmol), K_2CO_3 (0.75 mmol), CF_3CH_2OH (2 mL), 100 °C, 12 h, isolated yield; PMP = para-methoxyphenyl; n.d. refers to not detected. [b]K_2CO_3 was added after 7 h and further reacted for 12 h. [c]Without **1**.

presence of K_2CO_3 for 12 h. Lowering the catalyst loading to 0.5 mol%, a mixture of **4a**, **5a** and **6a** were observed (Table 1, entry 1). Performing the reaction under air, **5a** was formed preferentially in 12 h with 0.5 mol% of **1** (Table 1, entry 2). Interestingly, when the base, K_2CO_3, was added after 7 h, and allowing the reaction mixture to react for a further 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 (SI, Table S1). For example, $[Cp^*IrCl_2]_2$, 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 76-93 % in 12 h (Table 2, **5a-e**). However, the reaction of electron-deficient aromatic alcohols tended 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 moderated to good yields for alcohols with varying chain length (Table 2, **5e-j**). 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-1*H*-indole (**5m**), only 46% yield was observed for 1-isobutyl-1*H*-indole (**5l**). When

Table 2. Substrate scope for dehydrogenative *N*-alkylation of indolines with alcohols[a]



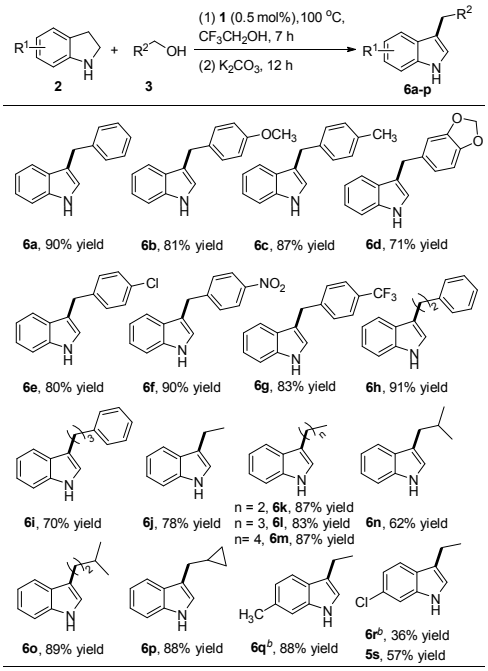
[a]Reaction conditions: **2** (1 mmol), **3** (1 mmol), **1** (0.005 mmol), K_2CO_3 (0.75 mmol), CF_3CH_2OH (2 mL), 100 °C, 12 h, under air, isolated yield. [b]With 1.5 mmol alcohol. [c]With 2 mmol alcohol.

two hydroxy groups were presented, only one could be alkylated, allowing for further functionalization of the free hydroxy group (**5n-p**). Satisfactory yields were obtained for substituted indolines with ethanol as alkylating reagent (**5q-t**).

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

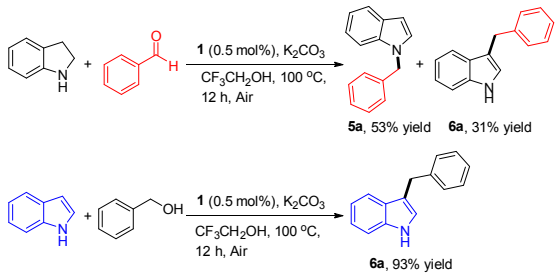
The mechanism of these coupling reactions was then considered. Aldehydes were believed to be intermediates for alkylation reactions via borrowing hydrogen.[5b,7] Reacting indoline with benzaldehyde under standard reaction conditions, both *N*-alkylated product **5a** and *C3*-alkylated product **6a** were obtained (Scheme 2), suggesting that aldehydes might serve as intermediate for these coupling reactions. Furthermore, the reaction of indole with benzyl

Table 3. Substrate scope for dehydrogenative *C3*-alkylation of indoline with alcohols[a]



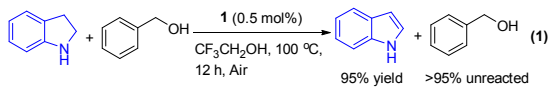
[a]Reaction conditions: **2** (1 mmol), **3** (1 mmol), **1** (0.005 mmol), and CF_3CH_2OH (2 mL) were stirred at 100 °C for 7 h under air; after cooling to r.t., K_2CO_3 was added and further stirred for 12 h, isolated yield. See SI for more details. [b]With 2 mmol alcohol.

Scheme 2. Mechanistic studies for possible intermediates



alcohol afforded the *C3*-alkylated product exclusively, suggesting indole as an intermediate for the *C3*-alkylation but not for the *N*-alkylation reaction.

An interesting question is how the addition time of the base, K_2CO_3, switched the coupling reaction from *N*-alkylation to C3-alkylation. Removing K_2CO_3 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 (eq. 1). This result



suggests that, in the absence of K_2CO_3, the iridacycle catalyst dehydrogenates indolines to indoles preferentially

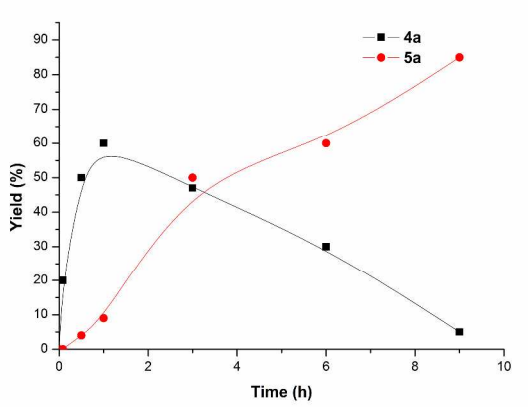
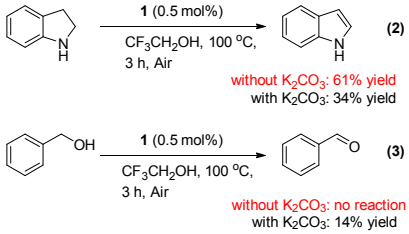


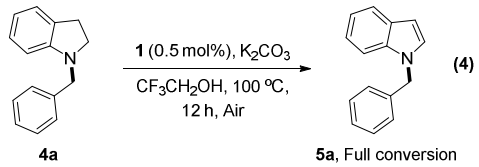
Figure 1. Kinetic profile for the reaction of **2a** and **3a** in the presence of K_2CO_3. Reaction conditions: **2a** (1 mmol), **3a** (1 mmol), **1** (0.005 mmol), K_2CO_3 (0.75 mmol), CF_3CH_2OH (2 mL), 100 °C, under air. Yields were determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

even in the presence of alcohols. Further experiments by subjecting benzyl alcohol or indoline alone to 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 (eq. 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. And when K_2CO_3 was introduced, the alcohol dehydrogenation began and the resulting aldehyde reacted with indole to give the *C3*-alkylated product.

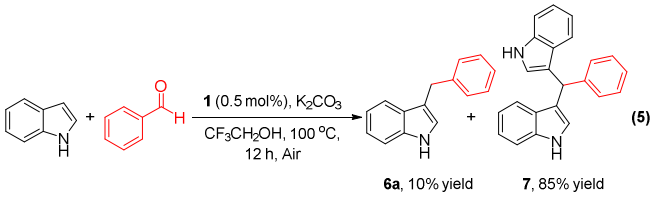


Another question is what the role of the iridacycle catalyst is in these transformations and how the products are formed. Control experiments showed that in the absence of **1**, neither indolines nor benzyl alcohols underwent dehydrogenation, indicating that **1** catalysed the dehydrogenation of both 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 the standard conditions of *N*-alkylation, full conversion of **4a** to **5a** was observed (eq. 4). These observations suggest that the reac-

tion first produces **4a** via a borrowing hydrogen process, which was then dehydrogenated to form **5a**.

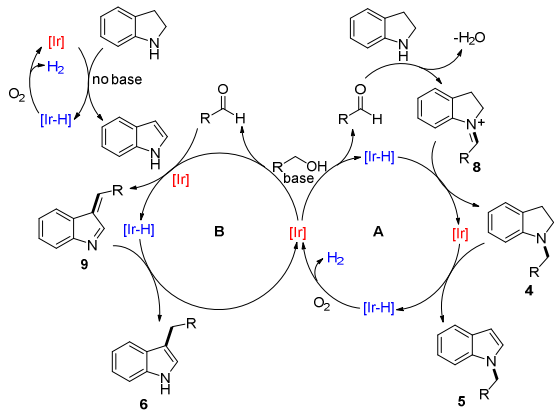


Experiments were also designed to probe the role of **1** in the *C3*-alkyaltion reaction. **6a** was believed to be formed via indole and benzaldehyde.[4c] No reaction took place between indole and benzaldehyde in the absence of **1** under the *C3*-alkylation conditions, suggesting that **1** is again 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[4c] and Beller[12] and their co-workers.



Based on the above analysis and literature,[3,4] catalytic cycles for both *N*- and *C3*-alkylation were proposed (Scheme 3). Cycle A describes the formation of **5** from indoline and alcohol via aldehyde and iminium intermediates. In this cycle, the iridium hydride, formed from dehydrogenation of alcohol in the presence of base, could reduce the iminium intermediate **8**, generated from indolines and aldehyde, to afford **4**, which is then dehydrogenated by the iridium catalyst to give **5**. Cycle B depicts the formation of **6** via the intermediacy of indole and aldehyde. In the absence of base, indoline is dehydrogenated to indole; and with the addition of base, alcohol dehydrogenation takes place to give aldehyde. Indole then reacts with the aldehyde by iridium catalysis to afford intermediate **9**, which is then transformed to **6** by the

Scheme 3. Proposed mechanism for the divergent formation of indoles



iridium hydride. The switch of selectivity from **6a** to **7** in the reaction of equation 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 argon (Table 1), and experiments showed that the *C3*-alkylation reaction went equally well under both argon and air (SI, Table S2). 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 (SI, section 8). It is interesting to note that cycle A involves a borrowing hydrogen–dehydrogenation process and cycle B involves a dehydrogenation–borrowing hydrogen process. And this iridacycle catalyst allowed the borrowing hydrogen process to be carried out under air.

In conclusion, by the use of an iridacycle catalyst, the divergent synthesis of indoles through selective coupling of indolines and alcohols has been developed. The iridacycle catalyst plays multiple roles in these transformations, which catalysed 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 oxidant or under oxidant free conditions.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publication website at DOI: xxx-xxx

Additional optimization studies, experimental procedures and characterization data, ^{1}H and ^{13}C NMR spectra

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Notes

The authors declare no competing financial interest.

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