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Cu_2O-CATALYZED C(sp^3)-H/C(sp^3)-H CROSS-COUPLING USING TEMPO: SYNTHESIS OF 3-(2-OXOALKYL)-3-HYDROXYOXINDOLES

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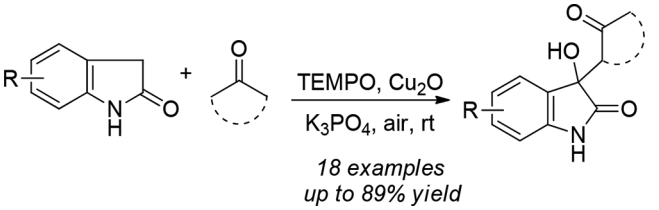
GRAPHICAL ABSTRACT



Abstract *A simple, convenient, and efficient oxidative cross-coupling reaction of oxindoles with ketones toward a variety of 3-(2-oxoalkyl)-3-hydroxyoxindoles in moderate to excellent yields has been developed. This transformation proceeds via a tandem oxidative cross-coupling by using 2,2,6,6-tetramethylpiperidine N-oxyl (TEMPO) in air as an environmentally benign oxidant. This methodology provides an alternative approach for the direct generation of all-carbon quaternary centers at the C3 position of oxindoles.*

Keywords Cross-coupling; 3-hydroxyindole; methyl ketone; TEMPO

INTRODUCTION

The direct oxidative cross-coupling reaction of two individual C−H bonds has been recognized as an ultimately ideal goal for the formation of carbon−carbon bonds.[1] Over the past few years the transition-metal-catalyzed oxidative cross-coupling reaction through cleavage of C−H bonds represent a more environmentally and economically attractive strategy and led to the emergence of new protocols.[2] Importantly, this strategy is not only advantageous with respect to the overall minimization of by-product formation but also allows for streamlining organic syntheses.[3]

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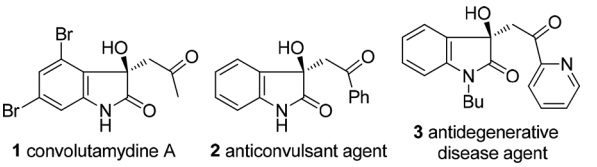


Figure 1. Naturally occurring and biologically bioactive 3-substituted 3-hydroxy-2-oxindoles.

However, the field has still many formidable issues, which continue to challenge the chemistry community. In particular, the direct oxidative C(sp^3)-H/C(sp^3)-H bond cross-coupling reactions represent the biggest challenge.

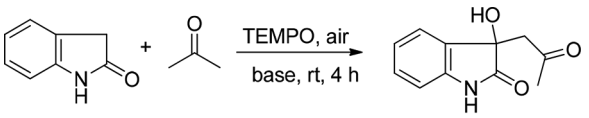
Many biologically active compounds and natural products possess an oxindole framework with a hydroxy-bearing tetrasubstituted stereogenic center at C3 (Fig. 1). Such motifs represent the substructures of many natural products, which have garnered interest because of their wide spectrum of biological activities, including antioxidant, anticancer, and neuroprotective properties.[4,5] Accordingly, much effort has been devoted in the past years to the preparation of these compounds.[6] These strategies mainly relied on the direct hydroxylation of 3-alkyl-substituted oxindoles,[7] nucleophilic additions to isatins,[8,9] and intramolecular arylation reactions.[10] Thus, the development of the direct construction of 3-substituted 3-hydroxy-2-oxindoles is still in high demand. However, the direct construction of 3-(2-oxoalkyl)-3-hydroxyoxindoles from oxindoles still remained elusive. Here, we report that 2,2,6,6-tetramethylpiperidine N-oxyl (TEMPO)[11] could effectively catalyzed aerobic oxidation of oxindoles for synthesis of 3-(2-oxoalkyl)-3-hydroxyoxindoles under mild reaction conditions.

RESULTS AND DISCUSSION

Initially, we used TEMPO (10 mol%) as the oxidant, K_3PO_4 as the base, and different copper catalysts for the model reaction of indolin-2-one **4a** and acetone **5a** at room temperature. As shown in Table 1, all copper catalysts could promote the coupling reaction and Cu_2O was the best catalyst, providing the product **6a** in 52% yield (Table 1, entry 5). Further investigations revealed that there was an obvious increase in yield when catalyst loading was increased to 25 mol % (Table 1, entry 8). Among the bases tested, K_3PO_4 was still found to be the most effective for this transformation. Other bases, such as $NaHCO_3$, Na_2CO_3, LiOH, NaOH, and K_2CO_3, exhibited lower efficiency than K_3PO_4 (Table 1, entries 10–14). After screening TEMPO loading (Table 1, entries 15–18), the greatest yield of **6a** was achieved when the reaction was carried out with Cu_2O (0.25 equiv), TEMPO (0.2 equiv), and K_3PO_4 (0.1 equiv) in acetone (0.5 mL) at room temperature (Table 1, entry 17).

With the optimized reaction conditions in hand, the scope and generality of the method were examined by varying the structures of the indolin-2-ones **4** and ketones **5**. As shown in Table 2, various valuable 3-(2-oxoalkyl)-3-hydroxyoxindoles **6** can be conveniently and efficiently obtained in moderate to good yields with high regioselectivity by this novel TEMPO-catalyzed oxidative cross-coupling reaction, indicating that this method is general and practically useful. In general, methyl ketones were suitable for this method, and the best yield in this work (89%) was obtained when

Table 1. Optimization of the reaction conditions[a]



4a **5a** **6a**

Entry	Catalyst (mmol)	TEMPO (mmol)	base (mmol)	Yield (%)[b]
1	$CuSC_4{\cdot}5H_2O$(0.02)	0.02	K_3PO_4 (0.02)	30
2	$CuCI_2$ (0.02)	0.02	K_3PO_4 (0.02)	13
3	$Cu(OAc)_2$ (0.02)	0.02	K_3PO_4 (0.02)	20
4	CuI (0.02)	0.02	K_3PO_4 (0.02)	35
5	Cu_2O (0.02)	0.02	K_3PO_4 (0.02)	52
6	Cu_2O (0.03)	0.02	K_3PO_4 (0.02)	60
7	Cu_2O (0.04)	0.02	K_3PO_4 (0.02)	66
8	Cu_2O (0.05)	0.02	K_3PO_4 (0.02)	69
9	Cu_2O (0.06)	0.02	K_3PO_4 (0.02)	69
10	Cu_2O (0.05)	0.02	$NaHCO_3$ (0.02)	32
11	Cu_2O (0.05)	0.02	Na_2CO_3 (0.02)	38
12	Cu_2O (0.05)	0.02	LiOH (0.02)	45
13	Cu_2O (0.05)	0.02	NaOH (0.02)	40
14	Cu_2O (0.05)	0.02	K_2CO_3 (0.02)	56
15	Cu_2O (0.05)	0.01	K_3PO_4 (0.02)	46
16	Cu_2O (0.05)	0.03	K_3PO_4 (0.02)	75
17	Cu_2O (0.05)	0.04	K_3PO_4 (0.02)	85
18	Cu_2O (0.05)	0.05	K_3PO_4 (0.02)	83

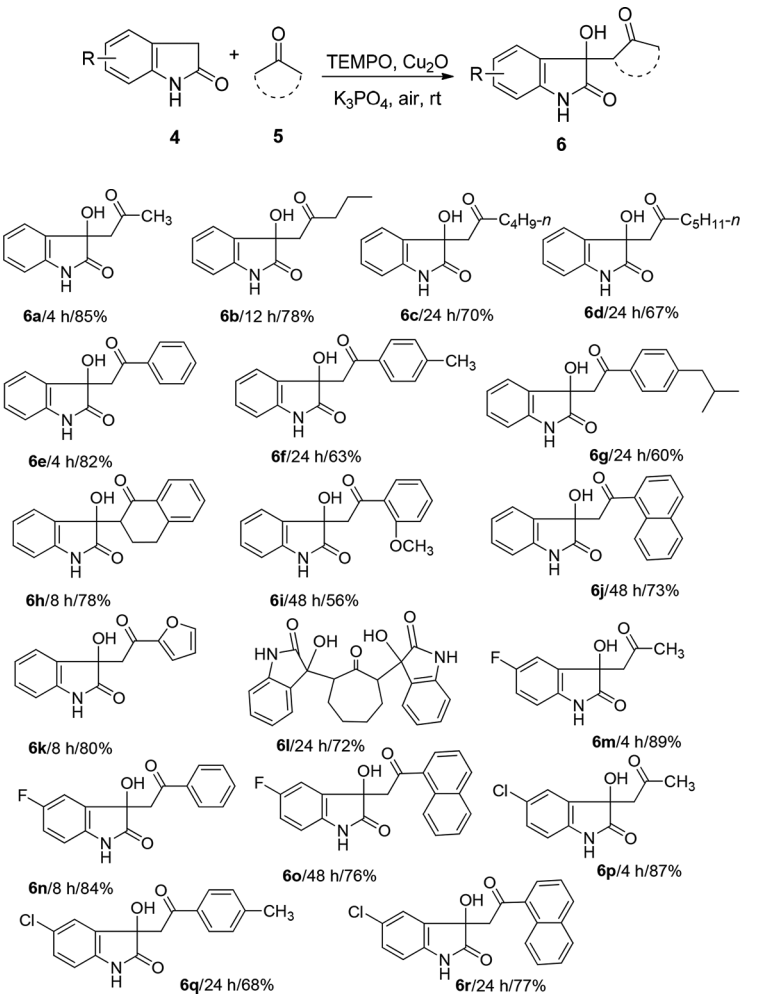
[a]Reaction conditions: oxindole (0.2 mmol) and acetone (0.5 mL) at rt for 4 h.
[b]Isolated yield.

acetone **5a** reacted with 5-fluoroindolin-2-one **4b**. The yields decreased when ketones with large steric bulk, such as 2-pentanone **5b**, 2-hexanone **5c**, and 2-heptanone **5d**, were used as the donors. Various aryl-substituted methyl ketones with electron-donating groups reacted under the present protocol to give the desired products **6e–6k** in good yields. The steric properties of the aryl ring did not appear to significantly affect the yield, as ortho-functionalized aryl substrates 1-(2-methoxyphenyl) ethanone **5i** and 1-(naphthalen-1-yl)ethanone **5j** performed equally well in the cross-coupling. Unexpectedly, cycloheptanone **5l** reacted with **4a** smoothly and produced the bis(3-hydroxyindolin-2-one) **6l** in 72% yield.

Interestingly, when evaluating the effect of different substituents at C5 position of oxindoles on reactivity, we observed that oxindoles with electron-withdrawing groups, such as F and Cl, reacted smoothly with ketones, affording the corresponding products in better yields as compared with unsubstituted oxindole **4a**.

In order to better understand the reaction mechanism, some control experiments were carried out. First, we tested the reaction in the absence of the ketone as coupling partner (Scheme 1). The oxidative product **7** was obtained in 86% yield, indicating that **7** may serve as an intermediate in the catalytic cycle. Second, 15% yield of **6a** was obtained in the absence of TEMPO, indicating that TEMPO is crucial for the oxidative cross-coupling. Third, the oxidative cross-coupling reaction of

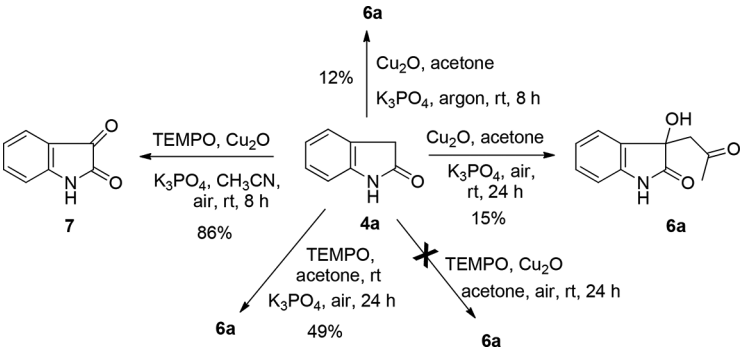
Table 2. Reactions of different indolin-2-ones with ketones[a]



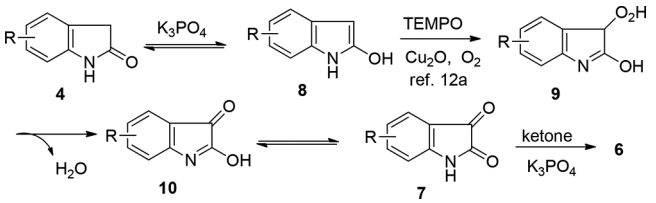
[a]Reaction conditions: **4** (0.2 mmol), **5** (0.5 mL), Cu_2O (0.05 mmol), TEMPO (0.04 mmol), and K_3PO_4 (0.02 mmol) at room temperature. Isolated yield based on **4**.

4a with acetone was attempted under an argon atmosphere (in the absence of molecular oxygen). The result showed that the reaction was carried out inefficiently, and the desired product **6a** was obtained with a poor yield of 12%. The result demonstrated that dioxygen is necessary for an efficient oxidative cross-coupling reaction. Fourthly, the reaction of **4a** with acetone in the absence of Cu_2O resulted in the formation of **6a** in a lower yield (49%) and a longer reaction time (24 h). Fifth, we also carried out this reaction in the absence of K_3PO_3 but no expected product was observed.

Based on the previous studies[12] and these results, a hypothesized mechanism of this oxidative cross-coupling reaction is shown in Scheme 2. Initially, tautomer **8**



Scheme 1. Control experiments.



Scheme 2. Plausible reaction path.

of indole **4** was oxidized in the presence of TEMPO, Cu_2O, and O_2 into intermediate **9**. Then, a rapid dehydration in **9** gave intermediate **10,** which tautomerizes to **7**. Finally, the nucleophilic addition of ketones to **7** afforded the corresponding products.

CONCLUSIONS

In summary, we have developed an efficient oxidative cross-coupling reaction of oxindoles with ketones using Cu_2O as catalyst and TEMPO in air as oxidant with excellent regioselectivity under mild conditions. This reaction provides a novel method for the generation of all-carbon quaternary centers at the C3 position of oxindoles. Moreover, it has several advantages: (1) an inexpensive and environmentally friendly TEMPO has been used in air as oxidant, (2) the operationally simple and broad substrate make it potentially useful, (3) it is highly regioselective (1,3′-linkage), and (4) this oxidative cross-coupling reaction proceeds without exclusion of moisture or air from the reaction mixture and allows the isolation of the desired 3-(2-oxoalkyl)-3-hydroxyoxindoles in moderate to excellent yields.

EXPERIMENTAL

Oxindole (0.2 mmol) was added to a solution of TEMPO (0.04 mmol), Cu_2O (0.05 mmol), and K_3PO_4 (0.02 mmol) in ketone (0.5 mL) under an air atmosphere and the mixture was stirred at room temperature for 4–48 h. The reaction mixture

was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent–EtOAc/PE = 1:4) to yield the corresponding product **6**.

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SUPPLEMENTAL MATERIAL

Experimental procedures and full spectroscopic data for all new compounds can be accessed on the publisher's website.

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