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Nickel-Catalyzed Regioselective Cross-Dehydrogenative Coupling of Inactive $C(sp^3)$−H Bonds with Indole Derivatives

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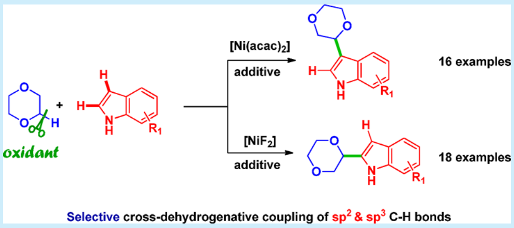
S *Supporting Information*

ABSTRACT: A nickel-catalyzed regiosepecific C2- versus C3-oxidative cross-coupling reaction of indoles with 1,4-dioxane and other inactive $C(sp^3)$−H bonds is described. The divergent synthesis of $C(sp^3)$−$C(sp^2)$ bonds was achieved in satisfactory yields with di-*tert*-butyl peroxide (DTBP) as the oxidant, which provides an efficient strategy for the selective construction of cyclic ethers containing heteroaromatic core structures.



Over the past decades, transition-metal catalyzed C−H functionalization has become one of the most fundamental processes in the synthesis of complex molecules.[1] It has had a huge impact on synthetic organic chemistry, medicinal chemistry, and material sciences.[2] As such, advances that accomplish the selective activation of C−H bonds based on recently developed dehydrogenative cross-coupling (CDC) reactions have received special research attention.[3] Direct C−H bond functionalization would bypass the need for prefunctionalized reaction partners and lead to a more atom economical and environmentally friendly process. A diverse range of transformations has been developed using palladium,[4a−e] copper,[4f−i] and iron[4j−l] catalysts. More recently, organocatalysis has also been proven to be an alternative to these transition-metal mediated oxidative couplings involving $C(sp^3)$−H bond cleavages.[5] However, the regioselectivity of these reactions remains challenging due to their low reactivity of the reaction partners and the lack of a coordination site for the transition-metal catalyst.

Cyclic ethers are ubiquitous structural motifs that frequently appear in natural products.[6,7a] Construction of these cyclic rings in complex organic molecules is sometimes demanding and always requires complicated synthetic routes.[7] Therefore, the strategy based on the direct functionalization of $C(sp^3)$−H bonds adjacent to the oxygen of ethers represents one of the interesting topics in synthetic chemistry.[8] Pioneered by the study of Li's group in 2008,[9] some developments have taken place. Lei's group developed a direct $C(sp^3)$−H arylation of tetrahydrofuran and 1,4-dioxane in the presence of nickel catalyst.[10a] Ji's group demonstrated the direct oxidative coupling of inactive $C(sp^3)$−H bonds in 1,4-dioxane with α,α-diaryl allylic alcohols.[10b] Very recently, Liu's group reported the selective construction of diverse α-functionalized ethers in the use of trityl ion and Lewis acid catalyst under ambient temperature.[10c] The $C(sp^3)$−H bonds adjacent to oxygen atoms usually have relatively lower bond dissociation energy (BDE), thus the cleavages of these C−H bonds will easily take place. Many oxidants are proven to be effective for promoting the activation step via a single electron transfer process.[11] However, when coupled with another nonprefunctionalized partner, its regioselectivity control can be quite challenging.

Our group has also developed a DTBP-mediated cross-coupling reaction of isochroman and indole derivatives on the C3 position.[12] When we try to extend the substrate scope to 1,4-dioxane and other simple cyclic ethers, we found the yields are relatively low under previous optimized conditions. We first envisioned that introducing a transition-metal catalyst would increase yields. However, besides 3-(1,4-dioxan-2-yl)-1*H*-indole, the C2 substituted indole was also observed. Consequently, we endeavored to develop the effective catalytic processes that exploit selective and controllable in this $C(sp^3)$−$C(sp^2)$ bond forming reaction between 1,4-dioxane and indole derivatives (Scheme 1).

We commenced our investigation by screening the direct coupling of 1,4-dioxane (**1a**) with indole (**2a**) in the presence of $Ni(acac)_2$ as the catalyst and DTBP as the oxidant under a solvent-free condition. Reaction gave a 2:3 mixture of C3- and C2-substituted indoles **3a** and **4a**, respectively, with only 18%

Scheme 1. Representative Examples of Oxidative Cross-Coupling of Cyclic Ethers

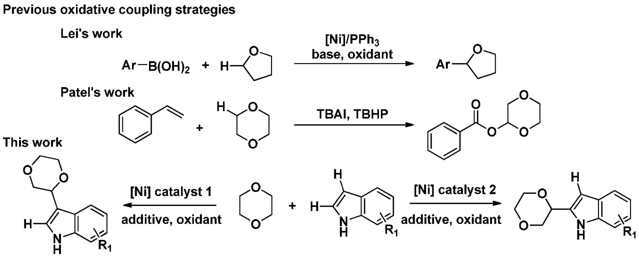


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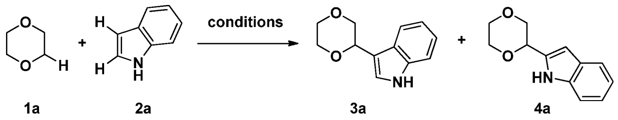
Table 1. Optimization of the Reaction Conditions[a]

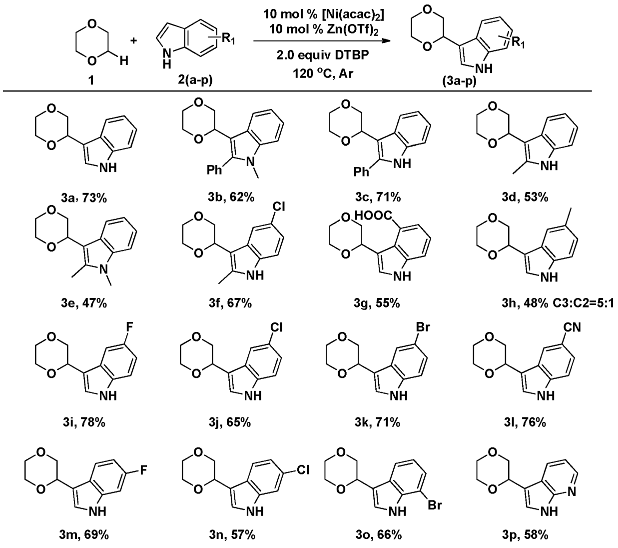


entry	catalyst	additive (equiv)	solvent	yield of **3** + **4** [%][b]	**3a**/**4a**[b]
1	$Ni(acac)_2$			18	2:3
2	$Ni(acac)_2$			35[c]	1:2
3	$Ni(acac)_2$		1,4-dioxane	63	2:3
4	$Ni(acac)_2$		MeCN		
5	$Ni(acac)_2$		DMF		
6	$Ni(acac)_2$	PPh_3(0.1)	1,4-dioxane	71	2:3
7	$Ni(acac)_2$	$Zn(OTf)_2$(0.1)	1,4-dioxane	68	19:1
8	$Ni(acac)_2$	$Zn(OTf)_2$(0.1)	1,4-dioxane	76[d]	19:1
9	$Ni(acac)_2$	$Zn(OTf)_2$(0.1)	1,4-dioxane	51[e]	19:1
10	$Ni(OAc)_2$	PPh_3(0.1)	1,4-dioxane	26	1:2
11	$NiCl_2$	PPh_3(0.1)	1,4-dioxane	16	1:2
12	$Ni(OH)_2$	PPh_3(0.1)	1,4-dioxane	44	1:5
13	NiF_2	PPh_3(0.1)	1,4-dioxane	72	1:9
14	NiF_2	$Zn(OTf)_2$(0.1)	1,4-dioxane	47	3:4
15	NiF_2		1,4-dioxane	49	1:9
16	$Co(acac)_3$		1,4-dioxane	31	3:2
17	$Cu(acac)_2$		1,4-dioxane	<5	
18	$Fe(acac)_3$		1,4-dioxane	24	3:5

[a] Unless otherwise noted, the reaction was carried out with indole (0.50 mmol), catalyst (0.05 mmol), **1a** (1.0 mL), and DTBP (1.0 mmol) at 120 °C in 24 h. [b] Yields and ratios were determined by GC−MS. [c] 130 °C. [d] Reaction conducted under argon atmosphere. [e] DTBP (0.6 mmol).

yield of the mixture (Table 1, entry 1). A higher temperature improved the yield to 35%, but still showed poor selectivity in 1:2 ratio. Diluting the solution by 1,4-dioxane and with the participation of PPh_3 would increase yield to 71%, but C2- and C3-forming reactions tend to be promoted simultaneously. Further optimizations in various solvents with additives were conducted (see Table 1, SI). Polar solvents such as DMF and MeCN would compete with the reaction between **1a** and **2a** and thus inhibited the formation of desired products. Careful monitoring of the reaction showed that **3a** might predominate at the beginning of the reaction with **4a** only starting to form as the reaction proceeded. Consequently, Lewis acids were thought to be effective for the regioselectivity control. This hypothesis was supported by the result in the presence of $Zn(OTf)_2$, which led to an exclusively C3-functionalized indole **3a** (Table 1, entry 7). Further optimization reveals that side reactions can be suppressed under argon atmosphere, which are beneficial to afford the target product in high yield and regioselectivity (Table 1, entry 8). Besides $Ni(acac)_2$, other metal salts were screened to further optimize the reaction. $Ni(OAc)_2$, $NiCl_2$, and $Ni(OH)_2$ switched the selectivity back in favor of the C2-position, but hard to achieve high regioselectivity (Table1, entries 10−12). To our delight, the use of NiF_2 led to the ratio of 1:9 of **3a**/**4a** in the presence of PPh_3 and thus demonstrated that the regioselectivity of nickel-catalyzed oxidative crossing coupling could be controlled (Table1, entry 13), whereas $Co(acac)_3$, $Cu(acac)_2$, and $Fe(acac)_3$ were all less effective for the reaction (Table1, entries 16−18).

Scheme 2. Regiosepecific C3 Coupling of Indole Derivatives with 1,4-Dioxane[a]

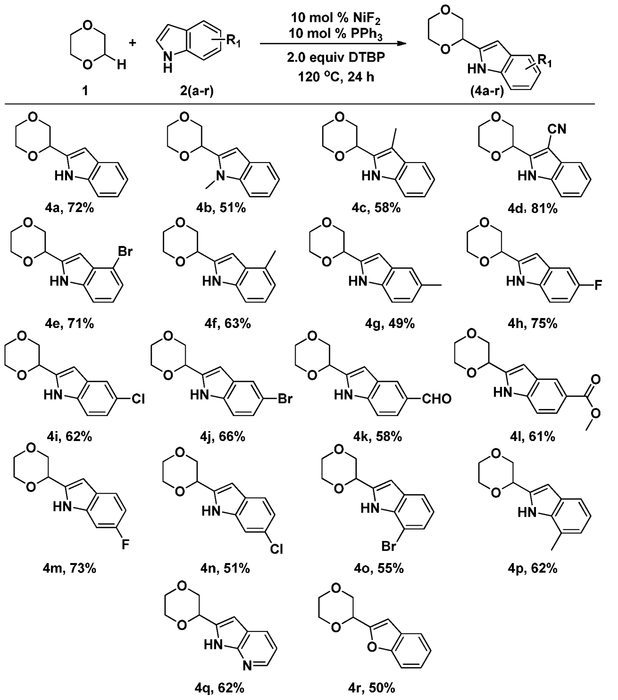


[a] Reaction conditions: indole (0.50 mmol), $Ni(acac)_2$ (0.05 mmol), $Zn(OTf)_2$ (0.05 mmol), **1a** (1.0 mL), and DTBP (1.0 mmol) at 120 °C in 24 h under argon atmosphere. Isolated yield.

With a set of optimized conditions in hand, we next examined the indole scope of this nickel-catalyzed oxidative C−C bond forming reaction. First, various indole derivatives were explored under standard conditions (Scheme 2). We found that both free (NH)-indoles and *N*-alkyl indoles were smoothly coupled with 1,4-dioxane, giving the target product in moderate to good yields and great selectivity. Importantly, the C3-functionalization process worked well for electron-deficient indoles, such as **3i**−**3n** and indoles with electron-neutral groups such as **3b** and **3c**. Electron-rich substituents such as 2-Me (**3d**) and 1,2-Me (**3e**) were tolerated, but affording the corresponding coupling products in relatively low 53% and 47% yields, respectively. Besides, the reaction of **1a** with 5-methyl-1*H*-indole produced a mixture of C3- and C2-alkyl indole regioisomers **3h** (5:1) in 48% combined yield. Of particular note was the use of 1*H*-indole-4-carboxylic acid (**2g**); the highly versatile product **3g** was obtained in 55% yield with the aryl carboxylic acid moiety intact. Beside indole derivatives, 1*H*-pyrrolo[2,3-*b*]pyridine was also well tolerated in the reaction and thus yielded 3-(1,4-dioxan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine(**3p**) in 58%. To this end, the first general method for the direct cross-coupling reaction of 1,4-dioxane and indoles at C3 position can be applied to a broad range of indole derivatives.

Next we further turned our attention to exploring the substrate scope of corresponding catalytic C2 functionalization (Scheme 3). When reactions performed with NiF$_2$ as the catalyst and PPh$_3$ as ligand, the coupling between 1,4-dioxane **1a** and indole **2a** resulted in a 1:9 mixture of the alkylated product **3a** and **4a**. The regioselectivity of the oxidative coupling process was switched in favor of the reaction at C2-position. Indoles with electron-rich substituent 3-Me (**4c**) or with electron-deficient substituents such as 5-F (**4h**) and 5-CHO (**4k**) all gave the desired products in satisfactory yields. Generally, indoles bearing electron-donating groups demonstrated lower yields compared to that with electron-deficient substituents, however, leading to complete regiospecificity at C2−C(sp^2)−H bond. In addition, the reaction was also extended to other electron-rich heteroaromatic. 1*H*-Pyrrolo[2,3-*b*]pyridine and benzofuran led to the coupled products **4q** and **4r** in moderate yields and exclusive regioselectivities.

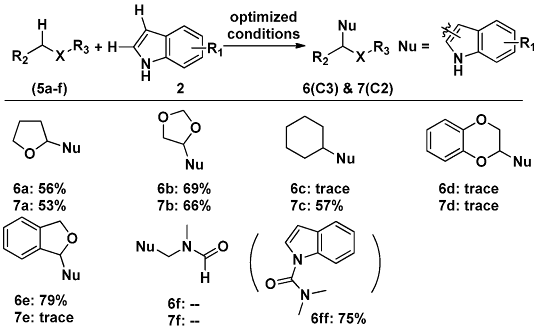
Scheme 3. Regiosepecific C2 Coupling of Indole Derivatives with 1,4-Dioxane[a]



[a]Reaction conditions: indole (0.50 mmol), [NiF$_2$] (0.05 mmol), PPh$_3$ (0.05 mmol), **1a** (1.0 mL), and DTBP (1.0 mmol) at 120 °C in 24 h. Isolated yield.

Besides 1,4-dioxane, other ether candidates were further investigated for these optimized oxidative coupling conditions (Scheme 4). The reaction proved general for commonly encountered saturated cyclic ethers including tetrahydrofuran (**5a**) and 1,3-dioxolane (**5b**). Cyclic benzyl ethers such as 1,3-dihydroisobenzofuran (**5e**) was well compatible with the reaction, however, affording predominantly the C3-functionalization product, and only a trace of the C2-addition product was observed under optimized conditions. 2,3-Dihydrobenzo[*b*][1,4]dioxine (**5d**) was not compatible with the coupling. Besides cyclic ethers, the scope was further extended to cycloalkane (**5c**) and *N*,*N*-dimethylformamide (**5f**), whereas the *N*,*N*-dimethyl-1*H*-indole-1-carboxamide (**6ff**) was obtained instead of target product **6f** or **7f**.

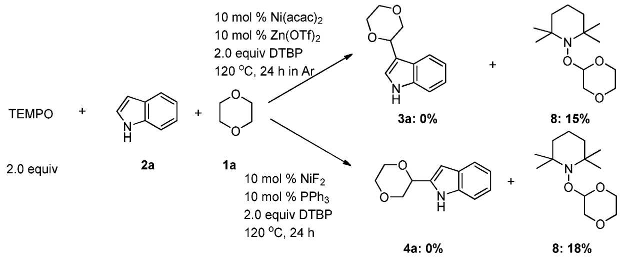
Scheme 4. Nickel-Catalyzed Regioselective Cross-Dehydrogenative Coupling of Inactive C(sp^3)−H Bond with Indole[a]



[a]Reaction conditions: C3 functionalization, indole (0.50 mmol), Ni(acac)$_2$ (0.05 mmol), Zn(OTf)$_2$ (0.05 mmol), **1a** (1.0 mL), and DTBP (1.0 mmol) at 120 °C in 24 h under argon atmosphere. C2 functionalization, indole (0.50 mmol), NiF$_2$ (0.05 mmol), PPh$_3$ (0.05 mmol), **1a** (1.0 mL), and DTBP (1.0 mmol) at 120 °C in 24 h. Isolated yield.

To gain some insight into the mechanism for the nickel-catalyzed oxidative cross-coupling of ethers with indole derivatives,[13] a control experiment was carried out (Scheme 5).

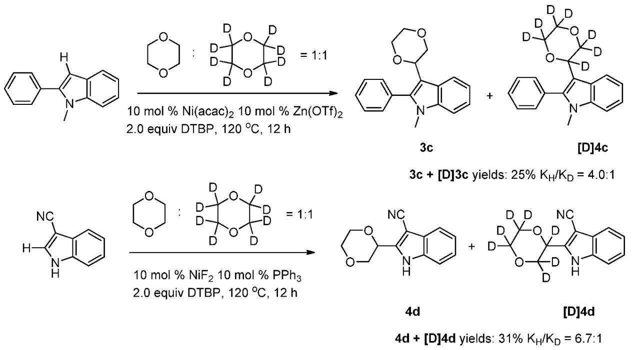
Scheme 5. Control Experiment



No target product was observed by the addition of TEMPO as a radical inhibitor. Instead, the TEMPO-1,4-dioxane adduct **8** was obtained in 15% and 18% yield, respectively, in C3- and C2-coupling conditions (determined by GC−MS analysis), indicating that a radial pathway might be involved in the process. Meanwhile, an intermolecular competing kinetic isotope effect (KIE) experiment was carried out (Scheme 6). As is depicted, a significant KIE was observed with $K_H/K_D = 4.0$ and $K_H/K_D = 6.7$. (The KIE was determined by ^{1}H NMR spectroscopy by analyzing the ratio of **3c** vs [D]**3c** and **4d** vs [D]**4d**.) This result indicates that C(sp^3)−H bond cleavage of 1,4-dioxane may be one of the rate-determining steps of this procedure.

In summary, a new regioselective Ni(II)-catalyzed C−H bond functionalization method was developed, which enables the cross-coupling of cyclic ethers and indole derivatives selectively at either the C3 or C2 position under standard conditions. This general procedure tolerates a broad range of substrates; not only various indole derivatives but also the inactive C (sp^3)−H bond containing compounds. This discovery could be of great

Scheme 6. KIE Experiment



significance on the selective elaboration of other heteroaromatic core structures. Further efforts in our laboratory are devoted to the exploitation of regio- and stereocontrol over other types of heteroaromatic compounds and a more detailed mechanistic investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02217.

Experimental procedures and characterization data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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