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Mild and Selective Ru-Catalyzed Formylation and Fe-Catalyzed Acylation of Free (N−H) Indoles Using Anilines as the Carbonyl Source

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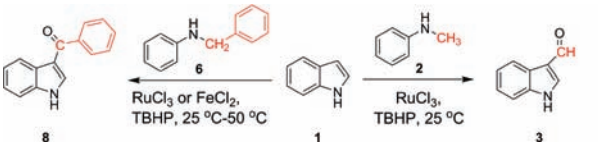
Supporting Information

ABSTRACT: C3-selective formylation and acylation of free (N−H) indoles under mild conditions can be achieved by using Ru- and Fe-catalyzed oxidative coupling of free (N−H) indoles with anilines, respectively. Both processes are operationally simple, compatible with a variety of functional groups and generally provide the desired products in good yields. ^{13}C-labeling experiments unambiguously established that the carbonylic carbon in the formylation products originated from methyl group of N-methyl aniline.

The synthesis and transformation of indoles has been and continues to be a focus of research efforts for synthetic organic chemists because the indole nucleus is found in countless biologically active molecules and medicinally relevant structures.[1] 3-Formylindoles and 3-acylindoles are versatile starting materials for syntheses of a broad range of indole derivatives since their carbonyl groups can readily undergo a variety of transformations such as C−C and C−N coupling reactions and reductions.[2]

Traditionally, 3-formylindoles are synthesized by Vilsmeier−Haack,[2a,b,3a,3b] Reimer−Tiemann,[4] Rieche[2c,5] and Duff[6] reactions, which generally require heating at elevated temperatures with excess strong bases or acids in workup processes. Owing to the harsh reaction conditions (e.g., high temperature, strong bases[2a,3a,3b,4] or acids[6]), these traditional indole formylation methods are not compatible with the functional groups labile under acidic or basic conditions. For the synthesis of 3-acylindoles, the most commonly used methods are Friedel−Crafts acylations,[7] Vilsmeier−Haack acylations,[3c,d] and the reactions of indole salts with acyl chlorides.[2d,8] Friedel−Crafts acylations require stoichiometric metal salts as Lewis acid promoters and strict exclusion of moisture,[7] and often involve troublesome N-protection and N-deprotection steps.[7a,b] Vilsmeier−Haack acylations use unacceptable amounts of environmentally unfriendly $POCl_3$, and suffer from lack of the amides used as carbonyl sources.[3c,d] The reactions of indole salts with acyl chlorides cannot tolerate the functional group sensitive to strong nucleophiles because Grignard reagents are used in these reactions.[2d,8] Accordingly, the general, mild and operationally simple method for both formylation and acylation of indoles is highly desirable.

Herein, we demonstrate that this goal can be realized by employing the transition metal-catalyzed oxidative coupling of free (N−H) indoles with anilines. We have established that the Ru-catalyzed reactions with *N*-methyl aniline lead to C3-formylation of indoles, whereas the Fe-catalyzed reactions with *N*-benzylaniline enable C3-acylation of indoles (eq 1). These two processes are both operationally simple, proceed under mild conditions with high regioselectivity in good yields, and have good functional group compatibility, thereby circumventing the aforementioned issues in traditional indole-formylation or acylation methods. To the best of our knowledge, the transformation of amines into carbonyl compounds via metal-catalyzed oxidative cross-coupling had not been reported before our work, although there have been many excellent studies on the oxidation of amines and the relevant transformations.[9,10]



(1)

The previous mechanistic studies have disclosed that both Vilsmeier−Haack formylation and acylation involve the formation of the initial iminium ion intermediate, followed by the subsequent electrophilic aromatic substitution to produce the second iminium ion, which is hydrolyzed to form the desired aryl aldehyde and aryl ketone.[11] Considering the same iminium ion intermediate is proposed as the key intermediate in the metal-catalyzed oxidative coupling of amines, we speculated that the suitable reaction conditions would enable the oxidative coupling of amines with electron-rich aromatic compounds to produce formylation or acylation products. Using the conditions recently developed by us for the Co- and Mn-mediated oxygenative coupling of indoles with β-keto esters,[12] the reaction of free (N−H) indole **1a** with 1.5 equiv of *N*-methyl aniline **2a** provided the promising result, albeit in about 5% yield. Further investigations revealed that 5 mol % of the hydrate $RuCl_3 \cdot xH_2O$, in combination with 4 equiv of *tert*-butyl hydrogenperoxide (TBHP) in a 70 wt % aqueous solution can catalyze this reaction at room temperature, furnishing 3-fomylindole **3a** in 30% yield (entry 1, Table 1). Our interest in this $RuCl_3$-catalyzed room-temperature transformation prompted us to investigate the impacts of various parameters on the reaction outcomes.

The results from the optimization studies are summarized in Table 1. Starting from the conditions in entry 1, we screened various oxidants and found that other oxidants including *tert*-butyl peroxybenzoate (TBPB), an analogue of TBHP, are either

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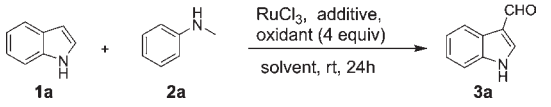
Table 1. Optimization of Ru-Catalyzed Indole Formylation[a]



entry	catalyst	oxidant	**2a** (equiv)	additive (equiv)	solvent	yield (%)[b]
1	$RuCl_3$	TBHP[c]	1.5	none	DMA	30
2	$RuCl_3$	H_2O_2[d]	1.5	none	DMA	10
3	$RuCl_3$	TBPB[e]	1.5	none	DMA	0
4	$RuCl_3$	O_2 (1 atm)	1.5	none	DMA	0
5	$RuCl_3$	TBHP	1.5	PivOH (1)	DMA	32
6	$RuCl_3$	TBHP	1.5	PivOH (3)	DMA	38
7	$RuCl_3$	TBHP	1.5	PivOH (5)	DMA	63
8	$RuCl_3$	TBHP	1.5	PivOH (7)	DMA	53
9	$RuCl_3$	TBHP	2	PivOH (5)	DMA	73
10	$RuCl_3$	TBHP	2	PivOH (5)	DMF	25
11	$RuCl_3$	TBHP	2	PivOH (5)	DMSO	72
12	**$RuCl_3$**	**TBHP**	**2**	**PivOH (5)**	**NMA**[f]	**81**
13	$RuCl_3$[g]	TBHP	2	PivOH (5)	NMA	61
14	none	TBHP	2	none	NMA	0
15	$FeCl_2$[h]	TBHP	2	PivOH (5)	NMA	40

[a] Reaction conditions: 0.5 mmol scale, and 5 mol % $RuCl_3 \cdot xH_2O$ at 25 °C for 24 h. [b] Isolated yield. [c] TBHP = *tert*-butyl hydrogenperoxide. [d] 35 wt % solution in water. [e] TBPB = *tert*-butyl peroxybenzoate. [f] NMA = *N*-methylacetamide. [g] 1 mol % $RuCl_3 \cdot xH_2O$. [h] 10 mol % $FeCl_2$.

ineffective or less effective than TBHP (entries 2−4). Although the reaction in entry 1 gave a poor yield, **1a** was completely consumed due to the oxidative decomposition. Recently, it has been established that carboxylic acids can efficiently inhibit the decomposition of indoles under oxidative conditions.[12,13] Indeed, the introduction of 5 equiv of pivalic acid into the reaction system significantly suppressed the decomposition of indole and therefore enhanced the reaction efficiency (entry 7). The yield of **3a** was further improved to 73% when increasing the amount of **2a** from 1.5 to 2 equiv (entry 9). The effect of solvent on the reaction efficiency was also observed (entries 10−12). Among the tested solvents, *N*-methylacetamide gave the best result (entry 12). The reduction of $RuCl_3$ loading to 1 mol % gave rise to a decrease in yield (entry 13). No formylation product was obtained in the absence of $RuCl_3$ (entry 14). Interestingly, 10 mol % $FeCl_2$ also effected formylation of indole under otherwise identical conditions, although less effective than $RuCl_3$ (entry 15).

To evaluate the potential of various amines to function as formylation reagents, other amines were also subjected to the reaction conditions optimized for **2a** (entry 12, Table 1) As shown in Table 2, only *N*,*N*-dimethylaniline **2d** afforded **3a** in only 29% yield, and other amines were ineffective, which clearly illustrated that the choice of amines is crucial to achieving indole formylation. The ability of *N*-methylaniline and *N*,*N*-dimethylaniline to formylate indole stems from their *N*-aryl subunit that may play a role in stabilizing the charged iminium intermediate.

With the optimized reaction conditions in hand, we explored the substrate scope using **2a** as fomylating reagent. The Ru-catalyzed C3-selective formylation of free (N−H)

Table 2. Oxidative Transformation of Indole with Various Amines

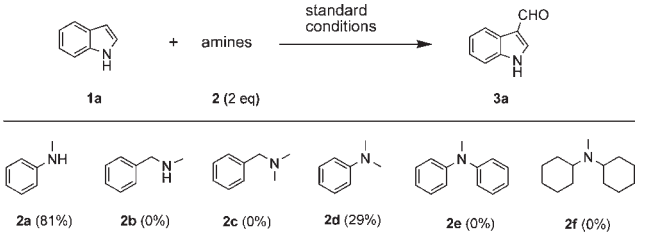
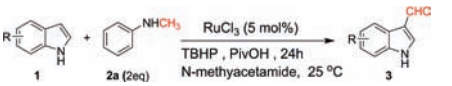


Table 3. Scope of Ru-Catalyzed Indole Formylation[a]



entry	product	Isolated yield	entry	indole	Isolated yield
1	**3a**	81%	9	**3i**	63%
2	**3b**	71%	10	**3j**	60%
3	**3c**	80%	11	**3k**	73%
4	**3d**	66%	12	**3l**	75%
5	**3e**	70%	13	**3m**	70%
6	**3f**	63%	14	**3n**	73%
7	**3g**	50%	15	**3o**	70%
8	**3h**	54%	16	**3p**	34%

[a] Reaction conditions: indole (0.5 mmol), *N*-methyl aniline (1 mmol), $RuCl_3 \cdot xH_2O$ (0.025 mmol), TBHP (2 mmol, 70 wt % in water), PivOH (2.5 mmol), *N*-methylacetamide (1 mL, 0.5 M), 25 °C, 24 h.

indoles was compatible with a range of substituents in all positions on the benzene ring of indole, and generated the corresponding products in reasonable to good yields. Notably, C−Cl, C−Br, and C−I bonds remained intact during the reaction (entries 12−15, Table 3), providing an additional handle for further elaboration of products. Compared with electron-donating groups, electron-withdrawing groups afforded modestly lower yields presumably because of the lowered nucleophilicity. For the same reason, electron-deficient *N*-acetyl indole was ineffective in the reaction. As an exception, the highly electron-rich 2-methylindole provided only 34% yield (entry 16) because its electron-richness makes it unstable under oxidative conditions.

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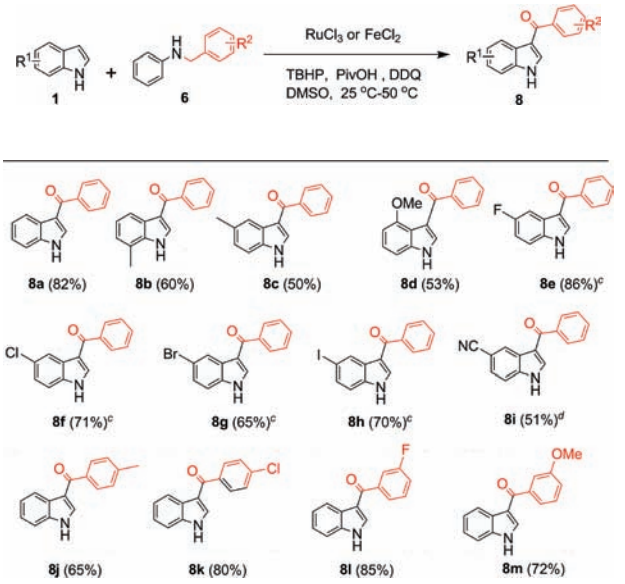
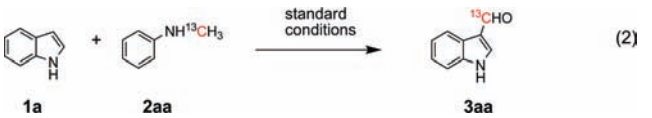
Table 4. Scope of Ru- or Fe-Catalyzed Acylation of Indole[a,b]



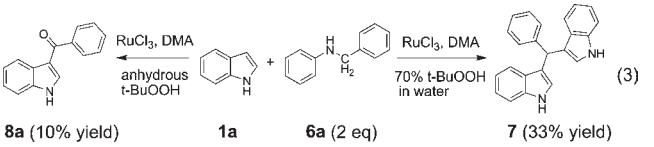
[a] Reaction conditions: indole (0.25 mmol), anilines (0.75 mmol), $FeCl_2$ (0.025 mmol), DDQ (0.025 mmol), TBHP (1.5 mmol, 5−6 M in decane), PivOH (1.25 mmol), DMSO (0.5 mL, 0.5 M), 25 °C, 24 h. [b] Isolated yields. [c] *N*-benzylaniline (0.5 mmol), TBHP (1 mmol). [d] *N*-benzylaniline (0.5 mmol), TBHP (1 mmol), $RuCl_3 \cdot xH_2O$ (0.0125 mmol), 50 °C, 24 h.

^{13}C-labeled methyl aniline **2aa** was used to explore the potential role of aniline in the formylation process. The reaction of **1a** with **2aa** gave the ^{13}C-labeled 3-formylindole (eq 2) which was confirmed by ^{1}H and ^{13}C NMR spectral analysis. The ^{13}C-labeling experiments clearly showed that the carbonylic carbon atom in the formylation product derived from the methyl group of *N*-methyl aniline.



(2)

The accomplishment of selective indole fomylation encouraged us to investigate whether the indole acylation can be realized via the oxidative coupling of indoles with amines. However, the reaction of *N*-benzylaniline (**6a**) with **1a** under the conditions newly established for indole formylation produced 3, 3′-(phenylmethylene)bis-indole **7** in 33% yield instead of the desired acylation product (eq 3). Compound **7** could result from the hydrolysis of the iminium intermediate generated form oxidation of **6a** because of the presence of a large amount of water.[14a] A similar reaction catalyzed by CuBr has been described by Bao and co-workers recently.[14b] As anticipated, replacing an aqueous solution of TBHP with anhydrous TBHP solution (5−6 M in decane) led to the formation of the acylation product 3-benzoylindole **8a** in 10% yield under otherwise identical conditions. Introducing 10 mol % DDQ, a reagent usually used for dehydrogenation,[11,15] into reaction system increased yield of **8a** to 30%. When DMSO was used as a solvent in place of DMA, the Ru-catalyzed process furnished a synthetically useful yield (66%). Gratifyingly, the more efficient transformation was achieved by employing $FeCl_2$ as a catalyst. In the presence of 10 mol % $FeCl_2$ as a catalyst and 6 equiv of TBHP, the reaction of **1a** with 3 equiv of **6a** in DMSO at 25 °C generated C3 acylation product in 82% yield.



(3)

Obviously, the readily available and nontoxic iron catalyst is more attractive.[16] The substrate scope of the Fe-catalyzed indole acylation reaction is expandable. As shown in Table 4, an array of free (N−H) indoles can be acylated on 3-position in synthetically useful yields, and electronically diverse benzoyl groups can be installed onto indole rings. The reaction of cyano-substituted indole is an exception in which 5 mol % $RuCl_3$ rather than $FeCl_2$ was required to obtain a synthetically useful yield. Unfortunately, *N*-alkyl anilines such as *N*-ethyl aniline and *N*-isopropyl aniline did not form the corresponding 3-acyl indole.

Further experiments have been done to obtain the insight into the mechanism of this oxidative coupling of indoles with amines. Similarly to the Ru-catalyzed oxidation of amines with TBHP,[17a] 10 mol % $FeCl_2$ catalyzed oxidation of *N*-benzylaniline with 4 equiv of TBHP gave imine as well as benzenamine and benzaldehyde in the absence of indole. However, neither imine nor the combination of benzenamine and benzaldehyde reacted with indole under standard conditions to give the corresponding 3-acylindole, which ruled out the possibility that imine or benzaldehyde is an intermediate in the reaction. *N*-((1H-Indol-3-yl)methyl)aniline was observed to generate 3-formylindole under the conditions established above for the Ru-catalyzed indole formylation (see Supporting Information). In light of these observations, the oxidative coupling of indole with amine to 3-formylindole or 3-acylindole may be initiated by the oxidation of amine via the Horner mechanism[17b,c] to form the iminium ion intermediate, in which $RuCl_3$ or $FeCl_2$ acts as a catalyst for the activation of TBHP. Subsequently, the nucleophilic indole captures the iminium ion intermediate to form the cross-dyhydrogenative-coupling product that undergoes further oxidation to the second iminium ion, followed by hydrolysis to generate 3-formylindole or 3-acylindole.

In conclusion, we have developed a convenient and general method for formylation and acylation of free (N−H) indoles via Ru- or Fe-catalyzed oxidative coupling of free (N−H) indoles with anilines. These reactions proceed under mild conditions with high regioselectivity and show good functional group compatibility. Further studies on their synthetic applications are in progress.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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