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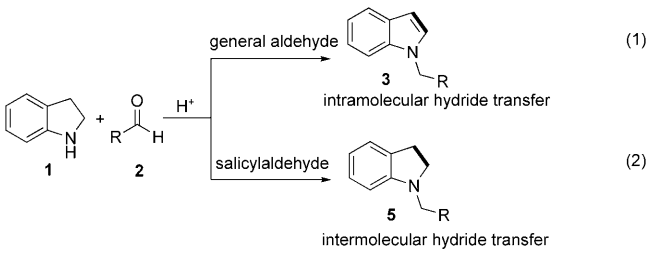
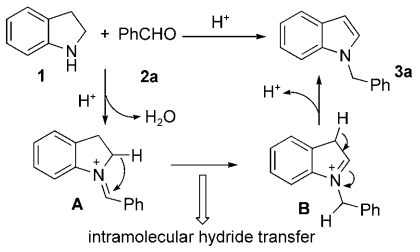
Tunable Hydride Transfer in the Redox Amination of Indoline with Aldehyde: An Attractive Intramolecular Hydrogen-Bond Effect

Hui Mao,[a] Runsheng Xu,[a] Jieping Wan,[a, b] Zhengyang Jiang,[a] Cuirong Sun,*[a] and Yuanjiang Pan*[a]

Analogous to atom economy[1] and step economy,[2] redox economy has received considerable attention in modern organic synthesis, especially in the total synthesis of natural products since it was proposed by Baran in 2008.[3] Through using the inherent reducing power of hydrogen to reduce other functional groups, redox isomerizations can reduce the additional steps of oxidation or reduction.[3b] Moreover, selective C–H bond functionalization has been accomplished via intramolecular hydride transfer in the process of redox isomerization.[4] Recently, redox amination has become a very powerful tool in C–N bond formation.[5] Our group has been interested in this field. Herein, we report a Brønsted acid-catalyzed intermolecular redox amination of indoline **1** with aldehyde **2**, which involves intramolecular hydride transfer and gives *N*-substituted product **3** [Eq. (1)]. *N*-Alkylindoles are prevalent in numerous biologically active natural products and pharmaceutical compounds[6] and this firstly presented manipulation is unprecedented among those established protocols.[7] Additionally, a novel type of amination involving intermolecular hydride transfer is also studied when salicylaldehyde is employed, which is switched by intramolecular hydrogen bond and leads to *N*-alkylindolines [Eq. (2)].





Scheme 1. A proposed hypothesis for the formation of *N*-benzylindole **3a**.

Our original hypothesis for the formation of *N*-benzylindole **3a** involves the condensation of indoline **1** with benzaldehyde **2a** in the presence of an acid (Scheme 1). The resulting iminium ion **A** is supposed to undergo intramolecular hydride transfer to furnish intermediate **B**. Ultimately, the final product **3a** is formed from **B** by deprotonation. The aromatization is considered to be the original motif of this redox process, which distinguishes indoline from some other cyclic secondary amine, such as tetrahydroquinoline and morpholine.

To investigate the feasibility of this redox process, we initially tested the reaction of benzaldehyde (1 equiv) with indoline (2 equiv) in the presence of AcOH (0.2 equiv) at 110 °C using toluene as reaction medium. Just as expected, the reaction gave *N*-benzylindole with 40 % yield (Table 1, entry 1). Inspired by these results, we further investigated this transformation under different conditions. Various Brønsted and Lewis acids were evaluated as catalysts in this reaction (Table 1, entries 2–7). Generally, Brønsted acids catalyzed this reaction more efficiently than Lewis acids, and benzoic acid was found to be the best among those tested. Next, we began to study the solvent effect, and tolu-

[a] H. Mao, R. Xu, Dr. J. Wan, Z. Jiang, Prof. Dr. C. Sun, Prof. Dr. Y. Pan
Department of Chemistry, Zhejiang University
Hangzhou 310027 (P. R. China)
Fax: (+86) 571-87951629
E-mail: cheyjpan@zju.edu.cn

[b] Dr. J. Wan
College of Chemistry and Chemical Engineering
Jiangxi Normal University, Nanchang 330022 (P. R. China)

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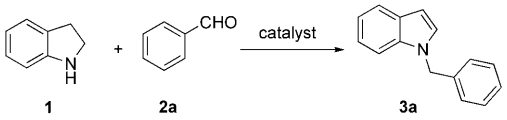
ene turned out to be the best medium compared with DMSO, DMF and 1,4-dioxane (Table 1, entries 8–10). Further optimization was focused on reaction temperature, and the best result was achieved at 125 °C (Table 1, entries 11–13). Remarkably, addition of 4 Å MS led to higher yields (Table 1, entry 14). The use of 2 equiv indoline was essential to allow full conversion of aldehyde and provide high yield.

Table 1. Optimization of intermolecular redox amination.[a]



1 2a 3a

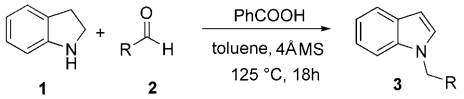
Entry	Catalyst	Solvent	T [°C]	Yield [%][b]
1	AcOH	toluene	110	40
2	TFA	toluene	110	41
3	*p*-TsOH	toluene	110	45
4	PhCOOH	toluene	110	60
5	$FeCl_3$	toluene	110	trace
6	TMSCl	toluene	110	20
7	$CoCl_2$	toluene	110	trace
8	PhCOOH	DMSO	110	58
9	PhCOOH	DMF	110	48
10	PhCOOH	1,4-dioxane	110	45
11	PhCOOH	toluene	115	65
12	PhCOOH	toluene	125	70
13	PhCOOH	toluene	130	67
14	PhCOOH	toluene	125	76[c]

[a] Benzaldehyde (0.5 mmol), indoline (1.0 mmol) and catalyst in 2 mL of solvent under nitrogen atmosphere for 18 h. [b] Yield of isolated product based on benzaldehyde. [c] 4 Å MS (20 mg) was added.

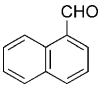
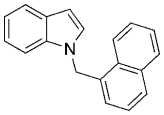
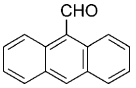
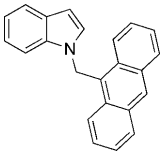
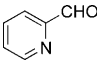
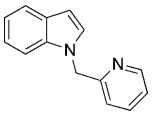
Under the established protocol, we next examined the scope of this redox amination with a variety of different aldehydes. As shown in Table 2, various aldehydes bearing electron-donating or -withdrawing groups on the aromatic ring were treated with indoline to smoothly afford corresponding *N*-alkylindoles in moderate to good yields (Table 2, entries 1–13). Generally, the aldehyde substrates having electron-donating groups demanded longer time and got lower yields (Table 2, entries 2–3). 1-Naphthaldehyde and 9-anthraldehyde were also found to react with indoline to give desired products in good yields (Table 2, entries 14–15). Furthermore, heteroaromatic aldehydes turned out to be excellent partners for the redox amination (Table 2, entries 16–18). While aromatic aldehydes having electron-donating groups at *para*-position or aliphatic aldehydes were employed, this redox process failed to give desired product.

Unexpectedly, when salicylaldehyde was employed in the standard condition, instead of our desired product, the reaction afforded *N*-alkylindoline **5a**, of which the structure was fully characterized by mass spectrometry and NMR spectroscopy. Encouraged by the novel amination, we subsequently examined the scope of the reaction, and typical results were summarized in Table 3.[8] To our delight, the reactions proceeded smoothly to give *N*-alkylindolines in 73–82% yields (Table 3, entries 1–4). In addition to indoline, the 2-methylindoline also showed good reactivity, albeit with longer time and lower yields (Table 2, entries 5–7).

Table 2. Representative intermolecular redox amination.[a]

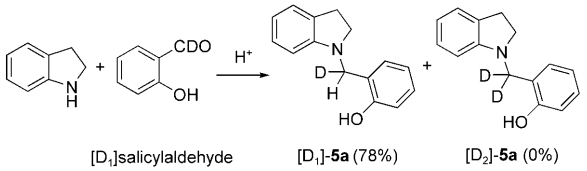


1 2 3

Entry	Aldehyde **2**	Product **3**	Yield [%][b]
1	R = H	**3a**	76
2	R = *o*-OMe	**3b**	69[c]
3	R = *o*-OMOM	**3c**	68[c]
4	R = *p*-F	**3d**	79
5	R = *o*-F	**3e**	81
6	R = *p*-Cl	**3f**	77
7	R = *o*-Cl	**3g**	78
8	R = *p*-Br	**3h**	75
9	R = *o*-Br	**3i**	77
10	R = *p*-CF_3	**3j**	80
11	R = *p*-NO_2	**3k**	80
12	R = *m*-NO_2	**3l**	82
13	R = *o*-NO_2	**3m**	85
14		**3n** 	73
15		**3o** 	70
16	X = O	**3p**	86
17	X = S	**3q**	84
18		**3r** 	80

[a] Aldehyde (0.5 mmol), indoline (1.0 mmol), PhCOOH (0.1 mmol) and 4 Å MS (20 mg) in 2 mL toluene under nitrogen atmosphere for 18 h. [b] Yield of isolated product based on aldehyde. [c] 30 h.

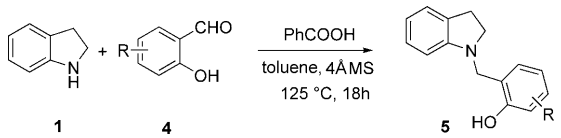
In view of our original hypothesis, the indoline-type product implies that this novel amination may involve intermolecular hydride transfer. In the reaction system, obviously, there are only two potential candidates, that is, salicylaldehyde[9] and indoline that can provide the external hydride.



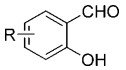
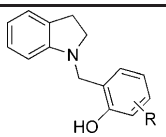
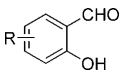
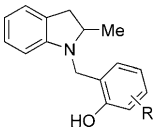
[D_1]salicylaldehyde [D_1]-**5a** (78%) [D_2]-**5a** (0%)

Scheme 2. Isotopic labeling reaction.

Table 3. Novel amination of indoline with salicylaldehyde.[a]



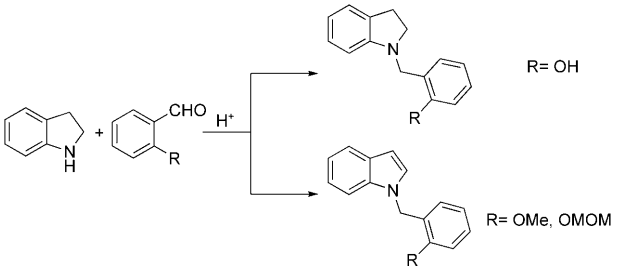
1 4 5

Entry	Salicylaldehyde **4**	Product **5**	Yield [%][b]
			
1	R = H	**5a**	82
2	R = 5-NO_2	**5b**	78
3	R = 5-Cl	**5c**	75
4	R = 3,5-dibromo	**5d**	73
			
5[c]	R = H	**5e**	77
6[c]	R = 5-Cl	**5f**	72
7[c]	R = 3,5-dibromo	**5g**	70

[a] Salicylaldehyde (0.5 mmol), indoline (1.25 mmol), PhCOOH (0.1 mmol) and 4 Å MS (20 mg) in 2 mL toluene under nitrogen atmosphere for 18 h. [b] Yield of isolated product based on benzaldehyde. [c] 2-Methylindoline (1.25 mmol) was added instead of indoline, 30 h.

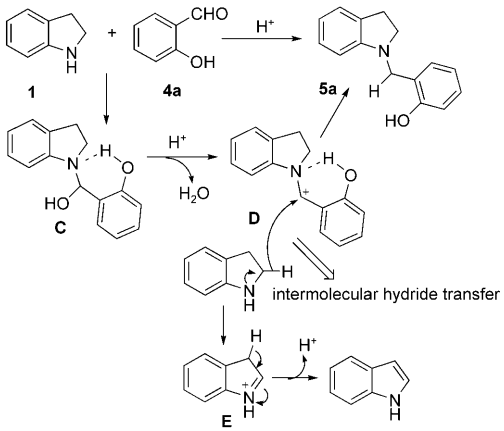
To investigate whether the hydride came from another molecular salicylaldehyde, an isotopic labeling reaction was carried out between indoline and [D_1]salicylaldehyde (Scheme 2), which was prepared by reduction of salicylic acid with $LiAlD_4$ and subsequent oxidation with PDC.[10] As shown in Scheme 1, the reaction gave [D]-**5a** with 78% isolated yield while no [D_2]**5a** was determined (see Supporting Information for the full determination of [D]-**5a**). According to the result from the deuterium labeling experiment, the external hydride is believed to come from another molecular indoline, which is also supported by the isolation of same amount of byproduct indole.[11]

On the other hand, as shown in Scheme 3, when the hydroxyl group of salicylaldehyde is protected by Me or MOMO, the product becomes indole-type, indicating that the hydroxyl group at *ortho*-position has an important impact on the reaction process.[12]



Scheme 3. Effect of substituent groups at the *ortho*-position.

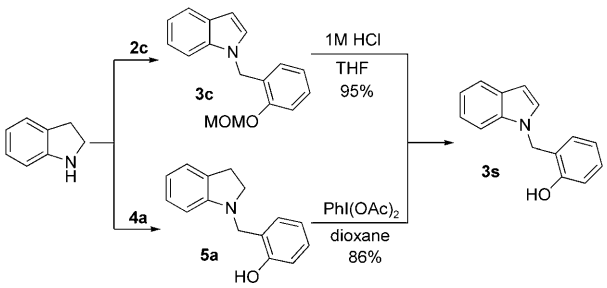
Based on these results, we propose a mechanism for this novel amination in Scheme 4. Initially, the indoline attacks



Scheme 4. Proposed mechanism for this novel amination.

salicylaldehyde to afford addition product **C**, which subsequently transforms into intermediate **D** in the presence of an acid. Due to the effect of intramolecular hydrogen bond (N–H···O) in **D**, the intramolecular hydride transfer is inhibited. After intermolecular hydride transfer from another molecular indoline to **D**, the final product **5a** is obtained. Meanwhile, the intermediate iminium ion **E**, generated from indoline, transforms into indole by deprotonation.

Although γ-hydroxy indole **3s** couldn't be obtained directly from the reaction of indoline with salicylaldehyde, two potential methods for its preparation had been achieved in Scheme 5. Compound **3c**, readily prepared from indoline, was converted to **3s** by deprotection in a straightforward fashion. And treatment of **5a** with $PhI(OAc)_2$ in dioxane also produced **3s** in good yield.[13]



Scheme 5. Synthesis of γ-hydroxy indole **3s**.

In summary, we have developed a Brønsted acid-catalyzed redox amination of indoline with aldehyde for the synthesis of *N*-alkylindoles and *N*-alkylindolines, in which an attractive intramolecular hydrogen bond effect was observed. Through this efficient and economic protocol, a series of *N*-alkylindoles were prepared from readily available aldehydes. Furthermore, by employing salicylaldehyde in the reaction, a novel type of amination involving intermolecular hydride transfer is also demonstrated to synthesize *N*-alkylindolines. We anticipate that this unique amination may stimulate sub-

sequent redox research. Further studies on the mechanism and synthetic applications are underway in our laboratory.

Experimental Section

Representative procedure (3a): To a solution of benzaldehyde (0.5 mmol), indoline (1.0 mmol) in toluene (2 mL) was added PhCOOH (0.1 mmol) and 4 Å MS (20 mg) under nitrogen atmosphere. The mixture was stirred at room temperature for 0.1 h and then heated at 125 °C for another 18 h. After the completion of the reaction, the solvent was evaporated off and the crude mixture was purified by flash column chromatography to give the product **3a** in 76 % yield.

Acknowledgements

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Keywords: hydride transfer · hydrogen bonds · indoles · redox amination · redox chemistry

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[8] For the optimization of this novel amination, see the Supporting Information.

[9] The aldehyde also can be a potential candidate to supply the hydride in some reactions, such as Cannizzaro reaction. For details, see: a) S. Cannizzaro, *Liebigs Ann.* **1853**, *88*, 129; b) T. A. Geissman, *Org. React.* **1944**, *2*, 94; c) J. Kagan, *Tetrahedron Lett.* **1966**, *7*, 6097.

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[11] See Table S1 in the Supporting Information.

[12] For another example about the effect of the hydroxyl group at *ortho*-position, see: M. Xie, X. Chen, Y. Zhu, B. Gao, L. Lin, X. Liu, X. Feng, *Angew. Chem.* **2010**, *122*, 3887; *Angew. Chem. Int. Ed.* **2010**, *49*, 3799.

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