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COMMUNICATION

Indoline Hemiaminals: A Platform for Accessing Anthranilic Acid Derivatives through Oxidative Deformylation

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2-Aminobenzoyl chlorides possess both the nucleophilic nitrogen atom and electrophilic carbonyl group, and thus selective acylation of nucleophiles is challenging: Self-dimerization and sluggish reaction occurs. Herein, we introduce a new synthetic protocol using 2-aminobenzoyl surrogates, allowing concise entry to decorated 2-aminobenzoyl derivatives in the absence of transition metal, acid chlorides, and specific reagents.

Introduction

Anthranilic acids are ubiquitous in bioactive natural products and pharmaceuticals, which also are embedded within the heterocyclic motifs (Fig. 1). *N*-Sulfonamide alkaloids, such as Sargassulfamide A (**1**) and **2**, possess a unique AChE (acetylcholinesterase) inhibitory effect.[1,2] Related cyclic analogues, pentasulfamides A (**3**), also are AChE inhibitors.[3] Indoloquinolone alkaloid 5*H*,6*H*-quinindolin-11-one (**4**) was isolated from the leaves of Justicia betonica.[4] 3-(2-Aminobenzoyl)indoles **5** and **6** shows VEGFR-2 inhibitory effect and cytotoxic against cancer cell lines, respectively.[5,6]

Given the ubiquity of 2-aminobenzoyl moiety, there is a powerful impetus to develop the synthetic protocol to make these scaffolds. The current protocol mainly relies on traditional methods, such as Friedel–Crafts acylation using 2-aminobenzoyl chlorides as acylating reagents.[7] However, the existence of 2-amino group on the benzoyl moiety precluded an expansion of these traditional methodologies, which employ alternative protocol using 2-nitrobenzoyl derivatives through a multi-step process including of reduction of the nitro-group/protection of the resulting amino group sequences,[8] or poor commercially available isatoic anhydrides.[9] In 2018, Waser and co-workers developed the direct C–H functionalization of 2-aminobenzaldehydes using hypervalent iodine reagents bearing indole units to provide 3-(2-aminobenzoyl)indoles (Scheme 1b).[10] One of the drawbacks of such metal-catalyzed C–H strategies is the use of precious metal catalyst. Despite recent progress, exploration of an alternative platform in the absence of precious metals to install medicinally relevant 2-aminobenzoyl moieties remains a challenging task.

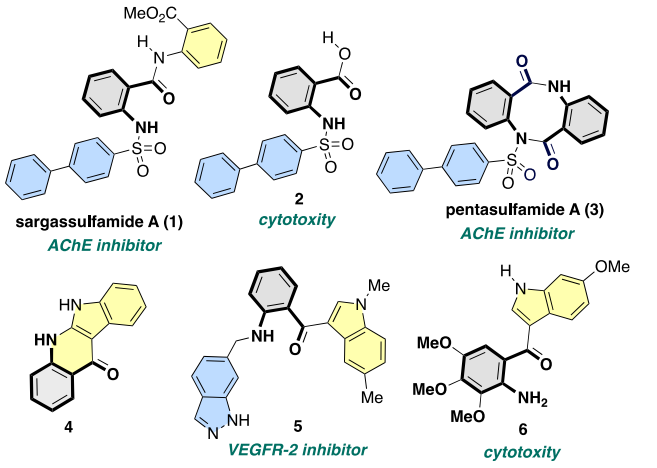

Fig. 1 Natural products and biological active materials bearing 2-Aminobenzoyl moiety.

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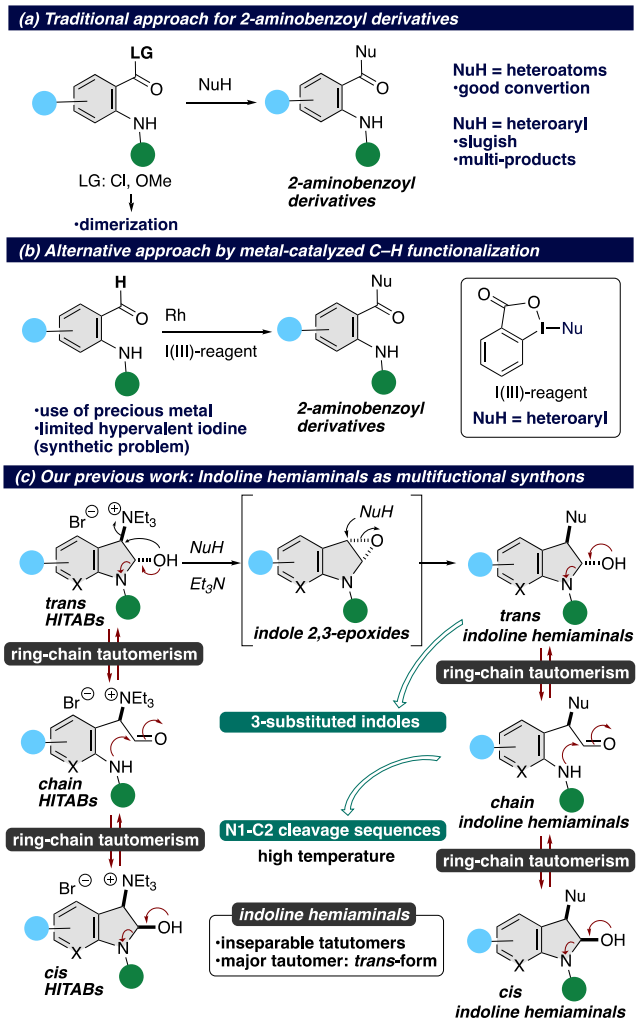
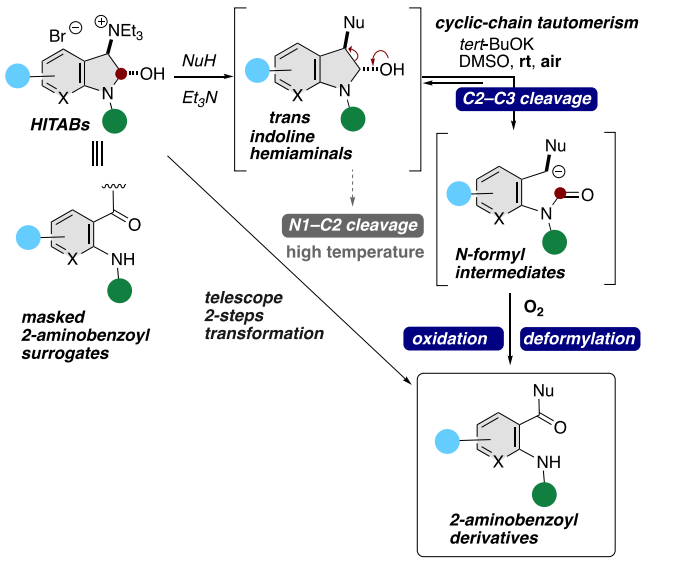


scheme 1 (a) Traditional approach for synthesis of 2-aminobenzoyl derivatives; (b) Alternative C–H approach (c) Our previous work.

In 2017, our group introduced indole-2,3-epoxide equivalents, HITABs (2-hydroxy-3-triethylammonium-2-hydroxyindoline bromide) that can act as a C3-electrophilic indole against a variety of nucleophiles to afford 3-substituted indoline hemiaminals (Scheme 1c).[11] Notably, both HITABs and 3-substituted indoline hemiaminals exist as an inseparable mixture of tautomers between *trans*-cyclic hemiaminals, linear aldehyde, and *cis*-cyclic hemiaminals.[12] During our campaign, we found that the obtained 3-substituted indoline hemiaminals engaged in the N1-C2 cleavage sequences such as ring-switch reactions[13], formation of 2-aminobenzyl compounds[14] and rearrangement of a nitrogen atom[15] through the tautomeric control. This activation mode in the tautomerism of indoline hemiaminals is compatible with both acidic and basic conditions. Inspired by these findings, we sought to merge the C2-C3 cleavage reactions with activation of indoline hemiaminals to explore a new synthetic platform that utilizes HITABs as anthranilic acid surrogates (C2-C3 cleavage, alternative cyclic-chain tautomerism, Scheme 2). Herein, we introduce a new synthetic protocol using 2-aminobenzoyl surrogate, allowing concise entry to decorated 2-aminobenzoyl derivatives in the absence of transition metal, acid chlorides, and specific reagents.



scheme 2 This work: Indoline hemiaminals as masked 2-aminobenzoyl surrogates.

Results and discussion

We started our investigations by evaluating the performance of *tert*-BuOK (3 equiv.) in the oxidative deformylation of indoline hemiaminal *trans*-**8aa** (*trans*:*cis* = 10:1), which exists in equilibrium with cyclic hemiaminal *cis*-**8aa** through linear aldehyde-**8aa** (Table 1). As shown, various solvents proved capable of promoting the expected transformation under air validating our hypothesis (entries 1–7). Among them, THF and DMSO outperformed other solvents such as toluene, MeCN, MeOH, CH_2Cl_2, and DMF (entries 1 and 7). Among the number of equivalents of *tert*-BuOK, 3 equiv. of *tert*-BuOK afforded the best result (entries 7 vs 8–10). Reaction at room temperature under argon atmosphere, which was implemented by backfilling with argon balloon, gave inferior yield (8%) without the formation of **10aa**, while the previous conditions (DMSO, 100 °C, under argon atmosphere) affords **10aa** in 85% yield (entry 11).[14] It is reported that a small amount of O_2 still exists as dissolved oxygen in the reaction system under argon atmosphere.[16] Also in our case, the residual dissolved oxygen in the reaction mixture may play as an oxidant. Small amounts of oxygen were proven to be necessary to start the reaction, as no product was isolated when the reaction was conducted in DMSO with freeze–pump–thaw (FPT) cycling under argon atmosphere (entry 12). When the reaction was employed under O_2 atmosphere, the yield maintained (80% yield, entry 13). This result suggests that the combination of air (O_2) and room temperature play a key role in differentiating the obtained products. Screening of bases showed that *tert*-BuOK is the superior base (entries 14–20). No reaction was observed at all in the absence of bases (entry 21).

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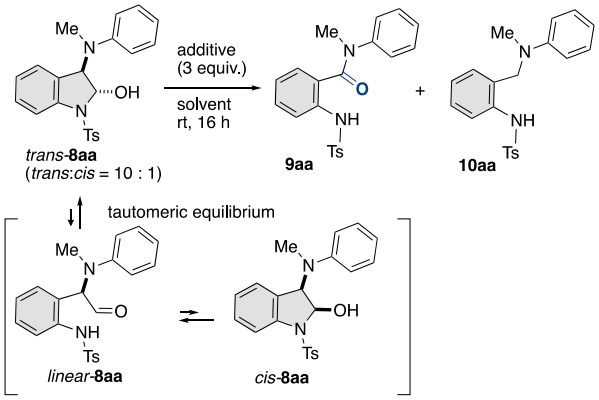
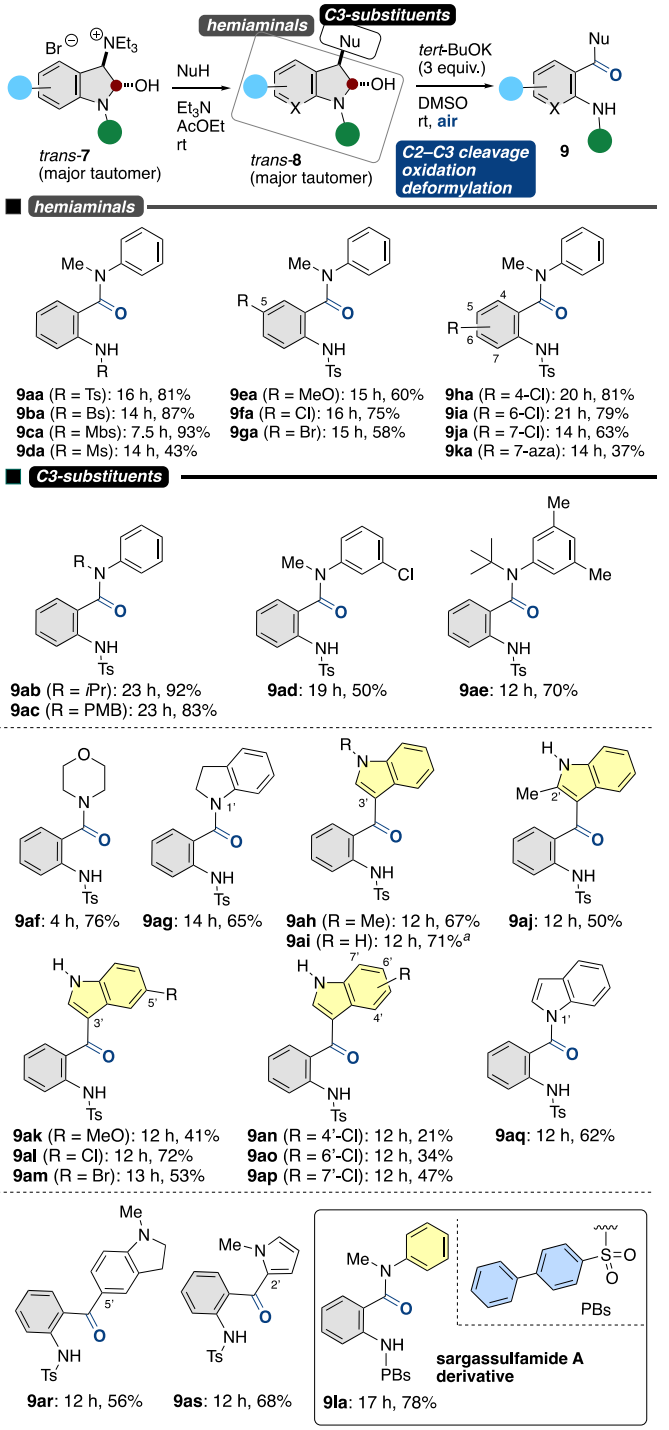
Table 1 Optimization of reaction conditions.[a]



Entry	Additive	solvent	Yield (%) of **9aa**[b]	Yield (%) of **10aa**[b]
1	***tert*-BuOK**	**THF**	**81**	**3**
2	*tert*-BuOK	toluene	75	1
3	*tert*-BuOK	MeCN	66	5
4	*tert*-BuOK	MeOH	65	0
5	*tert*-BuOK	CH_2Cl_2	71	0
6	*tert*-BuOK	DMF	76	4
7	***tert*-BuOK**	**DMSO**	**81**	**3**
8[c]	*tert*-BuOK	DMSO	61	3
9[d]	*tert*-BuOK	DMSO	72	2
10[e]	*tert*-BuOK	DMSO	49	0
11[f]	*tert*-BuOK	DMSO	1	0
12[g]	*tert*-BuOK	DMSO	0	0
13[h]	*tert*-BuOK	DMSO	80	0
14	*tert*-BuONa	DMSO	79	0
15	*tert*-BuOLi	DMSO	60	0
16	NaOH	DMSO	80	0
17	KOH	DMSO	77	0
18	K_2CO_3	DMSO	24	4
19	$CsCO_3$	DMSO	74	0
20	Et_3N	CH_2Cl_2	trace	-
21	none	DMSO	0	0

[a] Reaction conditions: **8aa** (1.0 mmol), additive (3.0 mmol), solvent (5 mL, 0.2 M) under air. [b] Isolated yields. [c] Using 5 equiv. of *tert*-BuOK. [d] Using 2 equiv. of *tert*-BuOK. [e] Using 1 equiv. of *tert*-BuOK. [f] Under argon. [g]The reaction was performed in DMSO with FPT cycling under argon. [h]Under O_2 (1 atm).

With optimal reaction conditions for model reaction in hand, we next investigated the substrate scope (Scheme 3e). First, the scope with respect to indoline hemiaminals **8** was examined. Notably, N-sulfonyl substituted substrates proceeded smoothly to give the corresponding products **9aa**–**9da** in 81%, 87%, 93%, and 43% yields, respectively. Substrates bearing electron-donating or withdrawing group at the 5-position on the indoline ring were found to be competent substrates, affording **9ea**–**9ga** in 58–75% yields. The reaction with 7-substituted substrates resulted in lower yields due to their steric factor (**9ja** and **9jk**), while the reactions with 4-, and 6-substituted substrates gave high yields of **9ha** (81%) and **9ia** (79%).

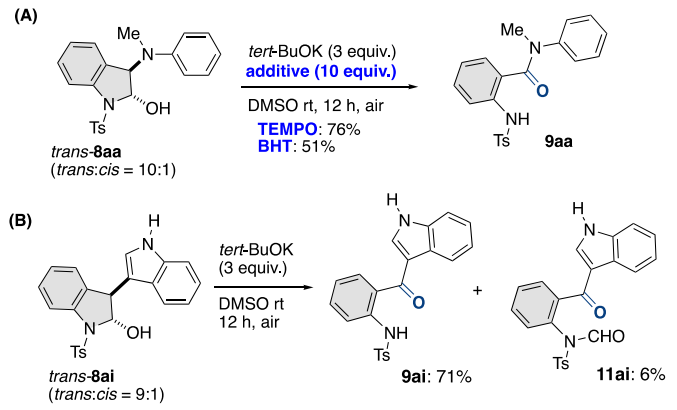


Scheme 3 Oxidative deformylation reactions of indoline hemiaminals: Reaction conditions: **8** (0.5 mmol), *tert*-BuOK (1.5 mmol) in DMSO (3 mL, 0.17 M) at rt under air. Isolated yields of **9** were based on **8**. [a]**11ai** was obtained in 6% yield.

Next, the scope of the nucleophiles was subsequently examined. To our delight, a variety of anilines are participated in our

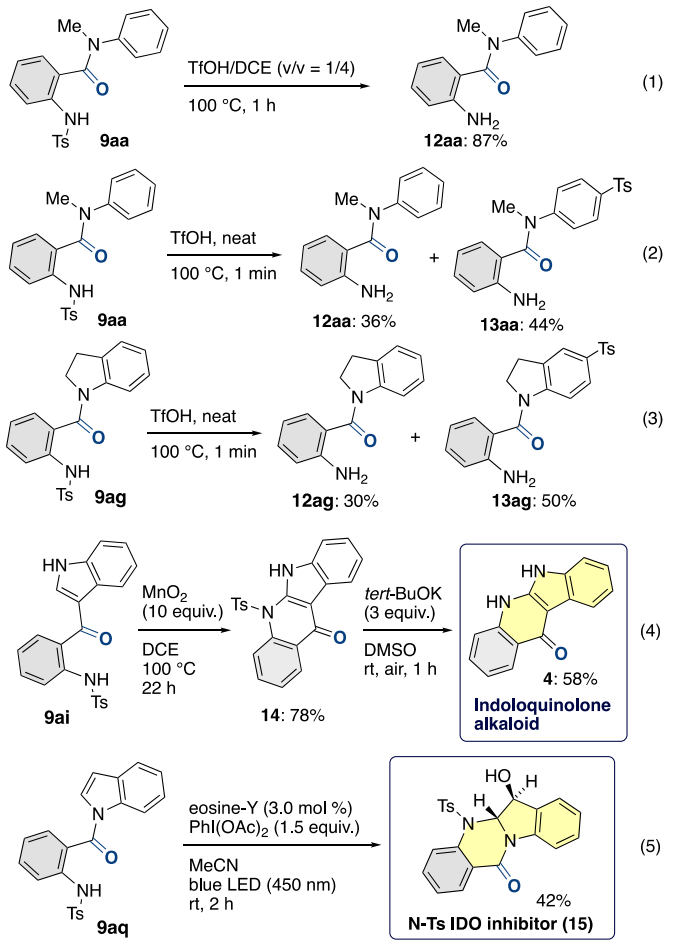
transformation and the corresponding products **9ad–9ae** were obtained in 92%, 83%, 50%, and 70% yields, respectively. Morpholine- or N-indoline-substituted hemiaminals can be also applied (**9af**: 76% yield; **9ag**: 65% yield). Importantly, the reactions of indole-substituted substrates containing N-Me (**9ah**), N-H (**9ai**), 5-MeO (**9aj**), 5-Cl (**9ak**), and 5-Br (**9al**) groups produced the corresponding products in good yields. Furthermore, substrates bearing C4, C-6, and C-7-substituted indoles worked (**9am–9an**). It is worthy to note that the Friedel–Crafts acylation of unsubstituted indoles occurs preferentially at the C-3 position due to the intrinsic nucleophilicity of indole. However, our transformation provides a selective access to N-acylating indole **9aq** in 62% yield. Other heterocycles such as *N*-methylindoline and *N*-methylpyrrole gave the 2-aminobenzoyl products **9ar** and **9as** in 56% and 68% yields, respectively.

To investigate the reaction mechanism, we conducted the reaction in the presence of radical scavengers (Scheme 4A). The reaction in the presence of 10 equiv of 2,2,6,6-tetramethylpiperidine 1-oxyl free radical (TEMPO) or 2,6-di-tert-butyl-4-hydroxytoluene (BHT) afforded a moderate decrease yield of **9aa**. These experiments provide evidence for an ion mechanism, although we could not completely rule out the radical mechanism.[17] We also observed the C2–C3 bond cleavage product **11ai** in the case of the reaction using *trans*-**8ai** (Scheme 4B), derived from a C2–C3 bond cleavage by O_2. [18]



Scheme 4 Control experiments.

The utility of 2-aminobenzoyl compounds was showcased by the follow-up chemistry (Scheme 5). For example, the tosyl group of **9aa** could be removed with TfOH in DCE at 100 °C, affording **12aa** in 87% yield (eq. 1). It is worthy to note that the tosyl group migrated to more electro-rich arene to provide **13aa** or **13ag** along with **12aa** or **12ag** under neat TfOH conditions (eq. 2 and 3).[19] Indoloquinolone alkaloid 5*H*,6*H*-quinindolin-11-one (**4**)[4] was obtained through the C–H amination of **9ai** in the presence of MnO_2[20] followed by removing of Ts group at indoloquinoline **14** (eq. 4). N-Ts indoleamine 2,3-dioxygenase inhibitor (**15**)[21] was also synthesized from the corresponding hemiaminal **9aq** through unprecedented hydroxyamination under blue LED ittadiation[22] in the presence of $PhI(OAc)_2$ (eq. 5).



Scheme 5 Follow-up-chemistry

On the basis of our results and precedents,[23] we propose the possible reaction mechanism for the production of 2-aminobenzoyl compounds (Scheme 6). First, deprotonation of indoline hemiaminal **8aa** by *tert*-BuO^- proceeds, leading to C2–C3 ring-opening intermediate **17aa** through the C2–C3 fragmentation of **16aa** at room temperature.[24] On the other hand, intermediate **17aa** undergoes N1–C2 ring-opening at high temperature[25] under argon atmosphere, leading to N1–C2 ring-opening intermediate **20aa**.[14] Then, oxidation of resulting intermediate **17aa** by O_2 through intermediate **18aa** occurs,[26] which may or may not involve a radical pathway,[27] affording N-formyl intermediate **11aa**.[28] Finally, a deformylation is realized by addition of *tert*-BuO^- towards formyl group and release of HCO_2H with 2-methylpentene, resulting a production of **9aa**.[29]

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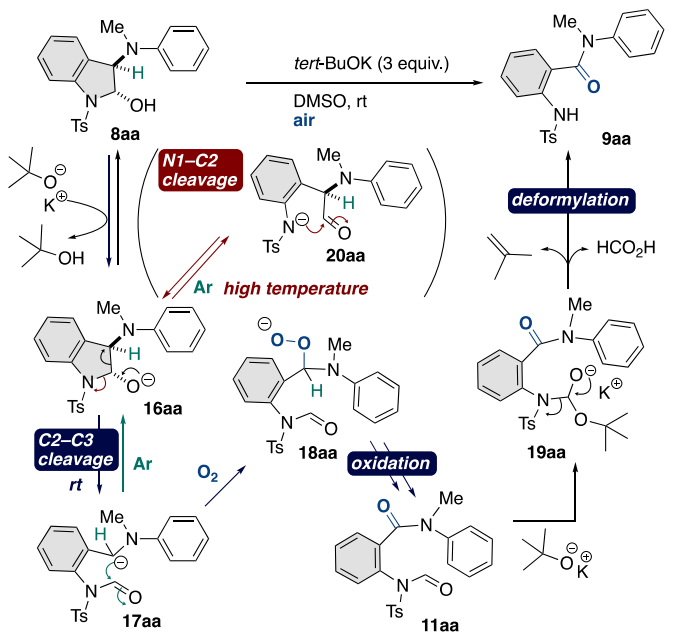

Scheme 6 Plausible mechanism.

Conclusions

In summary, we introduce indoline hemiaminals as a platform for a formal 2-aminobenzoylation that hinges on C2–C3 fragmentation followed by aerobic oxidation and deformylation sequence. In contrast to known protocol for the install of 2-aminobenzoyl moiety, our protocol provides access to a variety of indoles and aniline derivatives due to the late-stage manifestation of 2-aminobenzoyl moiety.

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Conflicts of interest

The author declares no competing interests.

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Raw data were generated at Okayama University in Japan. Derived data supporting the findings of this study are available in the published article and its online Supporting Information.