RESEARCH ARTICLE

Potassium *tert*-Butoxide-Mediated Ring-Opening of Indolines: Concise Synthesis of 2-Vinylanilines

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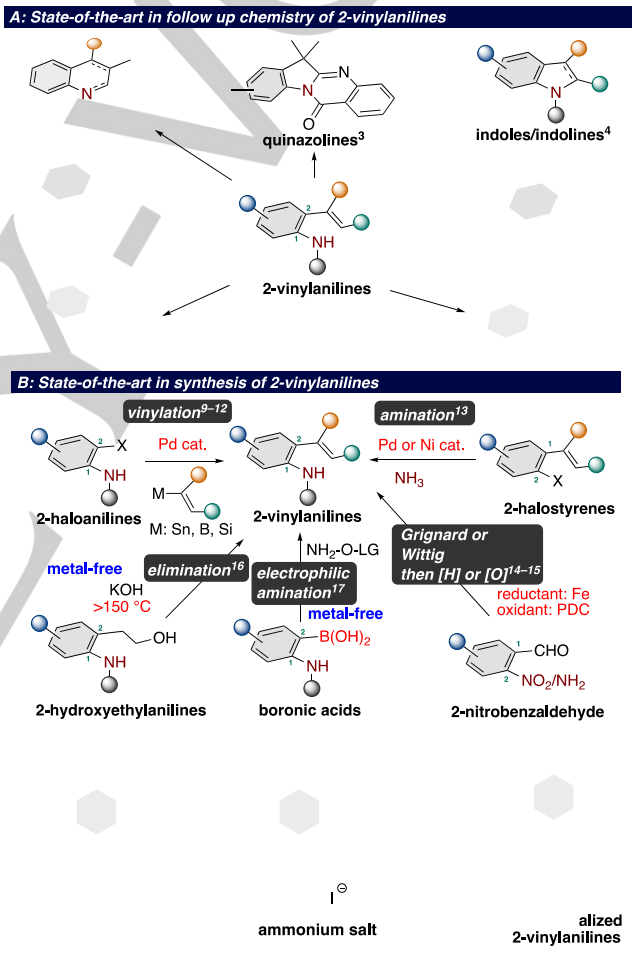
Abstract: A concise and metal-free procedure has been developed for the synthesis of 2-vinylanilines. Reactions of indolines with *tert*-BuOK in DMSO afford the decorated 2-vinylanilines in yields up to 92%. In addition, the 2, or 3-substituted indolines could be converted to trisubstituted alkenes. Also, the protocol can be scaled to afford gram quantities of the decorated 2-vinylanilines.

Introduction

2-Vinylanilines[1] are privileged substrates for accessing various heterocycles including quinolines,[2] quinazolines,[3] indoles,[4] indazoles,[5] benzoazepines,[6] 3-methyleneindolin-2-ones[7] and cinnolines[8] by cyclizations. A shared feature of a majority of these applications is the utilization of a high reactivity derived from 2-vinylanilines of both an electrophile and nucleophile: the amine can act as a nucleophile, while styrene moiety play an electrophilic role. In sharp contrast to broad applications of 2-vinylanilines, their synthesis has proven more challenging due to the intrinsic reactivity of both an electrophile and nucleophile. Thus, the synthesis of 2-vinylanilines is more difficult than their utilizations.

Recently, transition metal-catalyzed synthesis of 2-vinylanilines have been studied intensively and expands the opportunities for functionalization of the 2-vinylanilines (Scheme 1A). Palladium-catalyzed cross-coupling of 2-haloanilines with organotin reagents,[9,10] organoboronic acids,[11] organosilanes.[12] The other metal-catalyzed strategies uses an amination of 2-halostyrenes with ammonia as a nitrogen source.[13] Step-wise methodologies includes a Wittig reaction or a Grignard addition of aldehydes followed by reduction or oxidation.[14,15] Strong base-mediated metal-free traditional Hofmann elimination protocol requires harsh reaction conditions.[16] Other metal-free protocol includes a umpolung amination of 2-aminoboronic reagents with a designed amine reagent.[17] While synthesis of a densely functionalized 2-vinylaniline can be accomplished through a prefuctionalization protocol through ammonium salts or arynes,[18] a straightforward access to these molecules remains challenging. Thus, a simple metal-free straightforward transformation, especially in an atom-economical manner, is highly desirable.

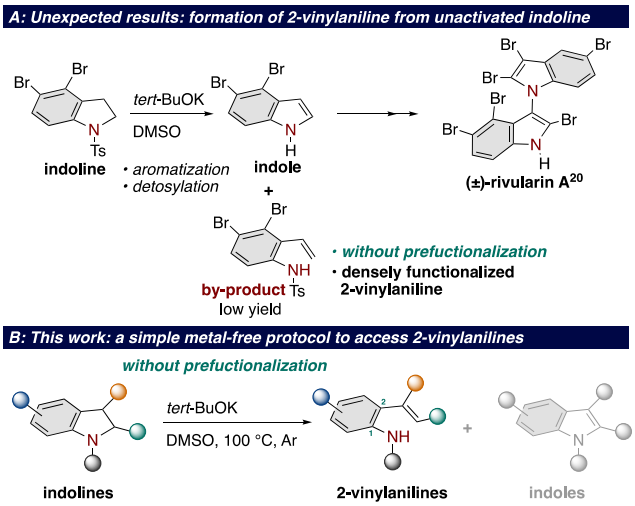
During our efforts on the indole alkaloid synthesis,[19] we recently reported the first total synthesis of polybrominated



Scheme 1. State-of-the-art in 2-vinylanilines

indole alkaloid (±)-rivularin A from 4,5-dibromoindoline (Scheme 2A).[20] The removal of tosyl group of 4,5-dibromoindoline by *tert*-BuOK afforded the desired indole with a substantial amount of no indole material as a by-product. After reinvestigation to reveal the side reaction, we determined that the structure of by-product is 3,4-dibromo-2-vinyl-aniline. Although the yield of the 2-vinylanilines is low, the result to access the densely substituted scaffolds has the potential to fill in the gap between utilizations and synthesis in the 2-vinylaniline chemistry. Considering the accessibility and

commercially availability of indolines,[21] we envisioned that this straightforward methodology could not only enable the concise 2-vinylindoline formation through ring-opening of indolines but also resulted in untapped formation of densely functionalized target molecules (Scheme 2B). We herein report the synthesis of 2-vinylanilines from indolines under transition metal-free conditions.



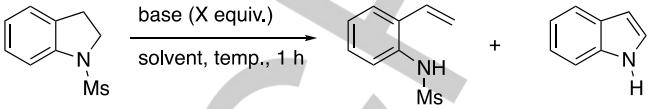
Scheme 2 (A) Unexpected results during the total synthesis of (±)-rivularin A; (B) This work.

Results and Discussion

We recognized that N-mesylindolines is an appealing substrate due to its bench-stability and easy-handling. However, the synthesis and application of N-mesylindolines were scarce.[21] We considered that the intramolecular elimination (ring-opening) step would be accelerated by using N-mesylindolines as a substrate due to their good leaving abilities.

Initially, we performed the reaction of N-mesylindoline **1aa** with *tert*-BuOK (1.5 equiv.) at 60 °C (oil-bath temperature) in DMSO under Ar atmosphere (run 1, Table 1). Gratifyingly, the desired 2-vinylaniline **2aa** was obtained in 52% yield along with a small amount of indole **3a**. Encouraged by the initial success, we conducted the optimization of the reaction conditions. Extended reaction time results in slight increased yield (65% yield, run 2). As the temperature increases, the yield of **2aa** increased (runs 1–5). At 100 °C (oil bath temperature), the best result (92% yield) was observed (run 3). Numbers of equivalents of *tert*-BuOK play an important role to operate our transformation. In the case of 1.1 equivalents of *tert*-BuOK, a slight decrease yield of **2aa** was observed (82% yield, run 6). While a large amount of *tert*-BuOK afforded a good yield of **2aa**, it remained unsatisfactory due to its reproducibility, which may be came from the solubility issue (run 7). Considering the reproducibility, 1.5 equivalents of *tert*-BuOK was still selected as the best equivalents. Then, a survey of the solvent was evaluated. Among various solvents (DMSO, DMF, THF, toluene, DCE, and MeCN), DMSO was still the best solvent (runs 3 vs. 8–12). To further improve the yield, a series of bases were evaluated (runs 13–20). The survey revealed that the strong bases were effective for our transformation and *tert*-BuOK was the best base (runs 3 vs. 13–20). Without use of *tert*-BuOK, the reaction at 100 °C did not proceed (run 21). Therefore, the optimal reaction conditions were decided: *tert*-BuOK (1.5 equiv.), DMSO (0.2 M), 100 °C, under argon (run 3).

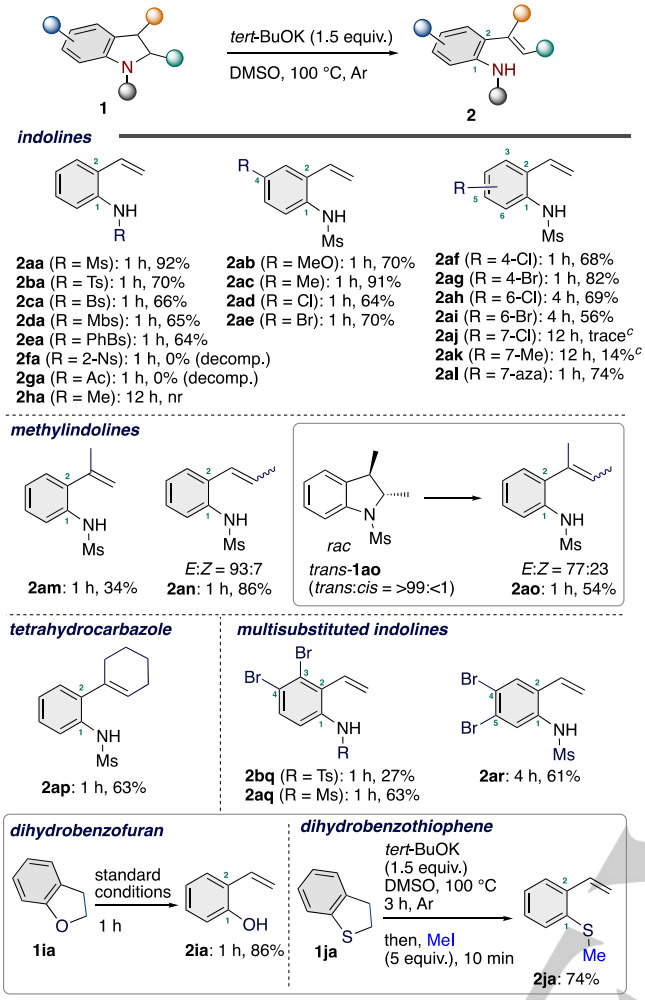
Table 1 Optimization of reaction conditions[a]



Run	base	X	Solvent	Temp., (°C)	Yield (%) **2da**[b]	Yield (%) **3a**[b]
1	*tert*-BuOK	1.5	DMSO	60	52	2
2[c]	*tert*-BuOK	1.5	DMSO	60	65	3
3	*tert*-BuOK	1.5	DMSO	80	69	2
4	***tert*-BuOK**	**1.5**	**DMSO**	**100**	**92**	**4**
5	*tert*-BuOK	1.5	DMSO	120	87	trace
6	*tert*-BuOK	1.1	DMSO	100	82	2
7	*tert*-BuOK	2.0	DMSO	100	91	4
8	*tert*-BuOK	1.5	DMF	100	54	4
9	*tert*-BuOK	1.5	THF	100	trace	–
10	*tert*-BuOK	1.5	toluene	100	0	41
11	*tert*-BuOK	1.5	DCE	100	nr	–
12	*tert*-BuOK	1.5	MeCN	100	49	3
13	*tert*-BuOLi	1.5	DMSO	100	21	2
14	*tert*-BuONa	1.5	DMSO	100	58	3
15	NaOEt	1.5	DMSO	100	17	1
16	KOH	1.5	DMSO	100	25	3
17	NaOH	1.5	DMSO	100	7	0
18	K_2CO_3	1.5	DMSO	100	nr	–
19	$CsCO_3$	1.5	DMSO	100	nr	–
20	DABCO	1.5	DMSO	100	nr	–
21	--	-	DMSO	100	nr	--

[a] Reaction condition: **1aa** (0.5 mmol), and base (0.5 x X mmol) in solvent (2.5 mL). [b] Isolated yields. [c] The reaction mixture was stirred for 2 h.

Next, we investigated the substrate scope of our transformation following the established reaction conditions. As shown in Scheme 3, our transformation shows broad functional group tolerance. Indolines with *N*-toluenesulfonyl (Ts, **1ba**), *N*-benzenesulfonyl (Bs, **1ca**), *N*-4-methoxybenzenesulfonyl (MBs, **1da**), and *N*-4-phenylbenzenesulfonyl (PhBs, **1ea**) were converted into 2-vinylanilines **2ba**, **2ca**, **2da**, and **2ea** in good yields,



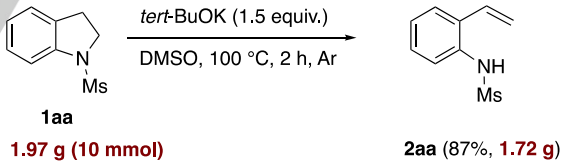
Scheme 3 Substrate scope[a,b]: [a] **1** (0.5 mmol) and *tert*-BuOK (0.75 mmol) in DMSO (2.5 mL) under Ar atmosphere at 100 °C (oil-bath temperature). [b] Isolated yields. [c] Using 3 equiv. of *tert*-BuOK.

respectively. However, the reaction using indolines with *N*-2-nitrobenzenesulfonyl (2-Ns, **1fa**), *N*-acetyl (**1ga**), and *N*-methyl (**1ha**), resulted in no reaction or decomposition of substrates. N-Mesylindolines bearing methoxy (**1ab**), methyl (**1ac**), chloro (**1ad**), and bromo (**1ae**) substituents at the 5-position of indolines were tolerated, delivering the corresponding 2-vinylanilines **2ab**, **2ac**, **2ad**, and **2ae** in 70%, 91%, 64%, and 70% yields, respectively. In addition, substituents (chloro: **1af** and bromo: **1ag**) at the sterically hindered 4-position were successfully converted into the desired products **2af** and **2ag** in 68% and 82% yields, respectively. Furthermore, we also conducted the reaction using 6-substituted indolines (**1ah** and **1ai**), and the desired products (**2ah** and **2ai**) could be obtained in moderate yields. Among the various positions of the substituents, our protocol is less-compatible with the 7-substituted indolines **1aj** and **1ak**. 2-Aminopyridines are valuable for medicinal chemist because they can serve as a versatile building block to access drug-like compounds.[22a] To access substituted 2-aminopyridines, few precedents without using 2-halopyridines as a substrate prompts us to explore a new synthetic route. To our delight, the reaction can be applied for the 7-azaindolines, giving rise to the 3-vinyl-2-aminopyridine **2al** in 74% yield, which is an intermediate for the synthesis of borazaroquinoline.[22b]

Encouraged by these results, we further broaden the scope of our protocol using multi-substituted indolines. While the reaction with 2-methylindoline (**1an**) smoothly proceeds to give the functionalized alkenes in 86% yield as a mixture of *E*- and *Z*-diastereomers (*E*:*Z* = 93:7), 3-methylindoline (**1am**) affords the product **2am** in 34% yield along with a recovery of unreacted starting material. These results suggests that substituents at the C3 position of indolines affects the outcome of our transformation maybe due to their steric hindrance. We also used *trans*-2,3-dimethylindolin **1ao** en route to the synthesis of trisubstituted alkene **2ao** in purpose of checking the possibility of an isomerization. The reaction afforded trisubstituted alkene **2ao** in 54% yield as a mixture of *E*- and *Z*-diastereomers (*E*:*Z* = 77:23). 2-Cyclohexeneaniline **2ap** was obtained using hexahydrocarbazole (**1ap**) as a substrate. Dibrominated indolines **1bq**, **1aq**, and **1ar** were tolerated (**2bq**: 27%, **2aq**: 63%, and **2ar**: 61%).

Lastly, the scope of other heterocycles was studied. As expected, dihydrobenzofuran **1ia** is compatible with our reaction conditions, delivering 2-vinylphenol **2ia** in 86%. 2-Vinylphenols are important substrates to access the various heterocycles and natural products.[23] Furthermore, we successfully employed dihydrobenzothiphene **1ja** followed by addition of MeI to pevent a reversible reaction and/or polymerization, delivering methylthiobenzene **2ja** in 74% yield. The thiobenzene derivative bearing vinyl group can act as a ruthenium olefin metathesis initiator.[24]

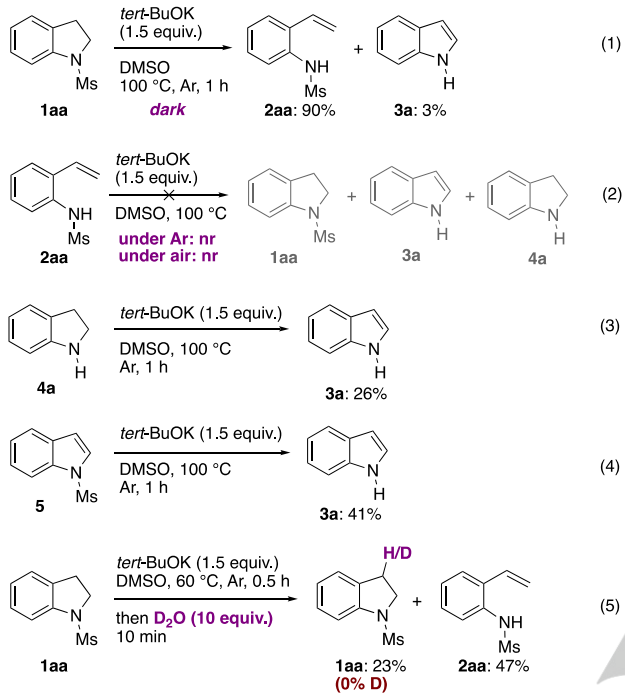
Gram-scale synthesis of **2aa** was performed to showcase the synthetic practicality (Scheme 4). The almost same high yield was observed when the reaction was performed on a 10 mmol scale.



Scheme 4 Gram-scale synthesis.

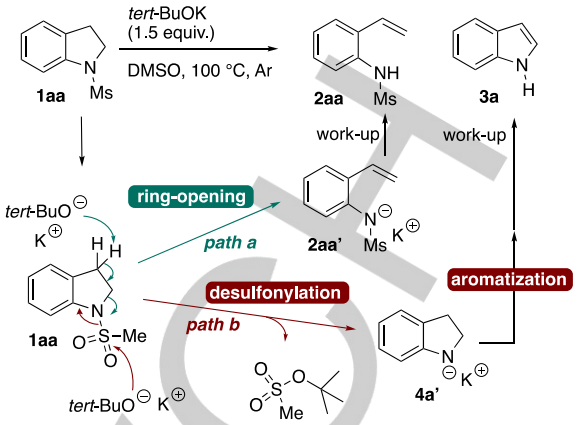
We then investigated the pathway for production of by-product **3a** (Scheme 5). In precedents, *tert*-BuOK promotes the reaction through radical pathway initiated by light or O_2.[25] We first examined the radical mechanism. In the absence of light, the reaction of **1aa** proceeds to afford the almost same results (eqn., 1). In addition, we confirmed that the reaction under air led to a trace formation of **2aa**. Thus, we could rule out the radical mechanism. Next, we hypothesized that the formation of by-products may be derived from the products through an intramolecular hydroamination of **2ba** under the standard conditions. Contrary to our hypothesis, the hydroamination did not occur under the standard conditions (eqn., 2). Generally, the aromatization of indolines would occur in the presence of the strong bases; indeed, our conditions can promote the aromatization on indoline **4a**, affording indole **3a** in 26% yield (eqn., 3). We could remove the mesyl group at the indole nitrogen atom under the standard conditions (eqn., 4). These results suggest that the pathway for formation of by-product **3a** exists several routes

(from **4a** or **5**). Finally, we conducted the deuterium-labeling experiments using D_2O (eqn., 5). After a short reaction of **1aa** with *tert*-BuOK at 60 °C, the reaction was quenched by D_2O, yielding the substrate with not deuterated at all. This imply that the elimination of sulfonamide moiety is a concerted E2 elimination rather than E1cb elimination.



Scheme 5 Control experiments.

Based on the above control experiments and the precedents,[16,26] plausible reaction pathway was shown in Scheme 6. First, intramolecular E2 elimination proceeds by deprotonation of **1aa** in the presence of *tert*-BuOK (path a), leading to intermediate **2aa'** through a ring-opening. With regards to the effect of the bulkiness of the substrates, the results shown in Scheme 3 (**2aj**, **2ak** and **2am**) suggest that the substituents near C3-position on the substrates lower the yields of the products by inhibiting the deprotonation at the C3-position by *tert*-BuOK. Finally, the salt **2aa'** is protonated by aqueous work-up to give the desired product **2aa**. On the other hands, the pathway for the formation of by-product **3a** can be proposed as shown below. Instead of the deprotonation of **1aa**, desulfonylation[26b] of **1aa** occurs through N–S bond cleavage by *tert*-BuOK and affords salt **4a'** (path b: desulfonylation), which leads to indole **3a** after protonation and aromatization sequence.



Scheme 6 Plausible mechanism.

Conclusions

In summary, we have developed the efficient protocol to access 2-vinylanilines from easily accessible indolines. This protocol using *tert*-BuOK not only offers a new utilization of indolines but also open an atom-economical route for the synthesis of 2-vinylanilines under metal-free conditions. It is worth mentioning that the sulfonyl substituent at the nitrogen atom played a pivotal role in both improvement of the product yield and the good functional group tolerance. Both 2- and/or 3- substituted indolines proved to be suitable substrates for our transformation. In addition, our protocol was also effectively applied to the formation of 2-vinylphenol and 2-vinylthiophenol. This protocol is promised for widespread application in the rich chemistry of 2-vinylanilines.

Supporting Information

The data that support the findings of this study are available in the Supporting Information of this article. The authors have cited additional references within the Supporting Information.[27–49]

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Conflict of interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary materials of this article.

Keywords: 2-vinylanilines •indolines • potassium *tert*-butoxide • elimination • ring-opening

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Heterocycles

Potassium *tert*-Butoxide-Mediated Ring-Opening of Indolines: Concise Synthesis of Vinylanilines

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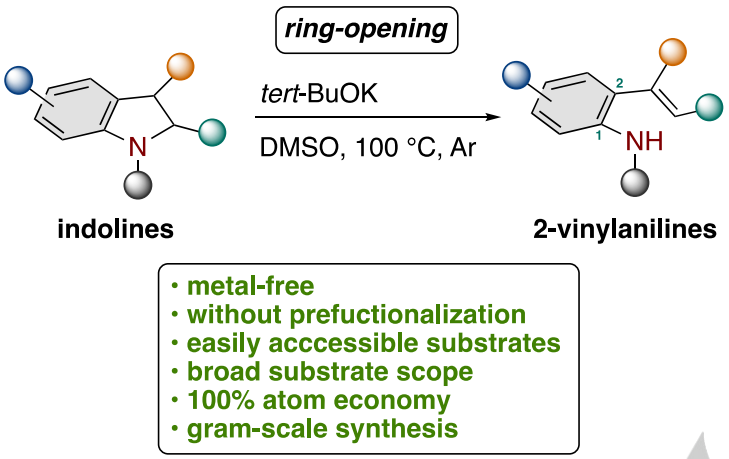

Metal-free Synthesis of 2-vinylanilines from indolines with Potassium *tert*-butoxide!!: concise synthesis of 2-vinylanilines was accomplished by a *tert*-BuOK-mediated ring-opening of indolines.