ARTICLE

Alkali-Amide Controlled Selective Synthesis of 7-Azaindole and 7-Azaindoline through Domino Reactions of 2-Fluoro-3-methylpyridine and Aldehydes

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Azaindoles and azaindolines are important core structures in pharmaceuticals and natural products, which have found wide applications in the field of medicinal chemistrty. In this study, we developed a novel one-pot method for selectively synthesizing 7-azaindoles and 7-azaindolines, which can be generated by reactions between the readily available 2-fluoro-3-methylpyridine and arylaldehyde. The chemoselectivity is counterion dependent, with $LiN(SiMe_3)_2$ generating 7-azaindolines and $KN(SiMe_3)_2$ furnishing 7-azaindoles. A range of substitutes can be introduced under these conditions, providing handles for further elaboration and functionalization.

Introduction

7-Azaindoles are privileged heterocycles with broad applications ranging from coordination chemistry to material science[1] and uses from optical probes to therapeutics.[2] As bioisosteres of indole, 7-azaindole often exhibited enhanced solubility and superior bioavailability.[3] These attractive pharmacological properties have led to the development of a number of clinically proven drugs and drug candidates, such as Zelboraf (vemurafenib),[4] (PLX4032),[5] pexidartinib,[6] venetoclax[7] and many others (Fig. 1).[2b, 8].

Like 7-azaindoles, the reduced derivatives, 7-azaindolines, are considered important pharmacophores (Fig. 1).[9] The chemical synthesis of 7-azaindoline derivatives remain challenging due to the presence of the sp^2 nitrogen atom.[10] Previous routes mainly involve hydrogenation of azaindoles[11] and the amination of strong aliphatic C–H bonds.[10] Thus, we were motivated to develop an improved synthetic approach to yield derivatives of 7-azaindolines in an efficient and economical manner.

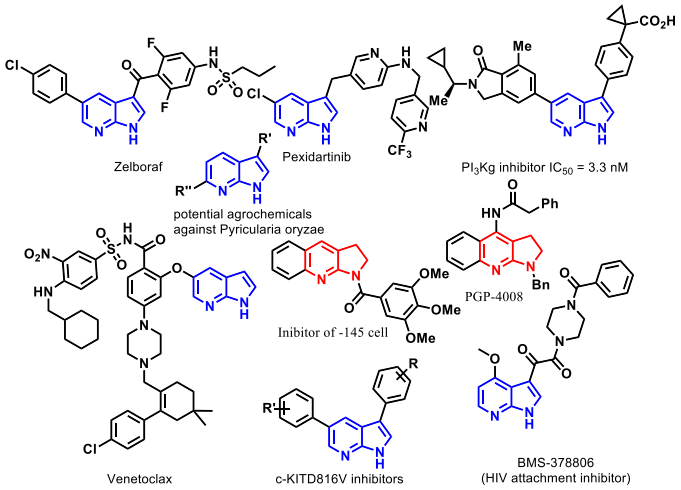

Fig. 1 Selected bioactive compounds containing 7-azaindole and 7-azaindoline motifs.

Many traditional methods for indole synthesis—such as Fischer, Bartoli, and Reissert approaches—are often unsuitable for generating azaindoles due to the electron-deficient nature of their pyridine-based starting materials.[12] Indeed, only pyridylhydrazines that bear electron-donating groups can be applied to the synthesis of azaindoles through Fischer's approach with reasonable yields.[13] Although many contemporary azaindole syntheses are transition-metal catalyzed,[14] the stringent requirements of trace heavy metal residue in fine chemicals has driven the desire for transition-metal-free approaches with easily accessible starting materials.

The current state-of-art for transition-metal-free preparation of azaindoles are often based on classic routes for parent indole syntheses. An example is the Hemetsberger-Knittel synthesis of azaindoles from azidoacetate and pyridine carboxaldehyde (Scheme 1a).[15] Likewise, 7-azaindole can be

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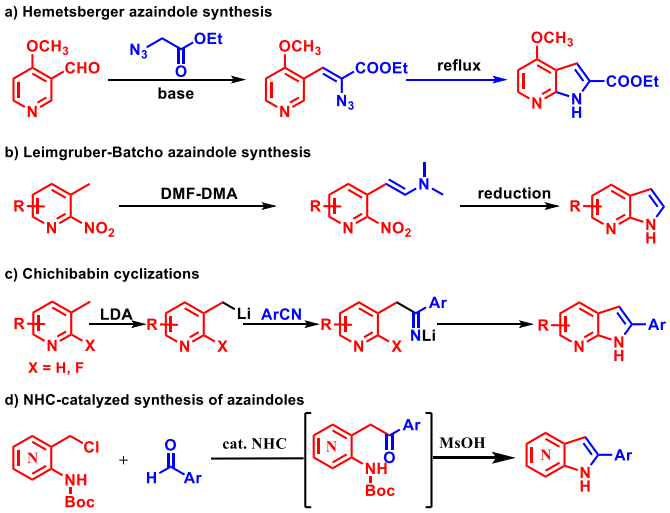
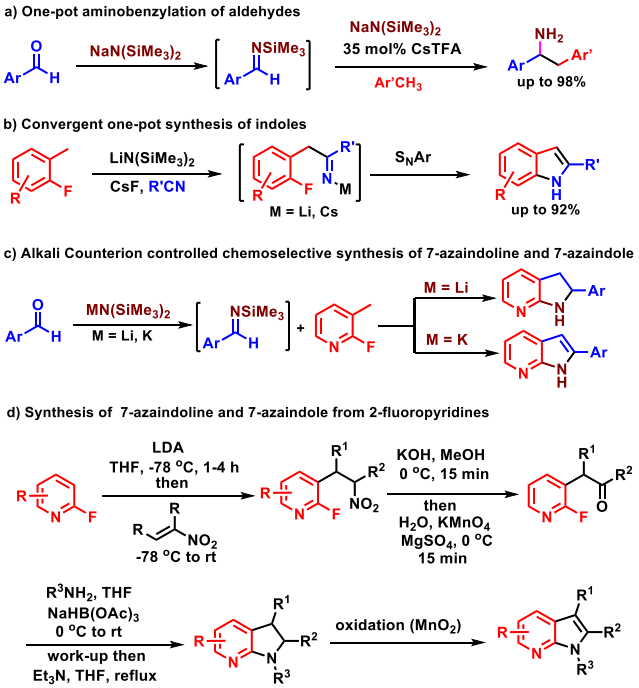
generated under reductive conditions by emulating Leimgruber-Batcho indole synthesis (Scheme 1b).[16] The Chichibabin cyclization yields 7-azaindoles, albeit with few examples reported (Scheme 1c).[17] As a valuable alternative, Scheidt and co-workers developed *N*-heterocyclic carbene catalyzed synthesis of azaindoles with aza-ortho-azaquinone methide precursor and aldehydes (Scheme 1d).[18]



Scheme 1 7-Azaindole synthesis by emulating the parent indole synthesis

We are interested in Brønsted bases ($MN(SiMe_3)_2$, M = Li, Na, K, Cs) promoted functionalization of weakly acidic C–H bonds. Our past efforts include: 1) the relatively weak "mixed base" ($LiN(SiMe_3)_2$/CsF, $NaN(SiMe_3)_2$/CsTFA), which can reversibly deprotonate methyl arenes at the benzylic positions. It is hypothesized that these deprotonations are facilitated by alkali-metal cation-pi interactions.[19] 2) The "mixed base" exhibits excellent chemoselectivity for deprotonation at benzylic positions. 3) The dual role of $MN(SiMe_3)_2$ could mediate C–N and C–C bond formations by condensation with benzaldehydes and deprotonation of weakly acidic benzylic C–H bonds. Representative examples developed with this strategy include one-pot aminobenzylation of aldehyde with toluenes (Scheme 2a)[20] and tandem synthesis of indoles with 2-fluorotoluenes (Scheme 2b),[21] among others.[22]

These recent findings led us to wonder if 7-azaindoline could be produced through tandem C–N and C–C bond formation by reactions of benzaldehydes, 2-fluoro-3-picoline and $MN(SiMe_3)_2$ as outlined in Scheme 2c. If such 7-azaindoline could be generated, we hoped to introduce a related method to access 7-azaindole analogs. Herein, we described the discovery of alkali counterion-controlled chemoselective synthesis of 7-azaindoles and 7-azaindolines using readily available starting materials, i.e., aldehydes and 2-fluoro-3-picoline (Scheme 2c). Compared with the previously reported approach by Nuhant and co-workers (Scheme 2d),[23] our method streamlines the syntheses by avoiding the use of stoichiometric oxidants. Our approach also provides an alternative to synthesize N-H free 7-azaindoles, which can be further derivatized with diverse functional groups via N–H functionalizations.



Scheme 2 Previous work for synthesis of indole and azaindoles

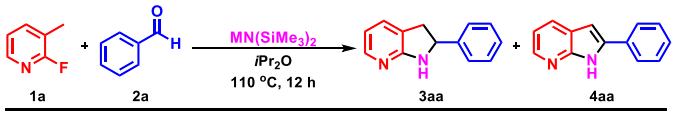
Results and discussion

To develop and optimize the proposed reactions, we first examined three different bases [$KN(SiMe_3)_2$, $NaN(SiMe_3)_2$, and $LiN(SiMe_3)_2$, 3 equiv.] affect the tandem reaction between 2-fluoro-3-picoline (**1a**, 1 equiv.) and benzaldehyde (**2a**, 1 equiv.). We performed the reactions in iPr_2O (diisopropyl ether) at 110 ℃ for 12 h (Table 1, entries 1 – 3). It was found that $KN(SiMe_3)_2$ led to the formation of 7-azaindoline **3aa** in an 18% AY. Surprisingly, 7-azaindole (**4aa**) was the main product (56% AY) (entry 1; AY = assay yield determined by ^{1}HNMR integration of the unpurified reaction mixture against an internal standard). Unlike $KN(SiMe_3)_2$, $NaN(SiMe_3)_2$ failed to promote the reaction (entry 2). In contrast, $LiN(SiMe_3)_2$ exclusively afforded 7-azaindoline (**3aa**) in 56% isolated yield while suppressing the formation of 7-azaindole (entry 3). Thus, $KN(SiMe_3)_2$ mainly promoted the 7-azaindole formation and $LiN(SiMe_3)_2$ exclusively mediated the 7-azaindoline formation.

We next evaluated other reaction parameters to determine how they impact the base-dependent chemoselectivity. To do this, we examined the impact of stoichiometry on the yield of **3aa** under the conditions of entry 3 (entries 4-6). Increasing the amount of 2-fluoro-3-picoline **1a** to 2 equiv. slightly improved the yield of **3aa** from 56% to 59% (entry 4). Further increasing the reaction concentration from 0.1 M (entry 4) to 0.2 M (entry 7) greatly improved the yield of **3aa** to 93% (entry 7). Notably, $LiN(SiMe_3)_2$ exclusively produces 2-phenyl 7-azaindoline **3aa**. Decreasing the temperature results in lower yield of 7-azaindoline and 7-azaindole (see Supporting Information for details). Therefore, 7-azaindoline was generated using 2 equiv. of 2-fluoro-3-picoline (**1a**), 1 equiv. of benzaldehyde (**2a**), 3 equiv. of $LiN(SiMe_3)_2$ in iPr_2O at 110 ℃ for

12 h. After screening the concentrations and bases combinations, the optimal conditions for tandem synthesis of 7-azaindole were those described in entry 11.

Table 1 Optimization studies.[a]

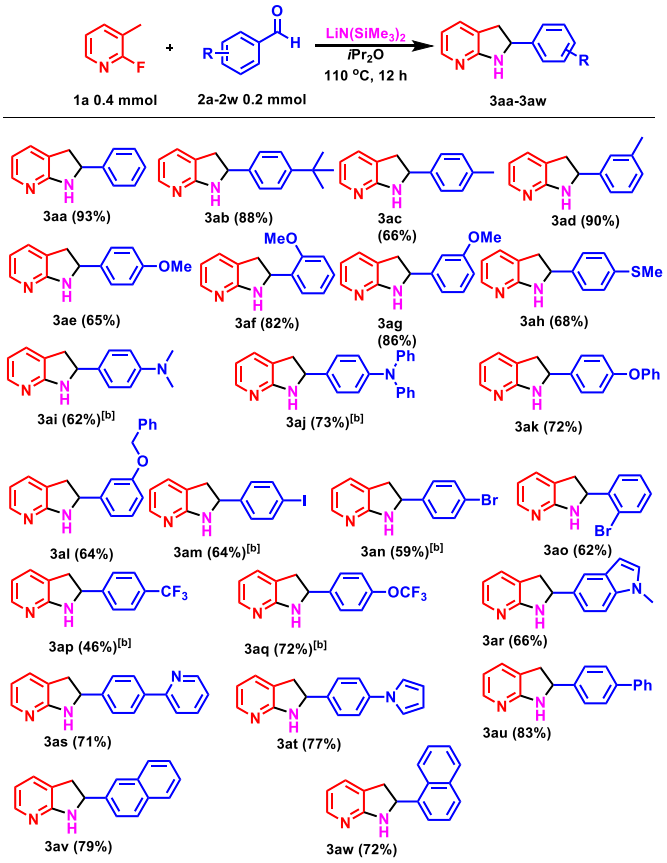


entry	1a/2a/ Base	Base	Solvent	Yield [%][b] 3aa	Yield [%][b] 4aa
1	1:1:3	$KN(SiMe_3)_2$	iPr_2O (1.0 mL)	18	56
2	1:1:3	$NaN(SiMe_3)_2$	iPr_2O (1.0 mL)	trace	trace
3	1:1:3	$LiN(SiMe_3)_2$	iPr_2O (1.0 mL)	56[c]	0
4	2:1:3	$LiN(SiMe_3)_2$	iPr_2O (1.0 mL)	59[c]	0
5	1:2:3	$LiN(SiMe_3)_2$	iPr_2O (1.0 mL)	22[c]	0
6	1:3:3	$LiN(SiMe_3)_2$	iPr_2O (1.0 mL)	Trace	0
7	2:1:3	$LiN(SiMe_3)_2$	iPr_2O (0.5 mL)	93[c]	0
8	1:1:3	$KN(SiMe_3)_2$	iPr_2O (0.2 mL)	Trace	66[c]
9	1:1:3	$KN(SiMe_3)_2$	iPr_2O (0.1 mL)	Trace	74/82[c]
10	1:1:3	$KN(SiMe_3)_2$	iPr_2O (0.05 mL)	Trace	66[c]
11	1:1:5	$KN(SiMe_3)_2$: $LiN(SiMe_3)_2$ =3:2	iPr_2O (1.0 mL)	Trace	86[c]

[a] Reaction performed on a 0.1 mmol scale in iPr_2O. [b] Yield determined by integration of the ^1H NMR of the unpurified reaction mixture. [c] Isolated yield.

With the optimized conditions in hand, we next examined the substrate scope of benzaldehydes (**1a**, Table 2) in the generation of 7-azaindoline derivatives. Benzaldehydes containing electron-donating functional groups, including 4-*t*Bu (**2b**), 4- and 3-Me (**2c**, **2d**), 4-, 2- and 3-OMe (**2e** – **2g**), 4-SMe (**2h**), 4-NMe_2 (**2i**), 4-NPh_2 (**2j**), 4-OPh (**2k**), 3-OBn (**2l**) and electron-withdrawing functional groups [4-I (**2m**), 4- and 2-Br (**2n**, **2o**), 4-CF_3 (**2p**), 4-OCF_3 (**2q**)] exhibited good to excellent reactivity, producing 7-azaindolines substituted at the C-2 position in 46-90% yield. The reaction conditions were also compatible with a wide range of substituted benzaldehydes including those that contained nitrogen-containing heterocycles (**2r**-**2t**). Likewise, 4-phenylbenzaldehyde (**2u**), 2-naphthaldehyde (**2v**) and 1-naphthaldehyde (**2w**) afforded the corresponding C-2 substituted 7-azaindolines with a yields of 72, 79 and 83%, respectively (**3au**-**3aw**). Under our conditions, aliphatic aldehydes were not tolerated (see Supporting Information).

Table 2 Substrate scope with benzaldehyde derivatives.[a]

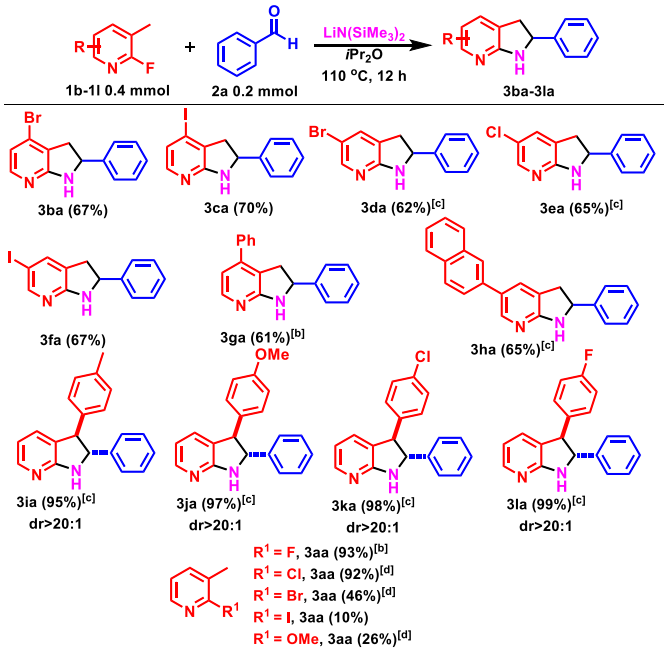


[a] Reactions performed on a 0.2 mmol scale with 2 equiv. of 2-fluoro-3-methylpyridine, 1 equiv. of benzaldehyde, 3 equiv. of $LiN(SiMe_3)_2$, in 1.0 mL iPr_2O. Yield is that of the isolated product. [b] With 3 equiv. of 2-fluoro-3-methylpyridine.

Next, we explored the substrate scope of the 2-fluoro-3-picolines. We found that a broad range of substituted 2-fluoro-3-picolines can yield the desired products under our standard reaction conditions (Table 3), although some substrates required further optimization. 2-Fluoro-3-picolines with substituted halogen at C-4 position, such as Br (**1b)** or I (**1c**), rendered the desire product in 67 and 70% yield, respectively. For the substrates containing Br (**1d**), Cl (**1e**) or I (**1f**) at the C-5 position of the 2-fluoro-3-picoline, 62-67% isolated yields were obtained. 2-Fluoro-3-picolines bearing electron-neutral functional groups also afforded the corresponding 7-azaindolines at 61-65% yield (**3ga, 3ha**). We also found that more structurally complex 2,3-disubstituted 7-azaindolines (**3ia** – **3la**) could be generated under our conditions with high diastereoselectivity (dr > 20:1). Based on analysis of the NOESY of compound **3ia**, we concluded that the trans isomers were generated in these transformations (see S3 for details).

We further examined how different leaving groups on 3-picolines affect the reactivity in our 7-azaindoline synthesis. When Cl was employed as leaving group, the yield of azaindoline is 92%. However, other leaving groups such as Br, I or OMe can only render 7-azaindoline in lower yields (Table 3).

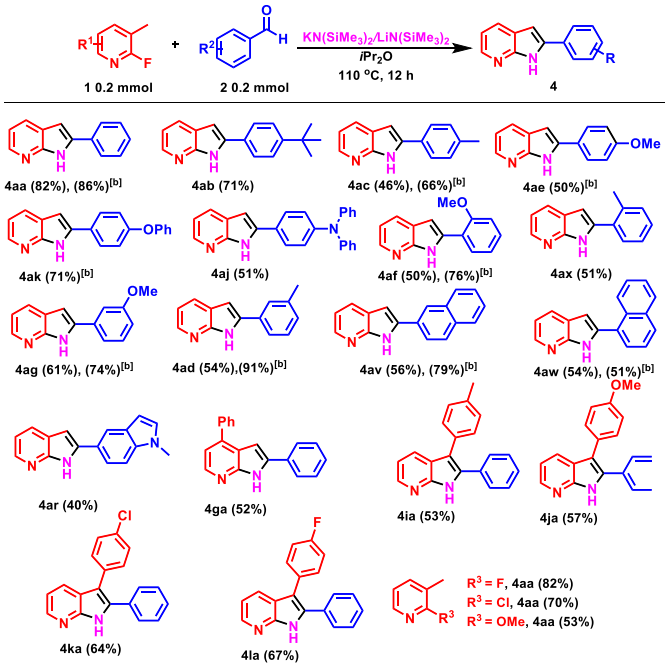
Table 3 Substrate scope with 2-fluoro-3-methylpyridine derivatives.[a]



[a] Reactions performed on a 0.2 mmol scale with 2 equiv. of 2-fluoro-3-methylpyridine, 1 equiv. of benzaldehyde, 4 equiv. of $LiN(SiMe_3)_2$ in 0.4 mL iPr_2O. Yield is that of the isolated product. [b] With 3 equiv. of $LiN(SiMe_3)_2$ and 1.0 mL iPr_2O. [c] With 3 equiv. of 2-fluoro-3-methylpyridine and 1.0 mL iPr_2O. [d] With 3 equiv. of 2-fluoro-3-methylpyridine.

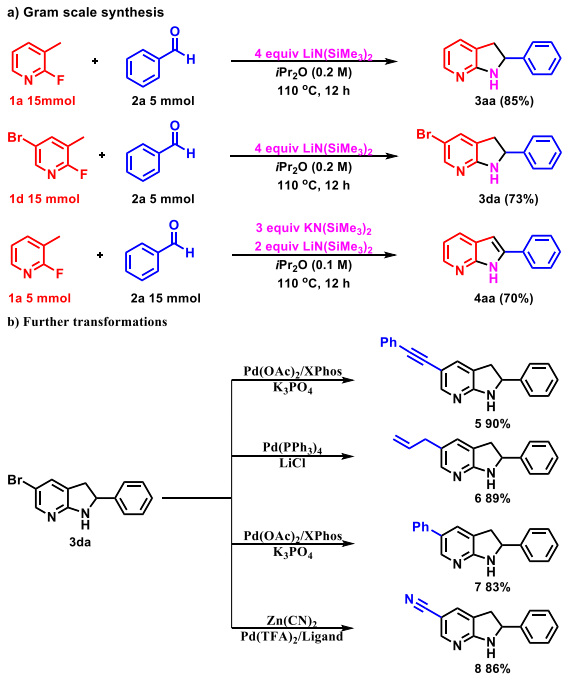
Next we turned our attention to explore the scope of benzaldehydes derivatives with 2-fluoro-3-picoline for synthesis of 7-azaindole (Table 4). The parent benzaldehyde led to the formation of desired product in 86% yield using a mixture of $KN(SiMe_3)_2$ and $LiN(SiMe_3)_2$. Benzaldehydes that contains electron-donating groups, such as 4-*t*-Bu, 4-methyl, 4-methoxy, 4-phenoxy and 4-*N*,*N*-diphenylamino, exhibited good reactivity and produced the corresponding products (**4ab**, **4ac**, **4ae**, **4ak**, **4aj**) in 46-71% yield. Substitutes at *meta* position are also tolerated, furnishing the products (**4af**, **4ax**) in 51-76% yield. 3-Methoxy and 3-methylbenzaldehyde afforded the corresponding products at 91% and 79% yield in the presence of mixed bases (**4ag**, **4ad**). π-Extended benzaldehydes, such as 2- and 1-naphthaldehyde, produced the products at 51-79% yields (**4av**, **4aw**). 7-Azaindole containing an indolyl group could be prepared in 40% isolated yield. Likewise, 4-phenyl substituted 2-fluoro-3-picoline furnished the product successfully (**4ga**). Interestingly, 2,3-disubstituted 7-azaindoles (**4ia – 4la**) were easy to prepare under our conditions in 53-67% isolated yield. We also explored the impact of different leaving groups on the reactivity of this transformation. As exemplified in Table 4, Cl and MeO substituted 3-picolines could generate the desired products at 70% and 53% yield, respectively.

Table 4 Substrate scope of azaindole synthesis.[a]



[a] Reactions performed on a 0.2 mmol scale with 1 equiv. of 2-fluoro-3-methylpyridine, 1 equiv. of benzaldehyde, 3 equiv. of $KN(SiMe_3)_2$ in 0.2 mL iPr_2O. Yield is that of the isolated product. [b] Reactions performed with 1 equiv. of 2-fluoro-3-methylpyridine, 3 equiv. of benzaldehyde, 3 equiv. of $KN(SiMe_3)_2$ and 2 equiv. of $LiN(SiMe_3)_2$

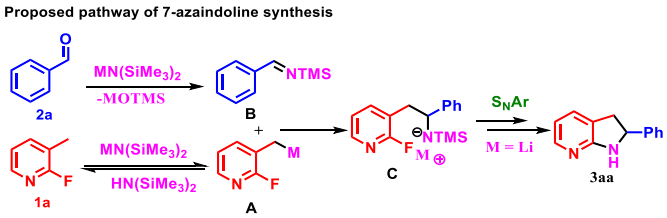
To demonstrate the utility of this method, we performed the gram scale synthesis of **3aa**, **3da** and **4aa** on 5 mmol scale and found that the desired product could be isolated in 85, 73 and 70% yield, respectively (Scheme 3a). It is worth noting that, most of the 7-azaindolines could be further functionalized. For example, transformation of **3da** via cross-coupling reactions was successful (Scheme 3b, see Supporting Information for detailed procedures).



Scheme 3 Gram scale synthesis and further transformations of **3da**

Mechanistic studies

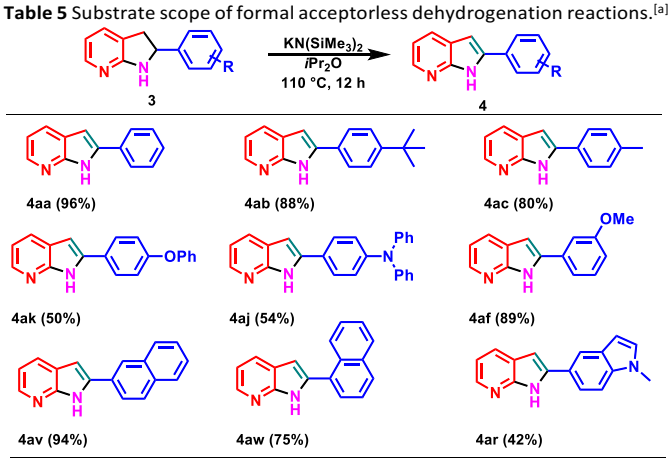
In analogy to the earlier work in our group,[20-21] we propose that 7-azaindoline synthesis proceeds by the pathway depicted in Scheme 4. In the presence of $LiN(SiMe_3)_2$, 2-fluoro-3-picoline (**1a**) is reversibly deprotonated to afford the alkali metal complex **A**. Then, the reactive intermediate **A** attacks the *in situ* generated imine **B** (formed by an aza-Peterson olefination with benzaldehyde (**2a**) and $LiN(SiMe_3)_2$) to form intermediate **C**. Finally, intermediater complex **C** undergoes S_NAr to furnish the desired product 7-azaindoline.



Scheme 4 Mechanistic studies of 7-azaindoline

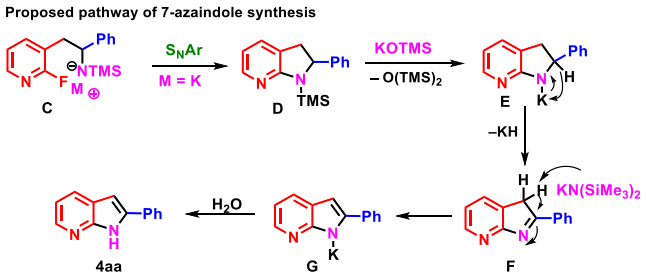
Unlike 7-azaindoline, we anticipated that 7-azaindole converted from 7-azaindoline through oxidation. To verify our hypothesis, we monitored the formation of 7-azaindoline and 7-azaindole over the course of the reaction. After 15 min, the formation of 7-azaindoline peaked at 52% yield, while 7-azaindole was at 26% yield. The yield of 7-azaindoline decreased over time after 15 min before its complete conversion at 6 h (see the SI, page S4). In contrast, the amount of 7-azaindole increased as reaction progressed. These results indicated 7-azaindoline is likely a viable substrate for the formation of 7-azaindole. To further explore our proposal, we synthesize 7-azaindole derivatives from 7-azaindoline in 42-96% yield (Table 5).

Table 5 Substrate scope of formal acceptorless dehydrogenation reactions.[a]



[a] Reactions performed on a 0.1 mmol scale with 3 (0.1 mmol), $KN(SiMe_3)_2$ (0.3 mmol) in iPr_2O (0.1 mL). Yield is that of the isolated product.

Two mechanisms was envisioned for the generation of the 7-azaindole from 7-azaindoline. The first is similar to the aerobic oxidative dehydrogenation of *N*-heterocycles in the presence of oxygen.[23-24] The second involves elimination of KH in the presence of $KN(SiMe_3)_2$, which should release hydrogen upon workup.[25] To avoid the influence of oxygen, we set up the reaction under an atmosphere of argon in the glovebox. However, the 7-azaindole was still formed in the presence of $KN(SiMe_3)_2$. This result suggested that the oxygen was not involved in this transformation. Base on the results in Table 5, we proposed a pathway for 7-azaindole formation as depicted in Scheme 5. Like the pathway of 7-azaindoline synthesis, the intermediate **D** could be generated under the standard conditions along with KOTMS. In the presence of KOTMS and $KN(SiMe_3)_2$, the intermediate **D** undergoes silyl-metal exchange and elimination of KH reaction to generate **F**.[26] Finally, the more acidic C–H bond of intermediate **F** is deprotonated in the presence of $KN(SiMe_3)_2$ to obtain **G**, which leads to the 7-azaindole after work up. If the key intermediate KH is generated in this transformation, hydrogen should be obtained when KH reacts with $HN(SiMe_3)_2$ or H_2O. Indeed, we successfully collected hydrogen from this transformation, suggesting the elimination of KH is possible. This process is a formal acceptorless dehydrogenation process, which can be compared with previous transformations with transition metals.[27] (see S4 for details)



Scheme 5 Mechanistic studies of 7-azaindole

Conclusions

In conclusion, we demonstrated a transition-metal-free approach to synthesize 2-aryl-7-azaindolines and 2-aryl-7-azaindoles in one-pot manner with high chemoselectivity. The is chemoselectivity is controlled by the counterion of the $MN(SiMe_3)_2$ base. This reaction is applicable to a variety of substrates with good functional group tolerance. 2,3-Diarylsubstituted-azaindoline or azaindoles are also readily accessible using this approach. This acceptorless dehydrogenation reaction may provide an alternative to the synthesis of dehydrogenated product from nitrogen heterocycles. Although metallic ion effects have been observed in previous transformation,[28] our study demonstrates the first observation of such effects in synthesizing 7-azaindole and 7-azaindoline. The easy access to azaindolines and azaindoles enabled by this synthetic approach, together with its highly controllable chemoselectivity, will streamline the synthesis of complex azaindolines and azaindoles for applications as pharmaceuticals and natural products. Due to its potential applications to generate bioactive heterocycles in a single step,

we anticipate that this tandem reaction will find wide applications in medicinal chemistry.

Author Contributions

XX performed the optimization of the reaction. The substrate scope and product characterization were performed by XX with help from MO, YW, TL, DX, and FX. The first draft was written by XX and JM and all authors contributed to revising the draft. The research was directed by JM under the helo of PJW.

Conflicts of interest

The authors declare no competing interests.

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