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## Introduction

Indole and indoline are the most common heterocycles widely found in nature, possessing unique biological activities.<sup>1</sup> Among them, ethylamino indole is involved in the entire metabolic process of the human body.<sup>2</sup> For example, tryptophan is one of the essential amino acids for humans, involved in protein synthesis.<sup>3</sup> Melatonin is a key hormone regulating the body's biological clock, and serotonin is an important neurotransmitter closely related to feelings of happiness and well-being.<sup>4</sup> Specifically, C4-ethylamino indole derivatives have also been proven to be dopamine receptor agonists. One such derivative, ropinirole, is a medication used to treat Parkinson's disease (PD) and restless legs syndrome (RLS). It is one of the most commonly prescribed medications in the United States.<sup>5</sup> On the other hand, C7-aminoindoline is a type of microtubule protein inhibitor and is considered an important antitumor drug (Fig. 1a).<sup>6</sup> Based on this, we envision that the one-step synthesis of C4-ethylamine indole and C7-aminoindoline using aziridine through C–N bond cleavage ring-opening reactions and C–H alkylation reactions is of significant importance.

Palladium/norbornene (Pd/NBE) chemistry, namely Catellani-type reactions,<sup>7</sup> provides a strategy for the multi-functionalization of arenes. This reaction integrates the features of C–H

## A switch strategy for the synthesis of C4-ethylamine indole and C7-aminoindoline *via* controllable carbon elimination<sup>†</sup>

Bo-Sheng Zhang, <sup>‡\*</sup>a Bao-Jie Deng, <sup>‡</sup>a Yuan-Xin Zhi, <sup>a</sup> Tian-Jiao Guo, <sup>a</sup> Yi-Ming Wang, <sup>a</sup> Xue-Ya Gou, <sup>b</sup> Zheng-Jun Quan, <sup>‡\*</sup>a Xi-Cun Wang <sup>‡\*</sup>a and Yong-Min Liang <sup>b</sup>

Controllable  $\beta$ -carbon elimination to extrude norbornene remains a long-standing challenge in palladium and norbornene chemistry. Herein, this manuscript describes a switchable synthesis of biologically active C4-ethylaminoindole and C7-aminoindoline scaffolds by controlling  $\beta$ -carbon elimination, utilizing aziridine as a C–H ethylation reagent through a C–N bond cleavage reaction. Furthermore, the protecting groups of the product can be easily removed, offering an unusual method for the synthesis of dopamine receptor agonists.

functionalization and cross-coupling.<sup>8</sup> In 2000, the cyclization reaction catalyzed by Pd/NBE cooperatively was first discovered by Lautens.<sup>9</sup> The cyclization reaction has since been widely used in materials chemistry, natural product synthesis, and pharmaceutical synthesis.<sup>8,10</sup> In 2009, Lautens discovered that using norbornadiene (NBD) instead of norbornene (NBE) in non-Catellani-type cascade cyclization reactions triggers a retro-Diels–Alder reaction, providing a method for synthesizing isoquinolinones and indoles.<sup>11</sup> In recent years, Liang,<sup>10d</sup> Kwong,<sup>12</sup> Cheng,<sup>13</sup> and our group<sup>10d,14</sup> developed a series of tandem cyclization reactions combining Catellani-type reactions with retro-Diels–Alder reactions. Interestingly, Cheng discovered that oxanorbornadiene exhibits better retro-Diels–Alder reaction activity than NBD in 2018.<sup>13a</sup> In recent years, the ring-opening C–H alkylation reaction of strained tricyclic heterocycles was achieved by Lautens,<sup>15</sup> Dong,<sup>16</sup> Zhou,<sup>17</sup> and Liang<sup>10d,14,18</sup> under Pd/NBE catalysis (Fig. 1c). However, C–H alkylation between *o*-idoanilines and aziridines under Pd/NBE cooperative catalysis is difficult due to the susceptibility of aziridine to nucleophilic attack leading to ring-opening reactions (Fig. 1b).<sup>19</sup>

$\beta$ -carbon elimination to extrude norbornene has consistently been a focal point of interest in Pd/NBE research.<sup>8g,20</sup> In 2018, the Dong group utilized the steric hindrance effect of C1 norbornene to effectively promote  $\beta$ -carbon elimination and achieve single C–H functionalization of aryl iodides without an *ortho*-substituent.<sup>20c</sup> In 2019, Dong made a breakthrough in the halogenated olefin version by using norbornene amides.<sup>21</sup> The Dong group further utilized this strategy to accelerate the extrusion of norbornene, inhibiting the formation of nitrene cyclization products and achieving the introduction of secondary amines in 2024.<sup>22</sup> Interestingly, the Jiao group used hybrid cycloolefin ligands to achieve norbornene-like  $\beta$ -carbon elimination.<sup>23</sup> However, controllable  $\beta$ -carbon elimination to extrude

<sup>a</sup>Gansu International Scientific and Technological Cooperation Base of Water-Retention Chemical Functional Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, 730070, China. E-mail: [zhangbs@nwnu.edu.cn](mailto:zhangbs@nwnu.edu.cn); [quanzhengjun@hotmail.com](mailto:quanzhengjun@hotmail.com); [wangxicun@nwnu.edu.cn](mailto:wangxicun@nwnu.edu.cn)

<sup>b</sup>State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

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<sup>‡</sup> These authors contributed equally.



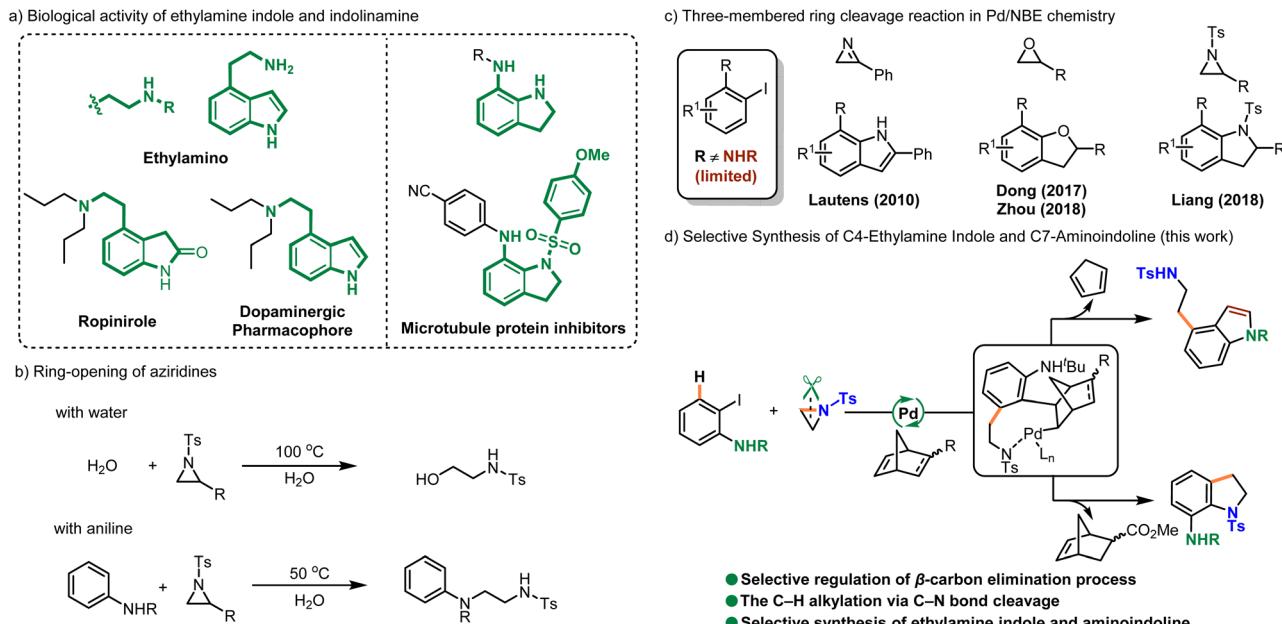


Fig. 1 Selective synthesis of C4-ethylamine indole and C7-aminoindoline.

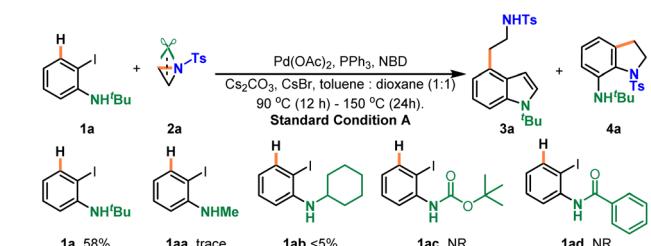
norbornene remains a long-standing challenge. Herein, this manuscript described a switchable synthesis of biologically active C4-ethylaminoindole and C7-aminoindoline scaffolds by controlling the  $\beta$ -carbon elimination, utilizing aziridine as a C–H ethylation reagent through a C–N bond cleavage reaction.

## Results and discussion

Initially, we used sterically hindered *N*-*tert*-butyl-*o*-iodoaniline as the substrate, aziridine as the ring-opening C–H alkylating reagent, and norbornadiene (NBD) instead of norbornene (NBE) to attempt to achieve the synthesis of C4-ethylaminoindole. After carefully studying various reaction parameters,  $\text{Pd}(\text{OAc})_2$  and triphenylphosphine were chosen as the Pd/ligand combination, cesium carbonate ( $\text{Cs}_2\text{CO}_3$ ) was used as the base, and a mixture of toluene and dioxane served as the solvent. Under an argon atmosphere, the reaction mixture was stirred initially at 90 °C for 12 hours, followed by an increase in temperature to 150 °C and further stirring for 24 hours. This procedure resulted in a 58% isolated yield of the C4-ethylamino indole **3a**, with no formation of the cyclized product **4a** resulting from  $\beta$ -carbon elimination. It is worth mentioning that we found that heating to 150 °C in the later stage promoted the retro-Diels–Alder reaction to release cyclopentadiene. Next, deviation experiments from the standard conditions were explored. We first investigated the use of a single solvent instead of a mixed solvent. When toluene was used as the solvent, the yield of C4-ethylamino indole **3a** decreased to 31%, and 8% of C7-aminoindoline **4a** was detected. When dioxane was used as the solvent, the yield of **3a** decreased to 40%. Notably, omitting  $\text{CsBr}$  as an additive also resulted in a yield of 48%. Subsequently, when we attempted to replace NBD with NBE, no target product **3a** was detected, while the yield of indoline **4a** increased to 16%. Potassium carbonate instead of cesium

carbonate as the base reduced the yield of the indole **3a** to 30%, with 12% indoline **4a** formed. Increasing the amount of cesium carbonate from 1.0 equivalent to 2.0 equivalents decreased the yield of the target product to 43%. Additionally, directly stirring at 140 °C for 24 hours resulted in a yield of 32% for **3a**, and formation of 18% of **4a** was detected. Finally, we investigated various protecting groups on the nitrogen of *o*-iodoaniline, such as methyl, cyclohexyl, *t*-butoxycarbonyl (Boc), and benzoyl, but none yielded the target product (Table 1).

Table 1 Optimization of reaction conditions for C4-ethylamine indole<sup>a</sup>



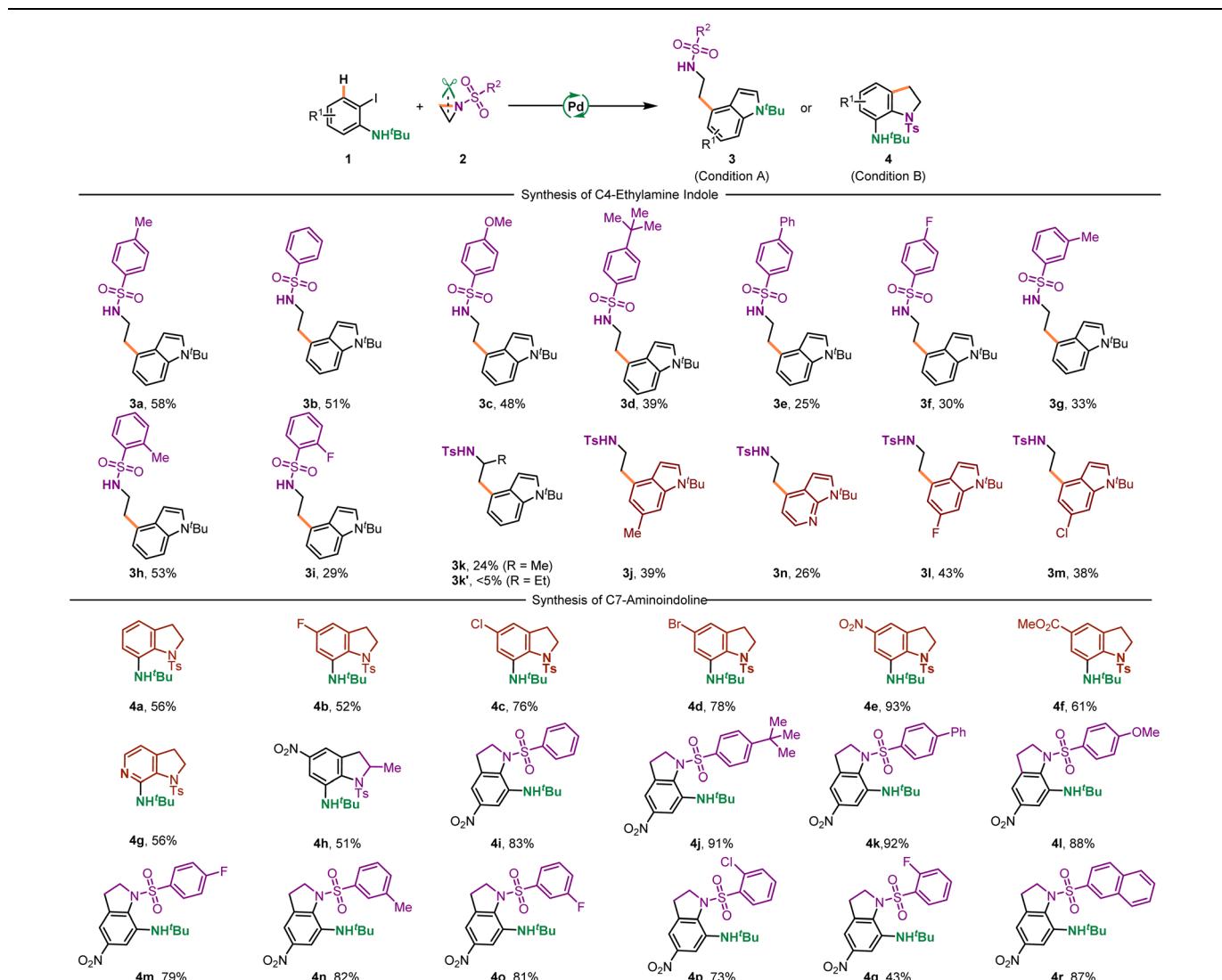
<sup>a</sup> Standard conditions A: substrate **1a** (0.2 mmol), **2a** (0.5 mmol, 2.5 equiv.),  $\text{Pd}(\text{OAc})_2$  (10 mmol%),  $\text{PPh}_3$  (25 mmol%),  $\text{CsBr}$  (1.0 equiv.),  $\text{Cs}_2\text{CO}_3$  (1.0 equiv.), NBD (0.6 mmol, 3.0 equiv.), toluene : dioxane (1 : 1, 2 mL) 90 °C 12 h, and then 150 °C, 24 h.



Table 2 Optimization of reaction conditions for C7-aminoindoline<sup>a</sup>

Entry	Deviation from the standard conditions	Yield (4a)	Yield (3a)
		Standard Condition B	
1	—	56	—
2	PPh <sub>3</sub> instead of P( <i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	40	—
3	NBE instead of N1	42	—
4	NBD instead of N1	19	Trace
5	Without KI	39	—

<sup>a</sup> Standard conditions B: substrate 1a (0.2 mmol), 2a (0.5 mmol, 2.5 equiv.), Pd(OAc)<sub>2</sub> (10 mmol%), P(*p*-Cl-C<sub>6</sub>H<sub>4</sub>)<sub>3</sub> (20 mmol%), KI (0.5 equiv.), K<sub>2</sub>CO<sub>3</sub> (0.6 mmol, 3.0 equiv.), N1 (0.2 mmol, 1.0 equiv.), toluene (2 mL), 100 °C, 24 h.

Table 3 Investigation of substrate scope<sup>a</sup>

<sup>a</sup> Standard conditions A: substrate 1 (0.2 mmol), 2 (0.5 mmol, 2.5 equiv.), Pd(OAc)<sub>2</sub> (10 mmol%), PPh<sub>3</sub> (25 mmol%), CsBr (1.0 equiv.), Cs<sub>2</sub>CO<sub>3</sub> (1.0 equiv.), NBD (0.6 mmol, 3.0 equiv.), toluene : dioxane (1 : 1, 2 mL) 90 °C 12 h, and then 150 °C, 24 h. Standard conditions B: substrate 1 (0.2 mmol), 2 (0.5 mmol, 2.5 equiv.), Pd(OAc)<sub>2</sub> (10 mmol%), P(*p*-Cl-C<sub>6</sub>H<sub>4</sub>)<sub>3</sub> (20 mmol%), KI (0.5 equiv.), K<sub>2</sub>CO<sub>3</sub> (0.6 mmol, 3.0 equiv.), N1 (0.2 mmol, 1.0 equiv.), toluene (2 mL), 100 °C, 24 h.

After achieving optimal conditions for generating C4-ethylamino indole, we aimed to direct the catalytic cycle towards β-carbon elimination to produce C7-aminoindoline 4a. After various conditional screenings, we found that when using *p*-chlorotriphenylphosphine as a ligand and 5-norbornene-2-carboxylate (N1) as a co-catalyst, indoline product 4a was obtained with a yield of 56%. After obtaining the optimal reaction conditions, simple control experiments were conducted. When triphenylphosphine was used instead of P(*p*-Cl-C<sub>6</sub>H<sub>4</sub>)<sub>3</sub> as the ligand, the yield decreased to 40%. Similarly, replacing N1 with NBE led to a reduced yield of 42%. However, when NBD is used instead of N1, the yield decreases to 19%, which may be due to the inhibition of β-carbon elimination. Lastly, omitting KI as an additive still yielded the target product with a 39% yield (Table 2).

After obtaining the optimal reaction conditions, we first studied the functional group tolerance of C4-ethylamine indole (Table 3). Both electron-donating groups ( $-Me$ ,  $-OMe$ ,  $^tBu$ , and  $-Ph$ ) and electron-withdrawing groups ( $-F$  and  $-Cl$ ) were suitable for this method. Notably, 2-methylaziridine underwent a selective ring-opening reaction to form the corresponding C4-ethylaminoindole product **3k**. More importantly, C4-ethylamino-aza-indole **3n** was successfully synthesized *via* this strategy.

Subsequently, we investigated the substrate scope of C7-aminoindoline. First, we studied the tolerance of functional groups on the indoline ring of the product. Both halogens ( $-F$ ,  $-Cl$ , and  $-Br$ ) and strong electron-withdrawing groups ( $-NO_2$  and  $-CO_2Me$ ) were suitable for the method, and the target products were obtained in 53–93% yield. It is noteworthy that the method can also achieve the biologically active C7-amino-aza-indoline scaffold (**4g**) with good yield. Specifically, 2-methylaziridine underwent a selective ring-opening reaction to produce the 2-methylindoline product **4h**. Additionally, aziridines with different benzenesulfonyl protecting groups on the nitrogen atom can be used to synthesize the corresponding C7-aminoindoline derivatives with antitumor activity.

Finally, we found that the *tert*-butyl group on the nitrogen atom of indole can be easily removed in hydrochloric acid, while the *p*-toluenesulfonyl group can be removed under basic conditions. Since pharmaceutically active indole or indoline molecules often have exposed N-H bonds, this further

enhances the application value of this synthetic method (Fig. 2). Additionally, the resulting C4-ethylaminoindole can be further converted into dopamine receptor agonists using established methods.<sup>24</sup>

Based on the above experimental results and our previous mechanistic studies,<sup>10d,14a</sup> we proposed a possible catalytic cycle (Fig. 3). First, *o*-iodoaniline **1a** undergoes oxidative addition with the Pd(0) complex to form intermediate **I**. Subsequently, it undergoes migratory insertion with norbornadiene (NBD) or norbornene (**N1**), followed by C–H bond activation and cyclization in the presence of carbonate, resulting in the formation of the aryl-norbornene-palladacycle ANP intermediate **II**. Among them, the common byproduct **II'**, which is detected in low-yielding cases as shown in Table 3, is generated from the reductive elimination reaction of intermediate **II**. Then, the intermediate **II** undergoes a ring-opening oxidative addition process with aziridine to generate the Pd(IV) intermediate **III**, and the C–H alkylation intermediate **IV** is obtained through reductive elimination. It is worth mentioning that intermediate **IV** can follow two distinct pathways, leading to the selective formation of C4-ethylaminoindole (Pathway A) and C7-aminoindoline (Pathway B), respectively. In Pathway A, intermediate **IV** is attacked by an anion, resulting in the cleavage of the N–Pd bond to form intermediate **V-1**. Its  $\sigma$  bond rotates and undergoes deprotonation to coordinate with the nitrogen atom of aniline, forming intermediate **VI-1**. Finally, the five-membered ring intermediate **VII-1** is obtained through reductive elimination, and it further forms C4-ethylaminoindole *via* a retro-Diels–Alder reaction. Density Functional Theory (DFT) calculations revealed that the retro-Diels–Alder reaction releases 18.2 kcal mol<sup>-1</sup>, indicating that the process is irreversible (Fig. 2c). In Pathway B, intermediate **IV** selectively undergoes a  $\beta$ -carbon elimination to extrude norbornene, followed by reductive elimination to yield C7-aminoindoline.

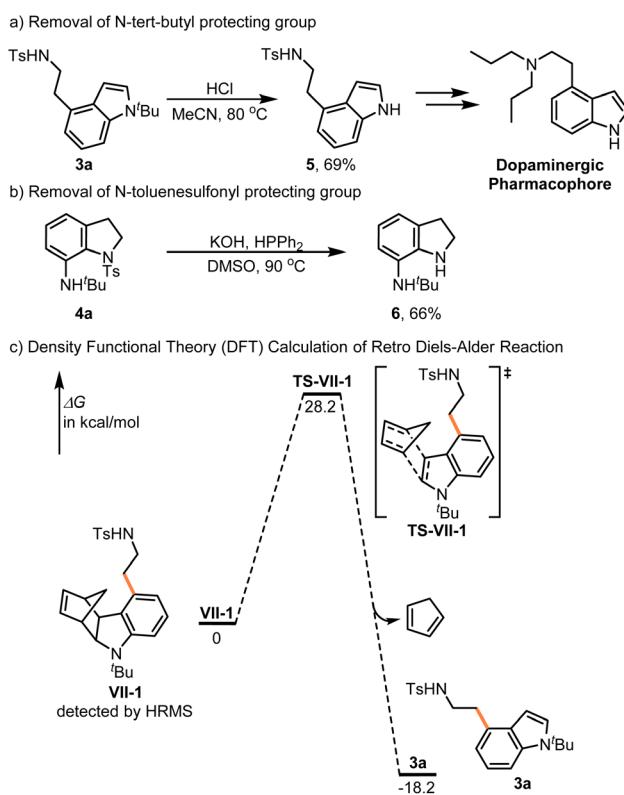


Fig. 2 Removal of protecting groups and density functional theory (DFT) calculation.

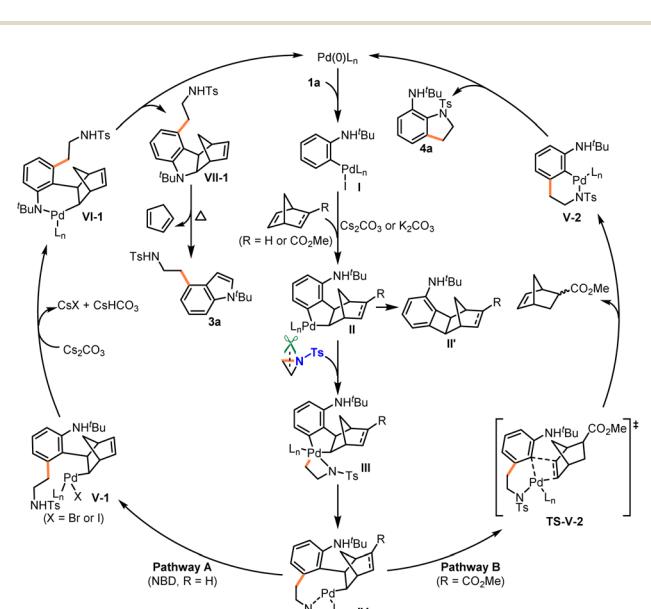


Fig. 3 Proposed reaction mechanism.



## Conclusions

In summary, we developed the first palladium-catalyzed regioselective synthesis of C4-ethylaminoindoles by utilizing the C–N bond ring-opening cleavage reaction of aziridine for the *ortho*-C–H ethylation of iodobenzene. Subsequently, by controlling  $\beta$ -carbon elimination to extrude norbornene, we further achieved the synthesis of the C7-aminoindoles. In addition, the reaction also effectively inhibited the nucleophilic addition of the amine group of *o*-iodoaniline to aziridine, making a smooth Pd/NBE catalytic cycle possible. Moreover, the *tert*-butyl or *p*-toluenesulfonyl protecting groups on C4-ethylaminoindole and C7-aminoindole were easily removed, providing a novel synthetic route to dopamine receptor agonists.

## Data availability

All data associated with this study are available in the article and ESI.<sup>†</sup>

## Author contributions

Conceptualization, B.-S. Z. and Y.-M. L.; methodology, B.-S. Z. and B.-J. D.; investigation, B.-J. D., Y.-X. Z., T.-J. G., and Y.-M. W.; writing – original draft, B.-S. Z. and B.-J. D.; writing – review & editing, B.-S. Z., B.-J. D., X.-Y. G. and Y.-M. L.; funding acquisition, B.-S. Z., X.-C. W., Z.-J. Q. and Y.-M. L.; resources, B.-S. Z., X.-C. W. and Z.-J. Q.; supervision, B.-S. Z., X.-C. W. and Z.-J. Q.

## Conflicts of interest

There are no conflicts to declare.

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