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

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

Controllable β-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 β-carbon elimination, utilizing aziridine as a C–H ethylamination 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.

Introduction

Indole and indoline are the most common heterocycles widely found in nature, possessing unique biological activities.[1] Among them, ethylamino indole is involved in the entire metabolic process of the human body.[2] For example, tryptophan is one of the essential amino acids for humans, involved in protein synthesis.[3] 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.[4] 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.[5] On the other hand, C7-aminoindoline is a type of microtubule protein inhibitor and is considered an important antitumor drug (Fig. 1a).[6] 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,[7] provides a strategy for the multi-functionalization of arenes. This reaction integrates the features of C–H functionalization and cross-coupling.[8] In 2000, the cyclization reaction catalyzed by Pd/NBE cooperatively was first discovered by Lautens.[9] The cyclization reaction has since been widely used in materials chemistry, natural product synthesis, and pharmaceutical synthesis.[8i,10] 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.[11] In recent years, Liang,[10d] Kwong,[12] Cheng,[13] and our group[10d,14] 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.[13a] In recent years, the ring-opening C–H alkylation reaction of strained tricyclic heterocycles was achieved by Lautens,[15] Dong,[16] Zhou,[17] and Liang[10d,14,18] under Pd/NBE catalysis (Fig. 1c). However, C–H alkylation between *o*-iodoanilines 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).[19]

β-carbon elimination to extrude norbornene has consistently been a focal point of interest in Pd/NBE research.[8g,20] In 2018, the Dong group utilized the steric hindrance effect of C1 norbornene to effectively promote β-carbon elimination and achieve single C–H functionalization of aryl iodides without an *ortho*-substituent.[20c] In 2019, Dong made a breakthrough in the halogenated olefin version by using norbornene amides.[21] 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.[22] Interestingly, the Jiao group used hybrid cycloolefin ligands to achieve norbornene-like β-carbon elimination.[23] However, controllable β-carbon elimination to extrude

[a]*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: zhangbsh@nwnu.edu.cn; quanzhengjun@hotmail.com; wangxicun@nwnu.edu.cn*

[b]*State Key Laboratory of Applied OrganicChemistry, Lanzhou University, Lanzhou 730000, China*

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‡ These authors contributed equally.

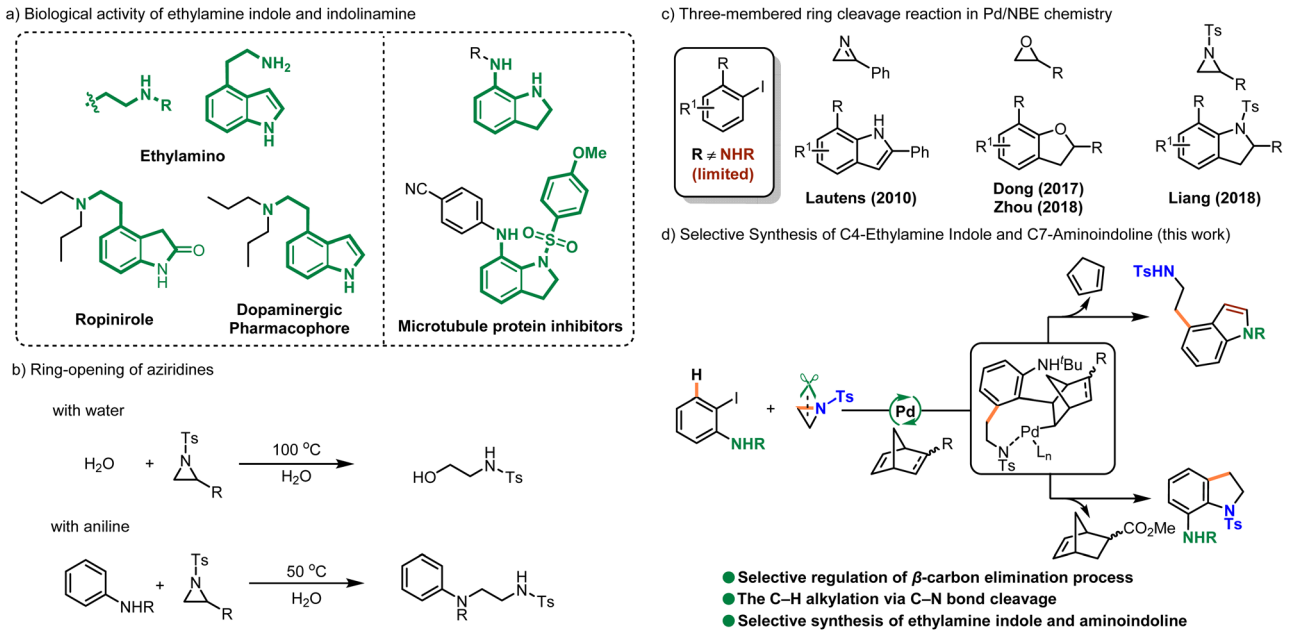


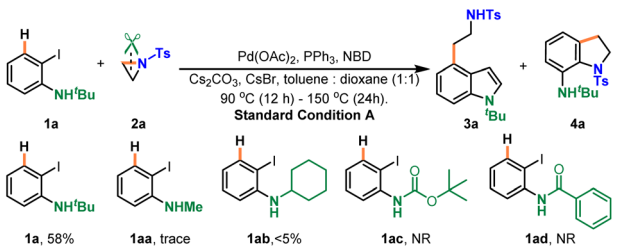
Fig. 1 Selective synthesis of C4-ethylamine indole and C7-aminoindoline.

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 β-carbon elimination, utilizing aziridine as a C–H ethylamination 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, $Pd(OAc)_2$ and triphenylphosphine were chosen as the Pd/ligand combination, cesium carbonate (Cs_2CO_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 β-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 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).

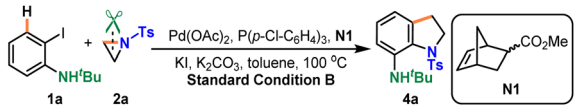
Table 1 Optimization of reaction conditions for C4-ethylamine indole[a]



Entry	Deviation from the standard conditions	Yield (**3a**)	Yield (**4a**)
1	—	58	Trace
2	Toluene or dioxane as solvent	31/40	8/trace
3	Without CsBr	48	Trace
4	NBE instead of NBD	0	16
5	K_2CO_3 instead of Cs_2CO_3	30	12
6	2.0 equiv. of Cs_2CO_3	43	Trace
7	140 °C and 24 h	32	18

[a] Standard conditions A: substrate **1a** (0.2 mmol), **2a** (0.5 mmol, 2.5 equiv.), $Pd(OAc)_2$ (10 mmol%), PPh_3(25 mmol%), CsBr (1.0 equiv.), Cs_2CO_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[a]

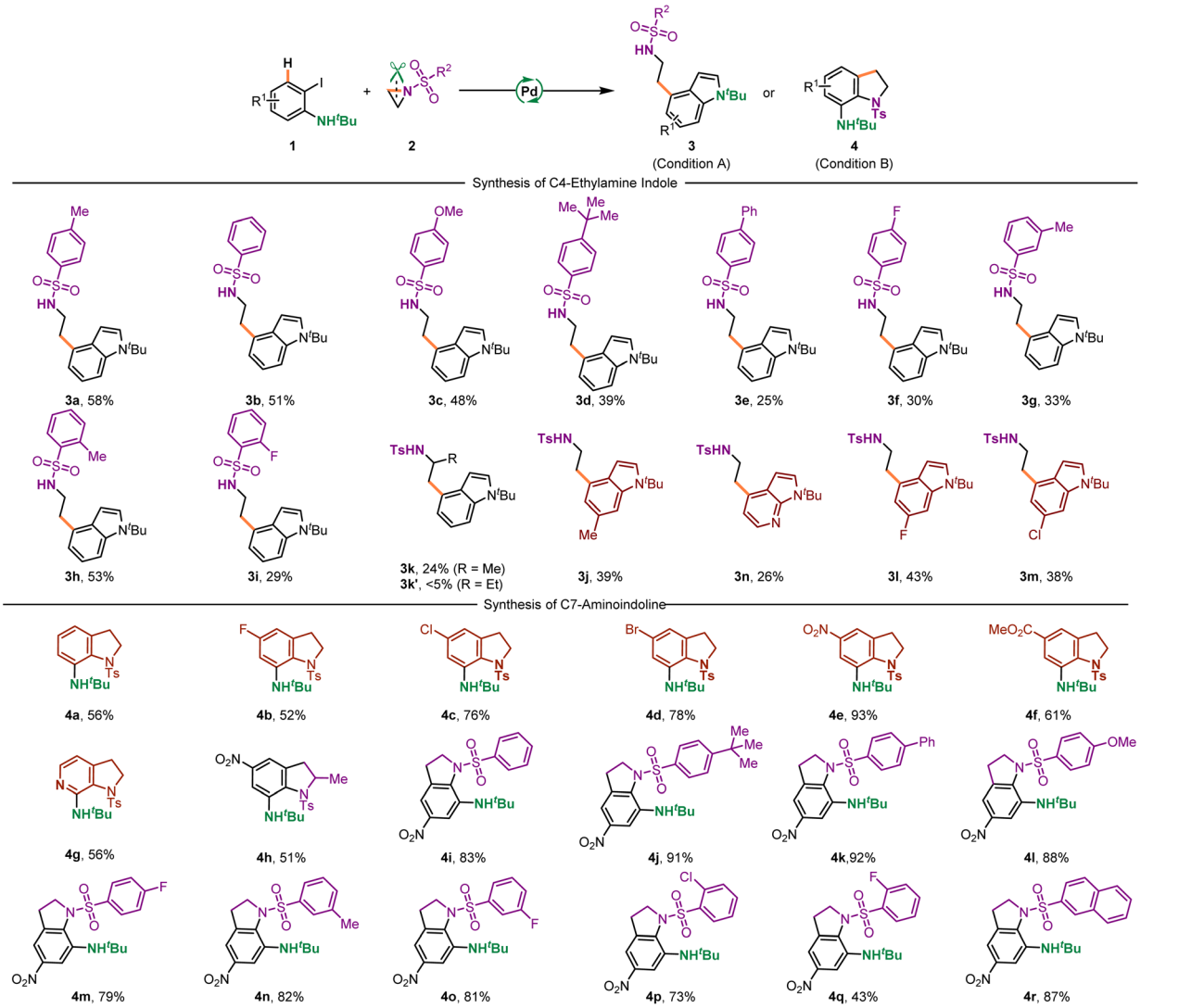


Entry	Deviation from the standard conditions	Yield (**4a**)	Yield (**3a**)
1	—	56	—
2	PPh_3 instead of P(p-Cl-C_6H_4)$_3$	40	—
3	NBE instead of **N1**	42	—
4	NBD instead of **N1**	19	Trace
5	Without KI	39	—

[a] Standard conditions B: substrate **1a** (0.2 mmol), **2a** (0.5 mmol, 2.5 equiv.), Pd(OAc)$_2$ (10 mmol%), P(p-Cl-C_6H_4)$_3$ (20 mmol%), KI (0.5 equiv.), K_2CO_3 (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_6H_4)$_3$ 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).

Table 3 Investigation of substrate scope[a]



[a] Standard conditions A: substrate **1** (0.2 mmol), **2** (0.5 mmol, 2.5 equiv.), Pd(OAc)$_2$ (10 mmol%), PPh_3(25 mmol%), CsBr (1.0 equiv.), Cs_2CO_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. Standard conditions B: substrate **1** (0.2 mmol), **2** (0.5 mmol, 2.5 equiv.), Pd(OAc)$_2$ (10 mmol%), P(p-Cl-C_6H_4)$_3$ (20 mmol%), KI (0.5 equiv.), K_2CO_3 (0.6 mmol, 3.0 equiv.), **N1** (0.2 mmol, 1.0 equiv.), toluene (2 mL), 100 °C, 24 h.

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, ^{t}Bu, 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.[24]

Based on the above experimental results and our previous mechanistic studies,[10d,14a] 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 σ 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^{-1}, indicating that the process is irreversible (Fig. 2c). In Pathway B, intermediate **IV** selectively undergoes a β-carbon elimination to extrude norbornene, followed by reductive elimination to yield C7-aminoindoline.

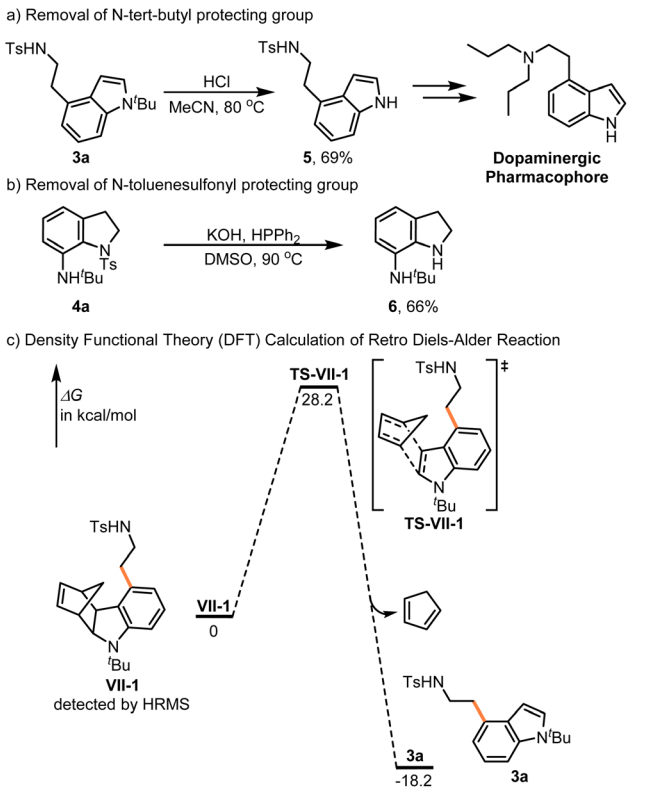


Fig. 2 Removal of protecting groups and density functional theory (DFT) calculation.

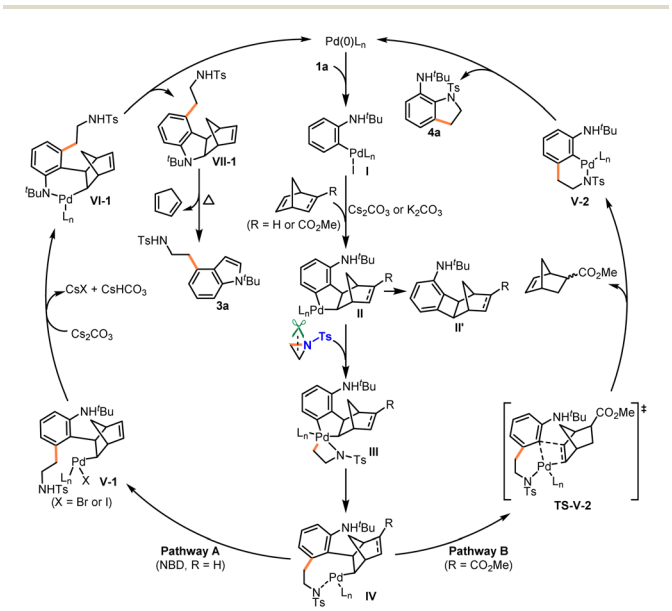


Fig. 3 Proposed reaction mechanism.

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 ethylamination of iodobenzene. Subsequently, by controlling β-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.†

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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