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A switch strategy for the synthesis of C4ethylamine indole and C7-aminoindoline *via* controllable carbon elimination[†]

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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.

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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 wellbeing.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 Catellanitype 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



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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 bv 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 C4ethylamino indole 3a decreased to 31%, and 8% of C7aminoindoline 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).





Deviation from the standard conditions Yield (3a) Yield (4a) Entry

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 ₂ CO ₃ instead of Cs ₂ CO 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%), PPh₃(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.



^a Standard conditions B: substrate 1a (0.2 mmol), 2a (0.5 mmol, 2.5 equiv.), Pd(OAc)₂ (10 mmol%), P(p-Cl-C₆H₄)₃ (20 mmol%), KI (0.5 equiv.), K₂CO₃ (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 C4ethylamino 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-2carboxylate (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).



^a Standard conditions A: substrate 1 (0.2 mmol), 2 (0.5 mmol, 2.5 equiv.), Pd(OAc)₂ (10 mmol%), PPh₃(25 mmol%), CsBr (1.0 equiv.), Cs₂CO₃ (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-C₆H₄)₃ (20 mmol%), KI (0.5 equiv.), K₂CO₃ (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 C7aminoindoline. 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 $(-NO_2 \text{ and} -CO_2Me)$ 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 2methylindoline product **4h**. Additionally, aziridines with different benzenesulfonyl protecting groups on the nitrogen atom can be used to synthesize the corresponding C7aminoindoline 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



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

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 C7aminoindoline (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 fivemembered 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. 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 C4ethylaminoindole 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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