

Cite this: *Chem. Sci.*, 2024, 15, 16169

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 31st July 2024
Accepted 5th September 2024

DOI: 10.1039/d4sc05111d

rsc.li/chemical-science

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,^b 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 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.

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.^{8a,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

^aGansu 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

^bState Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4sc05111d>

‡ These authors contributed equally.

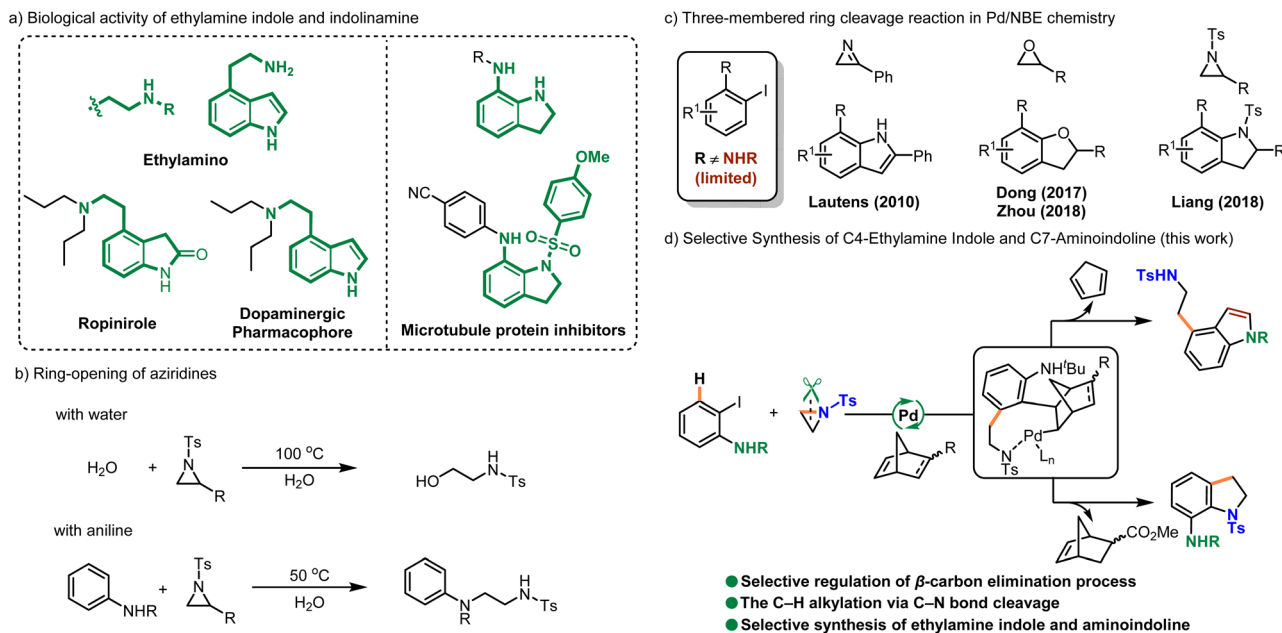


Fig. 1 Selective synthesis of C4-ethylamine indole and C7-aminoindoline.

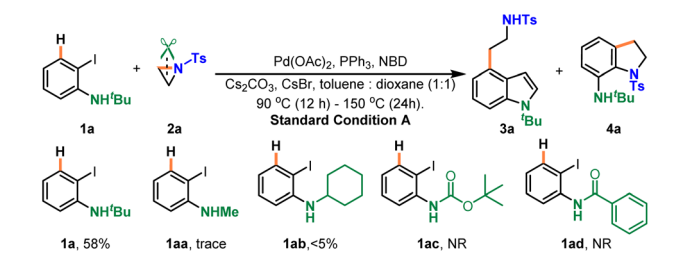
norbornene remains a long-standing challenge. Herein, this manuscript described a switchable synthesis of biologically active C4-ethylaminoindole and C7-aminoindoline scaffolds by controlling the β -carbon elimination, utilizing aziridine as a C-H ethylation reagent through a C-N bond cleavage reaction.

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, Pd(OAc)₂ and triphenylphosphine were chosen as the Pd/ligand combination, cesium carbonate (Cs₂CO₃) 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 ₂ CO ₃ instead of Cs ₂ CO ₃	30	12
6	2.0 equiv. of Cs ₂ CO 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.), 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.

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(<i>p</i> -Cl-C ₆ H 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-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 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-C₆H₄)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

(Condition A) (Condition B)	
Synthesis of C4-Ethylamine Indole	
 3a, 58%	 3b, 51%
 3c, 48%	 3d, 39%
 3e, 25%	 3f, 30%
 3g, 33%	 3h, 53%
 3i, 29%	 3j, 39%
 3k, 24% (R = Me)	 3l, <5% (R = Et)
 3m, 38%	 3n, 26%
 3o, 43%	 3p, 38%
Synthesis of C7-Aminoindoline	
 4a, 56%	 4b, 52%
 4c, 76%	 4d, 78%
 4e, 93%	 4f, 61%
 4g, 56%	 4h, 51%
 4i, 83%	 4j, 91%
 4k, 92%	 4l, 88%
 4m, 79%	 4n, 82%
 4o, 81%	 4p, 73%
 4q, 43%	 4r, 87%

^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 ($-Me$, $-OMe$, 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.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.

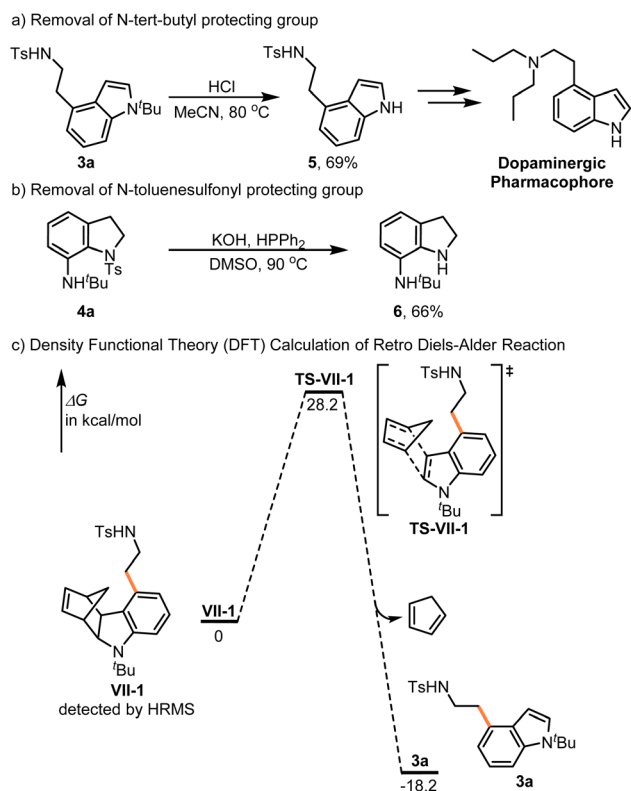


Fig. 2 Removal of protecting groups and density functional theory (DFT) calculation.

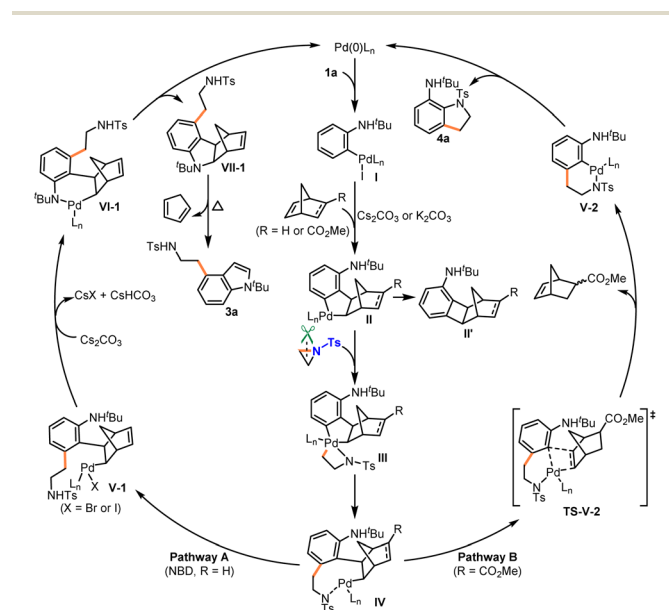


Fig. 3 Proposed reaction mechanism.

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 ethylation 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.

Acknowledgements

Financial support was received from the National Natural Science Foundation of China: 22101232 (B.-S. Z.), 22067018 (X.-C. W.), 22061038 (Z.-J. Q.) and 22171114 (Y.-M. L.) and the Long Yuan Youth Innovative Project of Gansu Province (2019–39).

Notes and references

- (a) R. D. Taylor, M. MacCoss and A. D. G. Lawson, Rings in Drugs, *J. Med. Chem.*, 2014, **57**, 5845–5859; (b) C. R. Jamison, J. J. Badillo, J. M. Lipshultz, R. J. Comito and D. W. C. MacMillan, Catalyst-controlled oligomerization for the collective synthesis of polypyrroloindoline natural products, *Nat. Chem.*, 2017, **9**, 1165–1169; (c) H. Wei, B. Li, N. Wang, Y. Ma, J. Yu, X. Wang, J. Su and D. Liu, Development and Application of Indolines in Pharmaceuticals, *ChemistryOpen*, 2023, **12**, e202200235.
- (a) F. Tylš, T. Páleníček and J. Horáček, Psilocybin – Summary of knowledge and new perspectives, *Eur. Neuropsychopharmacol.*, 2014, **24**, 342–356; (b) R. Tittarelli, G. Mannocchi, F. Pantano and S. F. Romolo, Recreational Use, Analysis and Toxicity of Tryptamines, *Curr. Neuropharmacol.*, 2015, **13**, 26–46.
- A. Slominski, I. Semak, A. Pisarchik, T. Sweatman, A. Szczesniowski and J. Wortsman, Conversion of L-tryptophan to serotonin and melatonin in human melanoma cells, *FEBS Lett.*, 2002, **511**, 102–106.
- (a) L. F. Mohammad-Zadeh, L. Moses and S. M. Gwaltney-Brant, Serotonin: a review, *J. Vet. Pharmacol. Ther.*, 2008, **31**, 187–199; (b) F. Auld, E. L. Maschauer, I. Morrison, D. J. Skene and R. L. Riha, Evidence for the efficacy of melatonin in the treatment of primary adult sleep disorders, *Sleep Med. Rev.*, 2017, **34**, 10–22.
- (a) J. M. Cassady and J. A. Clemens, Use of 4-(2-di-n-propylaminoethyl)indole or a salt thereof as a presynaptic dopamine autoreceptor stimulant, *US pat.*, 4378368A, 1981; (b) H. Wikstroem, J. H. Lii and N. L. Allinger, The dopaminergic moiety of the ergots. A controversial topic studied with molecular mechanics, *J. Med. Chem.*, 1987, **30**, 1928–1934; (c) D. J. Thompson and D. Vealer, Steady-state pharmacokinetic properties of a 24-hour prolonged-release formulation of ropinirole: Results of two randomized studies in patients with Parkinson's disease, *Clin. Ther.*, 2007, **29**, 2654–2666.
- (a) S. Mehndiratta, Y.-F. Chiang, M.-J. Lai, H.-Y. Lee, M.-C. Chen, C.-C. Kuo, C.-Y. Chang, J.-Y. Chang and J.-P. Liou, Concise syntheses of 7-anilino-indoline-N-benzenesulfonamides as antimitotic and vascular disrupting agents, *Bioorg. Med. Chem.*, 2014, **22**, 4917–4923; (b) S.-Y. Wang, X. Liu, L.-W. Meng, M.-M. Li, Y.-R. Li, G.-X. Yu, J. Song, H.-Y. Zhang, P. Chen, S.-Y. Zhang and T. Hu, Discovery of indoline derivatives as anticancer agents via inhibition of tubulin polymerization, *Bioorg. Med. Chem. Lett.*, 2021, **43**, 128095.
- (a) M. Catellani, F. Frignani and A. Rangoni, A Complex Catalytic Cycle Leading to a Regioselective Synthesis of *o,o'*-Disubstituted Vinylarenes, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 119–122; (b) D. Dupommier and T. Besset, New trends for transition metal-catalyzed *ortho/ippo* difunctionalizations of arenes, *Chem*, 2024, DOI: [10.1016/j.chempr.2024.07.003](https://doi.org/10.1016/j.chempr.2024.07.003).
- (a) J. Ye and M. Lautens, Palladium-catalysed norbornene-mediated C–H functionalization of arenes, *Nat. Chem.*, 2015, **7**, 863–870; (b) N. Della Ca', M. Fontana, E. Motti and M. Catellani, Pd/Norbornene: A Winning Combination for Selective Aromatic Functionalization via C–H Bond Activation, *Acc. Chem. Res.*, 2016, **49**, 1389–1400; (c) H.-G. Cheng, S. Chen, R. Chen and Q. Zhou, Palladium(II)-Initiated Catellani-Type Reactions, *Angew. Chem., Int. Ed.*, 2019, **58**, 5832–5844; (d) J. Wang and G. Dong, Palladium/Norbornene Cooperative Catalysis, *Chem. Rev.*, 2019, **119**, 7478–7528; (e) R. Li and G. Dong, Structurally Modified Norbornenes: A Key Factor to Modulate Reaction Selectivity in the Palladium/Norbornene Cooperative Catalysis, *J. Am. Chem. Soc.*, 2020, **142**, 17859–17875; (f) L.-Y. Liu, J. X. Qiao, K.-S. Yeung, W. R. Ewing and J.-Q. Yu, meta-Selective C–H Arylation of Fluoroarenes and Simple Arenes, *Angew. Chem., Int. Ed.*, 2020, **59**, 13831–13835; (g) H. Shi, Y. Lu,



- J. Weng, K. L. Bay, X. Chen, K. Tanaka, P. Verma, K. N. Houk and J.-Q. Yu, Differentiation and functionalization of remote C–H bonds in adjacent positions, *Nat. Chem.*, 2020, **12**, 399–404; (h) L. Guillemard, N. Kaplaneris, L. Ackermann and M. J. Johansson, Late-stage C–H functionalization offers new opportunities in drug discovery, *Nat. Rev. Chem.*, 2021, **5**, 522–545; (i) H.-G. Cheng, S. Jia and Q. Zhou, Benzo-Fused-Ring Toolbox Based on Palladium/Norbornene Cooperative Catalysis: Methodology Development and Applications in Natural Product Synthesis, *Acc. Chem. Res.*, 2023, **56**, 573–591.
- 9 (a) M. Lautens and S. Piguel, A New Route to Fused Aromatic Compounds by Using a Palladium-Catalyzed Alkylation–Alkenylation Sequence, *Angew. Chem., Int. Ed.*, 2000, **39**, 1045–1046; (b) B. Mariampillai, J. Alliot, M. Li and M. Lautens, A Convergent Synthesis of Polysubstituted Aromatic Nitriles via Palladium-Catalyzed C–H Functionalization, *J. Am. Chem. Soc.*, 2007, **129**, 15372–15379; (c) A. Rudolph, N. Rackelmann and M. Lautens, Stereochemical and Mechanistic Investigations of a Palladium-Catalyzed Annulation of Secondary Alkyl Iodides, *Angew. Chem., Int. Ed.*, 2007, **46**, 1485–1488; (d) D. A. Candito and M. Lautens, Palladium-Catalyzed Domino Direct Arylation/N-Arylation: Convenient Synthesis of Phenanthridines, *Angew. Chem., Int. Ed.*, 2009, **48**, 6713–6716; (e) H. Weinstabl, M. Suhartono, Z. Qureshi and M. Lautens, Total Synthesis of (+)-Linopexin by Utilizing the Catellani Reaction, *Angew. Chem., Int. Ed.*, 2013, **52**, 5305–5308; (f) A. Whyte, M. E. Olson and M. Lautens, Palladium-Catalyzed, Norbornene-Mediated, ortho-Amination ipso-Amidation: Sequential C–N Bond Formation, *Org. Lett.*, 2018, **20**, 345–348.
- 10 (a) P. Zhao, Y. Guo and X. Luan, Total Synthesis of Dalesconol A by Pd(0)/Norbornene-Catalyzed Three-Fold Domino Reaction and Pd(II)-Catalyzed Trihydroxylation, *J. Am. Chem. Soc.*, 2021, **143**, 21270–21274; (b) M. Bai, S. Jia, J. Zhang, H.-G. Cheng, H. Cong, S. Liu, Z. Huang, Y. Huang, X. Chen and Q. Zhou, A Modular Approach for Diversity-Oriented Synthesis of 1,3-trans-Disubstituted Tetrahydroisoquinolines: Seven-Step Asymmetric Synthesis of Michellamines B and C, *Angew. Chem., Int. Ed.*, 2022, **61**, e202205245; (c) B.-S. Zhang, Y.-X. Yang, J. C. A. Oliveira, Z.-Q. Zhang, S. Warratz, Y.-M. Wang, S.-X. Li, X.-C. Wang, X.-Y. Gou, Y.-M. Liang, Z.-J. Quan and L. Ackermann, Combined C–H amination and intermolecular alkyne insertion for a three-component cyclization, *Cell Rep. Phys. Sci.*, 2023, 101647; (d) B.-S. Zhang, Y. Li, Z. Zhang, Y. An, Y.-H. Wen, X.-Y. Gou, S.-Q. Quan, X.-G. Wang and Y.-M. Liang, Synthesis of C4-Aminated Indoles via a Catellani and Retro-Diels–Alder Strategy, *J. Am. Chem. Soc.*, 2019, **141**, 9731–9738.
- 11 P. Thansandote, D. G. Hulcoop, M. Langer and M. Lautens, Palladium-Catalyzed Annulation of Haloanilines and Halobenzamides Using Norbornadiene as an Acetylene Synthone: A Route to Functionalized Indolines, Isoquinolinones, and Indoles, *J. Org. Chem.*, 2009, **74**, 1673–1678.
- 12 W. C. Fu, Z. Wang, W. T. K. Chan, Z. Lin and F. Y. Kwong, Regioselective Synthesis of Polycyclic and Heptagon-embedded Aromatic Compounds through a Versatile π -Extension of Aryl Halides, *Angew. Chem., Int. Ed.*, 2017, **56**, 7166–7170.
- 13 (a) W. Lv, S. Wen, J. Yu and G. Cheng, Palladium-Catalyzed Ortho-Silylation of Aryl Iodides with Concomitant Arylsilylation of Oxanorbornadiene: Accessing Functionalized (Z)- β -Substituted Vinylsilanes and Their Analogues, *Org. Lett.*, 2018, **20**, 4984–4987; (b) W. Lv, J. Yu, B. Ge, S. Wen and G. Cheng, Palladium-Catalyzed Catellani-Type Bis-silylation and Bis-germylation of Aryl Iodides and Norbornenes, *J. Org. Chem.*, 2018, **83**, 12683–12693; (c) Q. Tian, J. Ge, Y. Liu, X. Wu, Z. Li and G. Cheng, Solvent-Controlled Enantiodivergent Construction of P(V)-Stereogenic Molecules via Palladium-Catalyzed Annulation of Prochiral N-Aryl Phosphonamides with Aromatic Iodides, *Angew. Chem., Int. Ed.*, 2024, e202409366; (d) Y. Zhang, Y. Chen, Q. Tian, B. Wang and G. Cheng, Palladium-Catalyzed Multicomponent Assembly of (Z)-Alkenylborons via Carbopalladation/Boronation/Retro-Diels–Alder Cascade Reaction, *J. Org. Chem.*, 2023, **88**, 11793–11800.
- 14 (a) B.-S. Zhang, Z.-Q. Zhang, T.-J. Guo, J. C. A. Oliveira, S. Warratz, B.-J. Deng, Y.-M. Wang, J.-S. Zhou, X.-Y. Gou, X.-C. Wang, Z.-J. Quan and L. Ackermann, Direct Synthesis of C4-Acyl Indoles via C–H Acylation, *Org. Lett.*, 2024, **26**, 4998–5003; (b) Y. An, B.-S. Zhang, Y.-N. Ding, Z. Zhang, X.-Y. Gou, X.-S. Li, X. Wang, Y. Li and Y.-M. Liang, Palladium-catalyzed C–H glycosylation and retro Diels–Alder tandem reaction via structurally modified norbornadienes (smNBDs), *Chem. Sci.*, 2021, **12**, 13144–13150.
- 15 (a) D. A. Candito and M. Lautens, Exploiting the Chemistry of Strained Rings: Synthesis of Indoles via Domino Reaction of Aryl Iodides with 2H-Azirines, *Org. Lett.*, 2010, **12**, 3312–3315; (b) P. Thansandote, M. Raemy, A. Rudolph and M. Lautens, Synthesis of Benzannulated N-Heterocycles by a Palladium-Catalyzed C–C/C–N Coupling of Bromoalkylamines, *Org. Lett.*, 2007, **9**, 5255–5258.
- 16 (a) R. Li, F. Liu and G. Dong, Palladium-catalyzed asymmetric annulation between aryl iodides and racemic epoxides using a chiral norbornene cocatalyst, *Org. Chem. Front.*, 2018, **5**, 3108–3112; (b) R. Li and G. Dong, Direct Annulation between Aryl Iodides and Epoxides through Palladium/Norbornene Cooperative Catalysis, *Angew. Chem., Int. Ed.*, 2018, **57**, 1697–1701; (c) Z. Wang, Y. Kuninobu and M. Kanai, Palladium-Catalyzed Oxirane-Opening Reaction with Arenes via C–H Bond Activation, *J. Am. Chem. Soc.*, 2015, **137**, 6140–6143; (d) G. Cheng, T.-J. Li and J.-Q. Yu, Practical Pd(II)-Catalyzed C–H Alkylation with Epoxides: One-Step Syntheses of 3,4-Dihydroisocoumarins, *J. Am. Chem. Soc.*, 2015, **137**, 10950–10953.
- 17 (a) C. Wu, H.-G. Cheng, R. Chen, H. Chen, Z.-S. Liu, J. Zhang, Y. Zhang, Y. Zhu, Z. Geng and Q. Zhou, Convergent syntheses of 2,3-dihydrobenzofurans via a Catellani strategy, *Org. Chem. Front.*, 2018, **5**, 2533–2536; (b) G. Qian,



- M. Bai, S. Gao, H. Chen, S. Zhou, H.-G. Cheng, W. Yan and Q. Zhou, Modular One-Step Three-Component Synthesis of Tetrahydroisoquinolines Using a Catellani Strategy, *Angew. Chem., Int. Ed.*, 2018, **57**, 10980–10984; (c) H.-G. Cheng, C. Wu, H. Chen, R. Chen, G. Qian, Z. Geng, Q. Wei, Y. Xia, J. Zhang, Y. Zhang and Q. Zhou, Epoxides as Alkylating Reagents for the Catellani Reaction, *Angew. Chem., Int. Ed.*, 2018, **57**, 3444–3448.
- 18 C. Liu, Y. Liang, N. Zheng, B.-S. Zhang, Y. Feng, S. Bi and Y.-M. Liang, Synthesis of indolines via a palladium/norbornene-catalyzed reaction of aziridines with aryl iodides, *Chem. Commun.*, 2018, **54**, 3407–3410.
- 19 (a) Z. Wang, Y.-T. Cui, Z.-B. Xu and J. Qu, Hot Water-Promoted Ring-Opening of Epoxides and Aziridines by Water and Other Nucleophiles, *J. Org. Chem.*, 2008, **73**, 2270–2274; (b) M. Zhu and B. Moasser, Aqueous ring opening of N-tosylaziridine with aniline derivatives, *Tetrahedron Lett.*, 2012, **53**, 2288–2291; (c) S. Sabir, G. Kumar, V. P. Verma and J. L. Jat, Aziridine Ring Opening: An Overview of Sustainable Methods, *ChemistrySelect*, 2018, **3**, 3702–3711.
- 20 (a) M. Catellani and E. Motti, Selective aryl coupling via palladacycles: a new route to m-alkylbiphenyls or m-terphenyls, *New J. Chem.*, 1998, **22**, 759–761; (b) Z. Dong, G. Lu, J. Wang, P. Liu and G. Dong, Modular ipso/ortho Difunctionalization of Aryl Bromides via Palladium/Norbornene Cooperative Catalysis, *J. Am. Chem. Soc.*, 2018, **140**, 8551–8562; (c) J. Wang, R. Li, Z. Dong, P. Liu and G. Dong, Complementary site-selectivity in arene functionalization enabled by overcoming the ortho constraint in palladium/norbornene catalysis, *Nat. Chem.*, 2018, **10**, 866–872; (d) H. Shi, A. N. Herron, Y. Shao, Q. Shao and J.-Q. Yu, Enantioselective remote meta-C–H arylation and alkylation via a chiral transient mediator, *Nature*, 2018, **558**, 581–585; (e) K.-J. Xiao, L. Chu, G. Chen and J.-Q. Yu, Kinetic Resolution of Benzylamines via Palladium(II)-Catalyzed C–H Cross-Coupling, *J. Am. Chem. Soc.*, 2016, **138**, 7796–7800.
- 21 J. Wang, Z. Dong, C. Yang and G. Dong, Modular and regioselective synthesis of all-carbon tetrasubstituted olefins enabled by an alkenyl Catellani reaction, *Nat. Chem.*, 2019, **11**, 1106–1112.
- 22 X. Liu, Q. Zhu and G. Dong, Beyond Tertiary Amines: Introducing Secondary Amines by Palladium/Norbornene-Catalyzed Ortho Amination, *Angew. Chem., Int. Ed.*, 2024, **63**, e202404042.
- 23 (a) Y.-X. Zheng and L. Jiao, Hybrid cycloolefin ligands for palladium-olefin cooperative catalysis, *Nat. Synth.*, 2022, **1**, 180–187; (b) F.-Y. Wang, Y.-X. Li and L. Jiao, Functionalized Cycloolefin Ligand as a Solution to Ortho-Constraint in the Catellani-Type Reaction, *J. Am. Chem. Soc.*, 2023, **145**, 4871–4881.
- 24 (a) T. Ankner and G. Hilmersson, Instantaneous Deprotection of Tosylamides and Esters with SmI₂/Amine/Water, *Org. Lett.*, 2009, **11**, 503–506; (b) X. Jiang, C. Zheng, L. Lei, K. Lin and C. Yu, Synthesis of 2-Oxindoles from Substituted Indoles by Hypervalent-Iodine Oxidation, *Eur. J. Org. Chem.*, 2018, **2018**, 1437–1442.

