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Synthesis of C4-Aminated Indoles via a Catellani and Retro-Diels-Alder Strategy

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KEYWORDS. Indole, Norbornene, Retro-Diels–Alder Strategy, Domino Reaction, C4-Amination

ABSTRACT: Highly functionalized 4-aminoindoles were synthesized via the three-component cross-coupling of *o*-iodoaniline, N-benzoyloxyamines and norbornadiene (NBD). The Catellani and retro-Diels–Alder strategy was used in this domino process. *o*-Iodoaniline, with electron-donating and sterically hindered protecting groups (PGs), made the reaction selective toward *ortho*-C-H amination. Based on density functional theory (DFT) calculations, the intramolecular Buchwald coupling of this reaction underwent a dearomatization and a 1,3-palladium migration process. The reasons for the control of the chemical selectivity by the protecting groups are given. Moreover, synthetic applications toward 4-piperazinylindole and a GOT1 inhibitor were realized.

1. INTRODUCTION

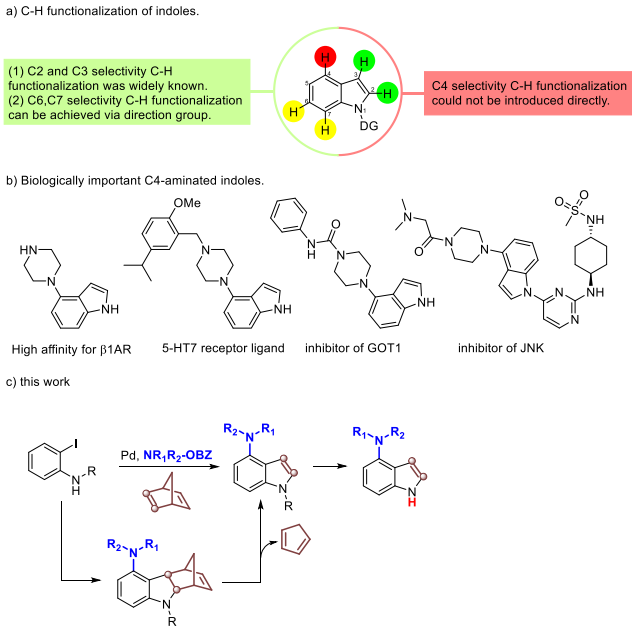
The indole heteroaromatic scaffold has been one of the most popular organic templates of the past century.[1] It is common in a wide variety of organisms and biologically active structures,[2] and the review "Rings in Drugs" reported that 24 drugs currently on the market contain indole rings.[3] Due to the high nucleophilic activity of the indole pyrrole side, selective C-H functionalization of the indole at the C2 or C3 position has been successfully obtained.[4] Recently, some sophisticated methods have been developed for introducing functional groups into the indole at the C6 or C7 sites by using removable directing groups (DGs) on the indole nitrogen atom.[5] Naturally, C4 C-H indole functionalization requires a directing group at the indole's C3 position (Scheme 1a).[6] Therefore, the direct construction of C4 position functionalized indoles is an unsolved problem that has attracted much attention.

4-Aminoindole is a widely bioactive molecular skeleton. 4-Piperazinylindole was identified and subsequently co-crystallized with the stabilized β1AR, yielding structures at 2.8 Å. This demonstrates that 4-piperazinylindole can be used as a molecular fragment applied to the G protein-coupled receptor (GPCR) target.[7] GPCR targets have been an important focus of research for the pharmaceutical industry, and over 60 new GPCR drugs have been launched in the past 10 years.[8] In addition, the 5-HT7 receptor is a member of a GPCR family, and a 5-HT7 receptor ligand may be used to treat depression.[9] It is important to note that the 5-year survival rate of pancreatic ductal adenocarcinoma (PDAC) is less than 1%, and this malignant tumor has one of the worst prognoses.[10] PDAC tumors are dependent on the glutamate oxaloacetate transaminase 1 (GOT1) metabolic pathway. Fortunately, 4-(1H-indol-4-yl)-N-phenylpiperazine-1-carboxamide was identified as an inhibitor of GOT1 via a high throughput screening of 800,000 molecules.[11] Moreover, the c-Jun N-terminal kinase (JNK) inhibitor still has this C4-Aminated Indole skeleton (Scheme 1b).[12] Although compounds with the 4-aminoindole skeleton are generally biologically active, the development of their synthetic methodology has been slow. To synthesize 4-aminoindole, 2-methyl-1,3-dinitrobenzene was synthesized from *o*-nitrotoluene by further nitration. Then 2-methyl-1,3-dinitrobenzene underwent a nucleophilic addition with N,N-dimethylformamide dimethyl acetal (DMFDMA) and a transition metal catalysis reduction to give 4-aminoindole (in a yield less than 5%).[13] The reaction conditions of the entire process were relatively harsh, and it was difficult to synthesize the highly functionalized 4-aminoindole. Therefore, the development of a series of C-H amination reactions to construct a 4-aminoindole skeleton from simple raw materials in one step is highly valuable.

In 1991, R. C. Larock first reported the construction of indole via the palladium-catalyzed cyclization coupling of *o*-haloaniline with substituted alkynes, and the reaction is now widely used and has been named the "Larock indole synthesis" by chemists.[14] In 2009, M. Lautens improved the "Larock indole synthesis" for the first time.[15] They used norbornadiene (NBD) instead of alkynes, and C2, C3-nonsubstituted indoles were successfully achieved via a retro-Diels-Alder strategy[16]. When the protecting group on the nitrogen of *o*-iodoaniline is electron-withdrawing, the reaction proceeds selectively toward the Buchwald cou-

pling. When halogenated alkanes were added, it was still impossible to change the direction of the reaction and produce the *ortho*-C-H functionalized products. Therefore, promotion of the reaction to first react in the direction of *ortho*-C-H functionalization and then successfully complete the intramolecular Buchwald coupling is an important unsolved problem.

Scheme 1. Approaches to Access C4-Aminated Indoles and its Biological Activity



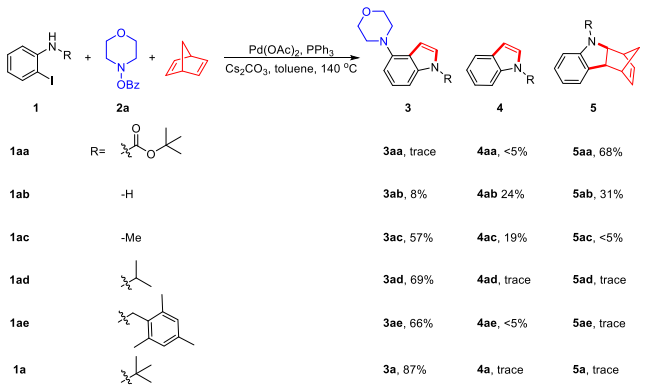
The Catellani reaction was discovered in 1997 and Pd/NBE chemistry was established.[17] In 2000, Lautens first used phosphorus ligands to broaden the chemical compatibility of Pd/NBE and established the Catellani-Lautens reaction system.[18] Thirteen years later, the Dong group achieved *ortho*-amination for the first time by using electrophilic amination reagents, providing a powerful tool for designing and constructing 4-aminoindole.[19] In 2016, Yu first developed a *meta*-C–H amination with pyridine-type DGs, which can be used to synthesize 3-fluoro-5-morpholinoaniline (an important synthetic intermediate of a BRAF inhibitor).[20] Over the past 20 years, Lautens and other research groups have developed a series of intramolecular Pd/NBE reactions to construct various heterocyclic or nonheterocyclic skeleton structures.[21] However, the construction of a C4-functionalized indole skeleton via domino reactions in a single step has not been reported to date.

2. RESULTS AND DISCUSSION

(1) Reaction Optimization.

Initially, we used the removable t-butyloxycarbonyl (Boc) group as the protecting group of *o*-iodoaniline to synthesize the 4-aminoindole skeleton structure in one step. Norbornadiene (NBD) was used instead of norbornene (NBE) as the *ortho*-C-H amination transient mediator for the Catellani reaction. Unfortunately, no desired product was detected, and the reaction proceeded toward the intramolecular Buchwald coupling without the retro-Diels-Alder reaction. When we used unprotected *o*-iodoaniline as the substrate, using gas chromatography-mass spectrometry (GCMS), we found that a small amount of desired product was generated and that some direct intramolecular Buchwald coupling product **5ab** was converted to the product **4ab** via a retro-Diels-Alder reaction. Therefore, we conjectured that the electron-donation group on the nitrogen atom could make the reaction proceed toward ortho-amination and promote the retro-Diels-Alder reaction. Therefore, we used N-methyl-*o*-iodoaniline as the substrate. Surprisingly, we obtained the 4-aminoindole product **3ac** in 57% yield, and almost all **5ac** was converted to **4ac**. Subsequently, we further investigated the use of isopropyl and tert-butyl as protecting groups to understand the effect of steric hindrance on the reaction direction. Gratifyingly, when we used *tert*-butyl as the protecting group, 4-aminoindole **3a** was obtained in 87% yield, and no other byproducts were detected by GCMS (Table 1). In addition, polysubstituted benzyl groups (**1ae**) can be used as protecting groups. Finally, monodentate phosphines were screened and triphenylphosphine is still the best ligand (Supporting Information, SI).

Table 1. Study on the Types of Protective Groups of *o*-Iodoaniline[a]



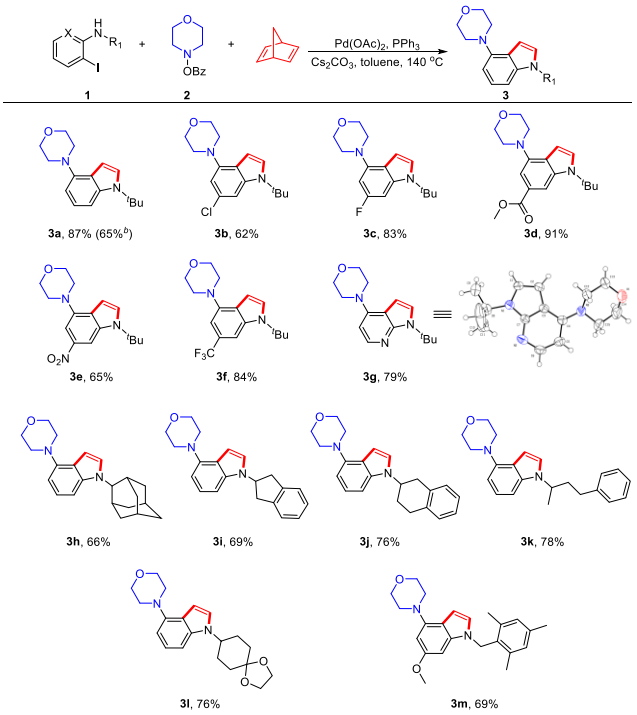
1aa	R=	**3aa**, trace	**4aa**, <5%	**5aa**, 68%
1ab	-H	**3ab**, 8%	**4ab** 24%	**5ab**, 31%
1ac	-Me	**3ac**, 57%	**4ac**, 19%	**5ac**, <5%
1ad		**3ad**, 69%	**4ad**, trace	**5ad**, trace
1ae		**3ae**, 66%	**4ae**, <5%	**5ae**, trace
1a		**3a**, 87%	**4a**, trace	**5a**, trace

[a] Reaction conditions: substrate **1** (0.2 mmol), **2** (0.4 mmol, 2.0 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), norbornadiene (0.7 mmol, 3.5 equiv.), Cs_2CO_3 (0.8 mmol, 4.0 equiv.), toluene (3.0 mL), 140 °C, 36 h. Isolated yields.

(2) Investigation of Substrate Scope.

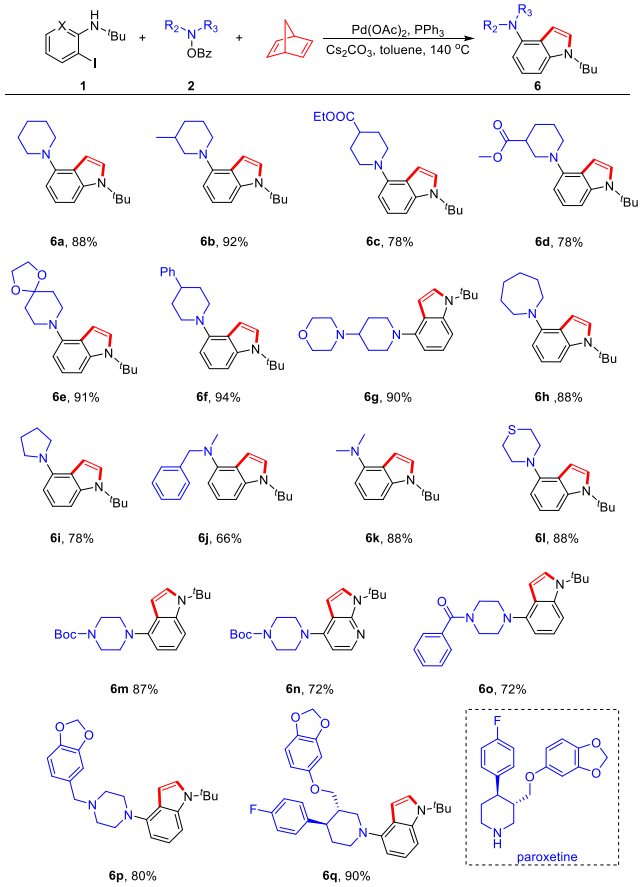
We first investigated the substrate scope of *o*-iodoanilines. *o*-Iodoanilines, with a halogen (-F, Cl) and a strongly electron-withdrawing group ($-NO_2$), were compatible with the reaction conditions and afforded the desired 4-aminoindole products in excellent yields (Table 2, **3b**-**3f**). It is worth mentioning that the heteroaromatic substrate 3-iodopyridin-2-amine reacted smoothly, and 4-amino-7-azaindole **3g** was obtained in 79% yield. Subsequently, we expanded the scope of the groups on the nitrogen atom of *o*-iodoaniline. Adamantane **3h** with a large steric hindrance, dihydroindene **3i**, tetrahydronaphthalene **3j** and 4-phenylbutan-2-yl **3k** containing aromatic hydrocarbons obtained the target products in high yield. These examples showed that a series of N-alkyl substituted indoles can be synthesized by this reaction. Notably, the coupling reaction of the indole with secondary or tertiary carbon is a difficult problem at present,[22] and this method provides a convenient route for the synthesis of these indole derivatives.

Table 2. Investigation of Substrate Scope[a]



[a] Reaction conditions: substrate **1** (0.2 mmol), **2** (0.4 mmol, 2.0 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), norbornadiene (0.7 mmol, 3.5 equiv.), Cs_2CO_3 (0.8 mmol, 4.0 equiv.), toluene (3.0 mL), 140 °C, 36 h. Isolated yields. [b] *o*-Bromoaniline instead of *o*-iodoaniline.

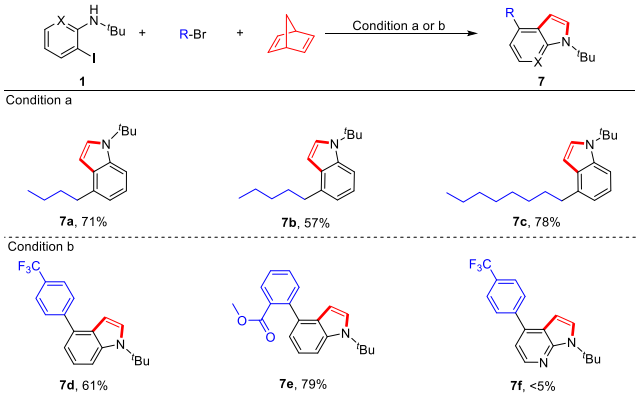
Table 3. Investigation of substrate scope for electrophilic amination reagents[a]



[a] Reaction conditions: substrate **1** (0.2 mmol), **2** (0.4 mmol, 2.0 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), norbornadiene (0.7 mmol, 3.5 equiv.), Cs_2CO_3 (0.8 mmol, 4.0 equiv.), toluene (3.0 mL), 140 °C, 36 h. Isolated yields.

We continued to expand the substrate scope for electrophilic amination reagents. Piperidine substituted with different sites and groups, thiomorpholine, and Boc-protected piperazine-derived amination reagents all afforded the desired products in excellent yields (Table 3). Nonhexacyclic amination reagents, such as azepane, pyrrolidine, dimethylamine and methylbenzyl ammonia, also afforded the target products in high yields, in contrast to the very low yields obtained for these substrates in the previous work. In addition, large volume amination reagents can also be used to obtain the products smoothly. In particular, the antidepressant drug paroxetine can be directly derived by this method (**6q**).

Table 4. Investigation of substrate scope for other electrophilic reagents[a]



[a] Conditions a: substrate **1** (0.2 mmol), **2** (1 mmol, 5.0 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), norbornadiene (0.8 mmol, 4.0 equiv.), Cs_2CO_3 (0.8 mmol, 4.0 equiv.), DMF (3.0 mL), 140 °C, 36 h. Conditions b: substrate **1** (0.2 mmol), **2** (1 mmol, 5.0 equiv.), $Pd(OAc)_2$ (10 mol%), TFP (20 mol%), norbornadiene (0.8 mmol, 4.0 equiv.), K_2CO_3 (0.8 mmol, 4.0 equiv.), DMF (3.0 mL), 140 °C, 36 h. Isolated yields.

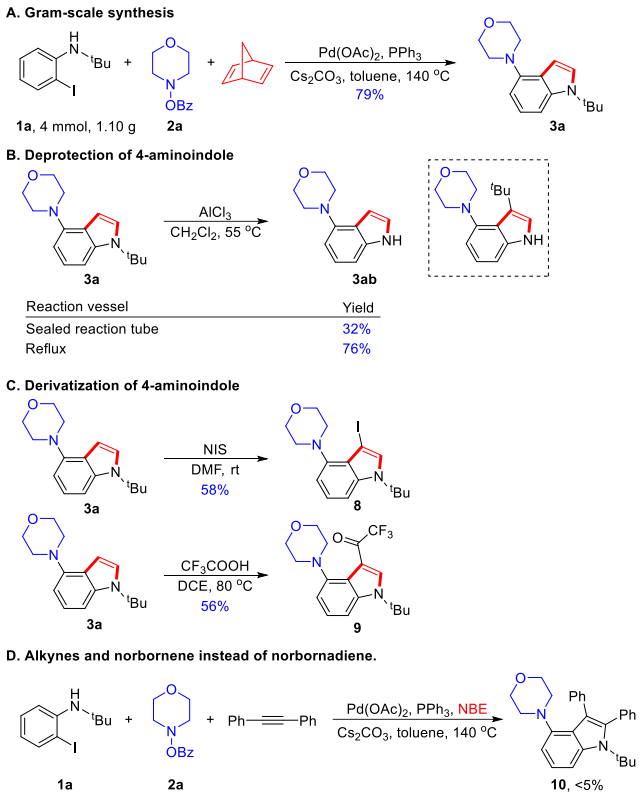
To further prove the practical value of this method, we expanded the scope of electrophilic reagents. We used alkyl and aryl bromides as electrophilic reagents, and the reaction conditions were reoptimized. When N,N-dimethylformamide was used as the solvent instead of toluene, 4-alkyl and aryl-substituted indoles were successfully obtained. Unfortunately, heterocyclic indole derivatives could not be synthesized by this method (Table 4).

(3) Synthetic Applications.

To demonstrate the industrialization potential of this method, the reaction was conducted on a 4 mmol scale, and 1.10 grams of **1a** was afforded (79% yield of isolated product). In addition, pharmaceutical compounds and natural products often have unprotected NH bonds, and therefore we carried out a deprotection experiment on 4-aminoindole. We tried to use trifluoroacetic acid, hydrochloric acid and a Lewis acid for deprotection. Finally, we found that the deprotected product **3ab** was obtained in 76% yield when aluminum chloride was used as the Lewis acid and DCM was used as the solvent at 55 °C. It is noteworthy that isobutylene can be produced when deprotec-

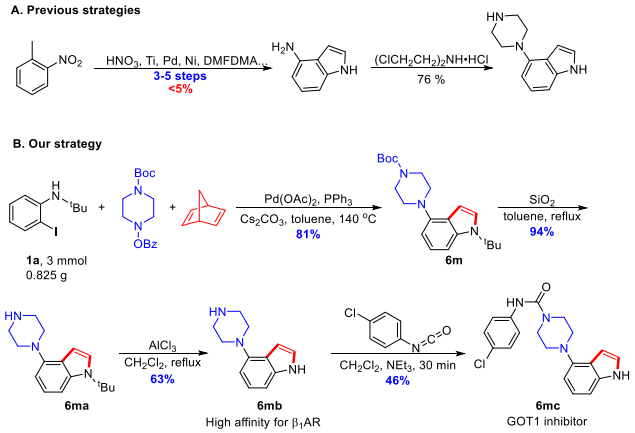
tion occurs under Lewis acid conditions. Therefore, when sealed reaction tubes were used, some C3-*tert*-butyl substituted 4-aminoindoles were produced, and the yield of the desired products was reduced. In addition, we performed iodization and Friedel-Crafts fluoroacetylation on indole **3a**. Finally, we tried to use diphenylacetylene and norbornene instead of norbornadiene according to Catellani's work,[17i] but only a trace amount of the desired product **10** was produced. This may be due to denorbornene reaction rate being much lower than the intramolecular Buchwald coupling (Scheme 2).

Scheme 2. Deprotection and Derivatization of Production.



The utility of this method was further demonstrated in the formal synthesis of 4-piperazinylindole used as a molecular fragment applied to the G protein-coupled receptor (GPCR) target, and we utilized it to further synthesize the GOT1 inhibitor used to treat pancreatic ductal adenocarcinoma (PDAC). In the past, the synthesis of 4-piperazinylindole required further nitrosation of *o*-nitrotoluene and purification of 2-methyl-1,3-dinitrobenzene from a variety of polynitrotoluene products, which was extremely uneconomical and environmentally unfriendly. In this case, 3-5 steps are required for the synthesis of 4-piperazinylindole, including a transition metal catalyzed reduction and the nucleophilic addition to N,N-dimethylformamide dimethyl acetal (DMFDMA). Through our strategy, we synthesized 4-piperazinylindole via a single step three-component tandem reaction and a simple deprotected process. Then, we stirred 4-piperazinylindole and 4-chlorophenyl isocyanate for 30 minutes in the presence of triethylamine as the base, and obtained the GOT1 inhibitor in 46% yield.

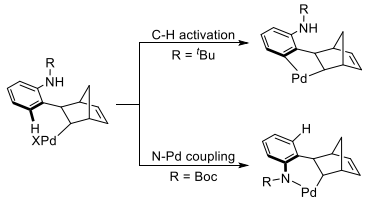
Scheme 3. Synthesis of Drug Building Blocks and GOT1 Inhibitor.



(4) Mechanistic Studies.

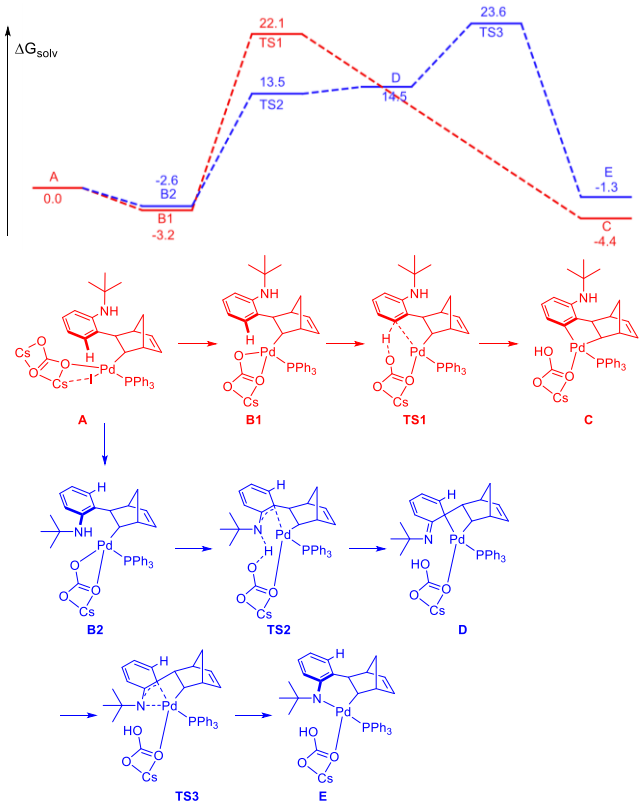
The DFT calculations were used to study the reaction of *o*-iodoaniline with different protecting groups (Boc, *t*-Bu). Cs_2CO_3 was taken into consideration in the whole mechanism study.[23] Before the C-H activation process, the removal of CsI released 3.2 kcal/mol for the *t*-Bu group intermediate **A** and 2.4 kcal/mol for the Boc intermediate **F** forming **B1** and **G1**. The barriers are 25.3 and 24.5 kcal/mol for C-H activation process, respectively. The benzene rings of intermediates **B1** and **G1** could be rotated to obtain intermediates **B2** and **G2**. It is noteworthy that the energy of **B2** is 0.6 kcal/mol larger than that of **B1** due to the high steric resistance of the *t*-butyl group. This is one of the reasons why the reaction moves towards C-H activation when the protecting group is *t*-butyl.

Scheme 4. C-H Bond Activation and Buchwald Coupling.

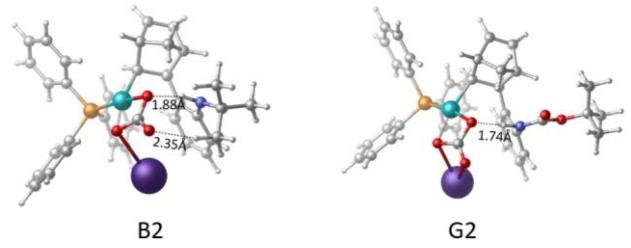


Subsequently, we studied the mechanism of the intramolecular C(sp^3)-N Buchwald coupling. For the intermediate **B2**, the distance between O in carbonate and H in the *tert*-butyl is 2.35 Å. Therefore, the steric hindrance between carbonate and *tert*-butyl prevents the Pd from attacking nitrogen atoms directly. According to a hydrogen bond between carbonate and amine and the coordination mode of Buchwald ligand and palladium,[24] we speculate that the coordination of benzene with palladium may cause the carbonyl group of the carbonate to leave. The results were surprising, the carbonate can remove the proton from the amine with a 16.1 kcal/mol barrier and the benzene ring can coordinate with the palladium forming intermediate **D**.[25] Then 1,3-Pd migration was occurred to obtain intermediate **E** (Scheme 5). After *ortho*-amination, the barriers of Buchwald coupling process decreased significantly. This may be due to the conjugation of secondary amine group (Scheme 7).

Scheme 5. Computed Gibbs Free Energy Profile (*t*-Butyl).



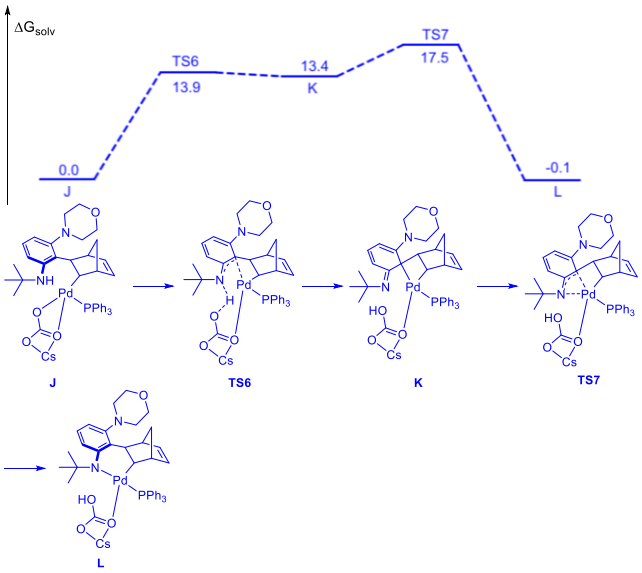
Scheme 6. The Steric Hindrance Between Tert-Butyl Groups and Carbonate in Intermediate B2 and G2.



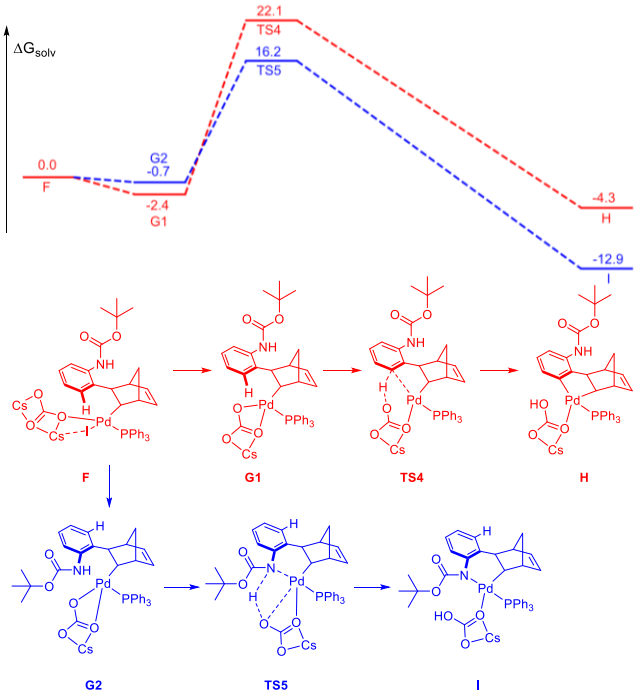
When the protecting group is Boc, we calculated it in the same way. But no dearomatization intermediates were formed similar to the intermediate **D**. Instead, the intermediate **I** was directly formed. This may be due to the little steric hindrance between Boc and carbonate (Scheme 6).[26] Therefore, we speculated that the process was a concerted metalation process, and then we found the **TS5** (Scheme 8).

In a short summary, when the protecting group is *t*-butyl, the barrier of the Buchwald coupling is 0.9 kcal/mol larger than that of the C-H activation. When the protecting group is Boc, the energy of the Buchwald coupling is 7.6 kcal/mol lower than that of the C-H activation. The calculated results are in agreement with the experimental results.

Scheme 7. Computed Gibbs Free Energy Profile (After *Ortho*-Amination).



Scheme 8. Computed Gibbs Free Energy Profile (Boc).



CONCLUSIONS

In summary, highly functionalized 4-aminoindoles were synthesized via the three-component cross-coupling of *o*-iodoaniline, N-benzoyloxyamines and norbornadiene. The Catellani and retro-Diels–Alder strategy was used in this domino process. Based on the DFT calculations, the intramolecular Buchwald coupling of this reaction underwent a dearomatization and 1,3-palladium migration process. The reasons for the control of chemical selectivity by protecting groups are given. Moreover, synthetic applications toward 4-piperazinylindole and a GOT1 inhibitor were realized.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

‡These authors contributed equally.

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REFERENCES

(1) (a) Van Order, R. B.; Lindwall, H. G. Indole. *Chem. Rev.* **1942**, *30*, 69-96. (b) Taber, D. F.; Tirunahari, P. K. Indole synthesis: a review and proposed classification. *Tetrahedron* **2011**, *67*, 7195-7210.

(2) (a) WOODWARD, A. W.; BARTEL, B. Auxin: Regulation, Action, and Interaction. *Ann. Bot.* **2005**, *95*, 707-735. (b) Galliford, C. V.; Scheidt, K. A. Pyrrolidinyl-Spirooxindole Natural Products as Inspirations for the Development of Potential Therapeutic Agents. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748-8758. (c) Trost, B. M.; Brennan, M. K. Asymmetric Syntheses of Oxindole and Indole Spirocyclic Alkaloid Natural Products. *Synthesis* **2009**, *2009*, 3003-3025. (d) Kochanowska-Karamyan, A. J.; Hamann, M. T. Marine Indole Alkaloids: Potential New Drug Leads for the Control of Depression and Anxiety. *Chem. Rev.* **2010**, *110*, 4489-4497. (e) Sharma, V.; Kumar, P.; Pathak, D. Biological importance of the indole nucleus in recent years: A comprehensive review. *J. Heterocycl. Chem.* **2010**, *47*, 491-502. (f) Zhang, M.-Z.; Chen, Q.; Yang, G.-F. A review on recent developments of indole-containing antiviral agents. *Eur. J. Med. Chem.* **2015**, *89*, 421-441.

(3) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. Rings in Drugs. *J. Med. Chem.* **2014**, *57*, 5845-5859.

(4) Sandtorv, A. H. Transition Metal-Catalyzed C H Activation of Indoles. *Adv. Synth. Catal.* **2015**, *357*, 2403-2435.

(5) Leitch, J. A.; Bhonoah, Y.; Frost, C. G. Beyond C2 and C3: Transition-Metal-Catalyzed C–H Functionalization of Indole. *ACS Catal.* **2017**, *7*, 5618-5627.

(6) (a) Yang, Y.; Gao, P.; Zhao, Y.; Shi, Z. Regiocontrolled Direct C−H Arylation of Indoles at the C4 and C5 Positions. *Angew. Chem. Int. Ed.* **2017**, *56*, 3966-3971. (b) Lanke, V.; Prabhu, K. R. Iridium(iii) catalyzed regioselective amidation of indoles at the C4-position using weak coordinating groups. *Chem. Commun.* **2017**, *53*, 5117-5120. (c) Chen, S.; Feng, B.; Zheng, X.; Yin, J.; Yang, S.; You, J. Iridium-Catalyzed Direct Regioselective C4-Amidation of Indoles under Mild Conditions. *Org. Lett.* **2017**, *19*, 2502-2505. (d) Liu, Q.; Li, Q.; Ma, Y.; Jia, Y. Direct Olefination at the C-4 Position of Tryptophan via C–H Activation: Application to Biomimetic Synthesis of Clavicipitic Acid. *Org. Lett.* **2013**, *15*, 4528-4531.

(7) (a) Christopher, J. A.; Brown, J.; Doré, A. S.; Errey, J. C.; Koglin, M.; Marshall, F. H.; Myszka, D. G.; Rich, R. L.; Tate, C. G.; Tehan, B.; Warne, T.; Congreve, M. Biophysical Fragment Screening of the β1-Adrenergic Receptor: Identification of High Affinity Arylpiperazine Leads Using Structure-Based Drug Design. *J. Med. Chem.* **2013**, *56*, 3446-3455. (b) Mewshaw, R. E.; Verwijs, A.; Shi, X.; McGaughey, G. B.; Nelson, J. A.; Mazandarani, H.; Brennan, J. A.; Marquis, K. L.; Coupet, J.; Andree, T. H. New generation dopaminergic agents. 5. heterocyclic bioisosteres that exploit the 3-OH-N1-phenylpiperazine dopaminergic template. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2675-2680.

(8) Congreve, M.; Langmead, C. J.; Mason, J. S.; Marshall, F. H. Progress in Structure Based Drug Design for G Protein-Coupled Receptors. *J. Med. Chem.* **2011**, *54*, 4283-4311.

(9) Pascual-Ramon, R.; Buschmann, H. H. Piperazinyl derivative 5-HT7 receptor ligands, compositions comprising them, and their therapeutic use. 2010. WO 2010012817 A1.

(10) (a) Rahib, L.; Smith, B. D.; Aizenberg, R.; Rosenzweig, A. B.; Fleshman, J. M.; Matrisian, L. M. Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States. *Cancer Res.* **2014**, *74*, 2913. (b) Bailey, P.; Chang, D. K.; Nones, K.; Johns, A. L.; Patch, A.-M.; Gingras, M.-C.; Miller, D. K.; Christ, A. N.; Bruxner, T. J. C.; Quinn, M. C.; Nourse, C.; Murtaugh, L. C.; Harliwong, I.; Idrisoglu, S.; Manning, S.; Nourbakhsh, E.; Wani, S.; Fink, L.; Holmes, O.; Chin, V.; Anderson, M. J.; Kazakoff, S.; Leonard, C.; Newell, F.; Waddell, N.; Wood, S.; Xu, Q.; Wilson, P. J.; Cloonan, N.; Kassahn, K. S.; Taylor, D.; Quek, K.; Robertson, A.; Pantano, L.; Mincarelli, L.; Sanchez, L. N.; Evers, L.; Wu, J.; Pinese, M.; Cowley, M. J.; Jones, M. D.; Colvin, E. K.; Nagrial, A. M.; Humphrey, E. S.; Chantrill, L. A.; Mawson, A.; Humphris, J.; Chou, A.; Pajic, M.; Scarlett, C. J.; Pinho, A. V.; Giry-Laterriere, M.; Rooman, I.; Samra, J. S.; Kench, J. G.; Lovell, J. A.; Merrett, N. D.; Toon, C. W.; Epari, K.; Nguyen, N. Q.; Barbour, A.; Zeps, N.; Moran-Jones, K.; Jamieson, N. B.; Graham, J. S.; Duthie, F.; Oien, K.; Hair, J.; Grützmann, R.; Maitra, A.; Iacobuzio-Donahue, C. A.; Wolfgang, C. L.; Morgan, R. A.; Lawlor, R. T.; Corbo, V.; Bassi, C.; Rusev, B.; Capelli, P.; Salvia, R.; Tortora, G.; Mukhopadhyay, D.; Petersen, G. M.; Australian Pancreatic Cancer Genome, I.; Munzy, D. M.; Fisher, W. E.; Karim, S. A.; Eshleman, J. R.; Hruban, R. H.; Pilarsky, C.; Morton, J. P.; Sansom, O. J.; Scarpa, A.; Musgrove, E. A.; Bailey, U.-M. H.; Hofmann, O.; Sutherland, R. L.; Wheeler, D. A.; Gill, A. J.; Gibbs, R. A.; Pearson, J. V.; Waddell, N.; Biankin, A. V.; Grimmond, S. M. Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature* **2016**, *531*, 47.

(11) Anglin, J.; Zavareh, R. B.; Sander, P. N.; Haldar, D.; Mullarky, E.; Cantley, L. C.; Kimmelman, A. C.; Lyssiotis, C. A.; Lairson, L. L. Discovery and optimization of aspartate aminotransferase 1 inhibitors to target redox balance in pancreatic ductal adenocarcinoma. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 2675-2678.

(12) Gong, L.; Han, X.; Makra, F.; Palmer, W. S.; Raptova, L. INHIBITORS OF JNK. 2011. US 20110034470 A1.

(13) (a) Somei, M.; Inoue, S.; Tokutake, S.; Yamada, F.; Kaneko, C. The Chemistry of Indoles. XIII. Syntheses of Substituted Indoles carrying an Amino, Nitro, Methoxycarbonyl, or Benzyloxy Group at the 4-Position and Their 1-Hydroxy Derivatives. *Chem. Pharm. Bull.* **1981**, *29*, 726-738. (b) Melhado, L. L.; Leonard, N. J. An efficient synthesis of azidoindoles and azidotryptophans. *J. Org. Chem.* **1983**, *48*, 5130-5133. (c) Bergman, J.; Sand, P. Synthesis of indoles via ring closure of 2-alkylnitroaniline derivatives. *Tetrahedron* **1990**, *46*, 6085-6112.

(14) Larock, R. C.; Yum, E. K. Synthesis of indoles via palladium-catalyzed heteroannulation of internal alkynes. *J. Am. Chem. Soc.* **1991**, *113*, 6689-6690.
(15) Thansandote, P.; Hulcoop, D. G.; Langer, M.; Lautens, M. Palladium-Catalyzed Annulation of Haloanilines and Halobenzamides Using Norbornadiene as an Acetylene Synthon: A Route to Functionalized Indolines, Isoquinolinones, and Indoles. *J. Org. Chem.* **2009**, *74*, 1673-1678.
(16) (a) Lv, W.; Wen, S.; Yu, J.; Cheng, G. 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) Lv, W.; Yu, J.; Ge, B.; Wen, S.; Cheng, G. Palladium-Catalyzed Catellani-Type Bis-silylation and Bis-germanylation of Aryl Iodides and Norbornenes. *J. Org. Chem.* **2018**, *83*, 12683-12693.
(17) (a) Catellani, M.; Frignani, F.; Rangoni, A. A Complex Catalytic Cycle Leading to a Regioselective Synthesis of o,o′-Disubstituted Vinylarenes. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119-122. (b) Catellani, M.; Motti, E.; Della Ca', N. Catalytic Sequential Reactions Involving Palladacycle-Directed Aryl Coupling Steps. *Acc. Chem. Res.* **2008**, *41*, 1512-1522. (c) Della Ca', N.; Sassi, G.; Catellani, M. A Direct Palladium-Catalyzed Route to Selectively Substituted Carbazoles through Sequential C-C and C-N Bond Formation: Synthesis of Carbazomycin A. *Adv. Synth. Catal.* **2008**, *350*, 2179-2182. (d) Maestri, G.; Della Ca', N.; Catellani, M. A catalytic synthesis of selectively substituted biaryls through sequential intermolecular coupling involving arene and ketone C–H bond functionalization. *Chem. Commun.* **2009**, *32*, 4892-4894. (e) Motti, E.; Della Ca', N.; Deledda, S.; Fava, E.; Panciroli, F.; Catellani, M. Palladium-catalyzed unsymmetrical aryl couplings in sequence leading to o-teraryls: dramatic olefin effect on selectivity. *Chem. Commun.* **2010**, *46*, 4291-4293. (f) Della Ca', N.; Maestri, G.; Malacria, M.; Derat, E.; Catellani, M. Palladium-Catalyzed Reaction of Aryl Iodides with ortho-Bromoanilines and Norbornene/Norbornadiene: Unexpected Formation of Dibenzoazepine Derivatives. *Angew. Chem., Int. Ed.* **2011**, *50*, 12257-12261. (g) Larraufie, M. H.; Maestri, G.; Beaume, A.; Derat, É.; Ollivier, C.; Fensterbank, L.; Courillon, C.; Lacôte, E.; Catellani, M.; Malacria, M. Exception to the ortho Effect in Palladium/Norbornene Catalysis. *Angew. Chem., Int. Ed.* **2011**, *50*, 12253-12256. (h) Maestri, G.; Motti, E.; Della Ca', N.; Malacria, M.; Derat, E.; Catellani, M. Of the Ortho Effect in Palladium/Norbornene-Catalyzed Reactions: A Theoretical Investigation. *J. Am. Chem. Soc.* **2011**, *133*, 8574-8585. (i) Catellani, M.; Motti, E.; Baratta, S. A Novel Palladium-Catalyzed Synthesis of Phenanthrenes from ortho-Substituted Aryl Iodides and Diphenyl- or Alkylphenylacetylenes. *Org. Lett.* **2001**, *3*, 3611-3614. (j) Wang, J.; Dong, G. Palladium/Norbornene Cooperative Catalysis. *Chem. Rev.* **2019**, 10.1021/acs.chemrev.9b00079. (k) Della Ca', N.; Fontana, M.; Motti, E.; Catellani, M. Pd/Norbornene: A Winning Combination for Selective Aromatic Functionalization via C–H Bond Activation. *Acc. Chem. Res.* **2016**, *49*, 1389-1400. (l) Cheng, H.-G.; Chen, S.; Chen, R.; Zhou, Q. Palladium(II)-Initiated Catellani-Type Reactions. *Angew. Chem. Int. Ed.* **2019**, *58*, 5832-5844. (m) Zhao, K.; Ding, L.; Gu, Z. Development of New Electrophiles in Palladium/Norbornene-Catalyzed ortho-Functionalization of Aryl Halides. *Synlett* **2019**, *30*, 129-140.
(18) Lautens, M.; Piguel, S. A New Route to Fused Aromatic Compounds by Using a Palladium-Catalyzed Alkylation – Alkenylation Sequence. *Angew. Chem.* **2000**, *112*, 1087-1088.
(19) (a) Dong, Z.; Dong, G. Ortho vs Ipso: Site-Selective Pd and Norbornene-Catalyzed Arene C–H Amination Using Aryl Halides. *J. Am. Chem. Soc.* **2013**, *135*, 18350-18353. (b) Dong, Z.; Wang, J.; Dong, G. Simple Amine-Directed Meta-Selective C–H Arylation via Pd/Norbornene Catalysis. *J. Am. Chem. Soc.* **2015**, *137*, 5887-5890. (c) Dong, Z.; Wang, J.; Ren, Z.; Dong, G. Ortho C-H Acylation of Aryl Iodides by Palladium/Norbornene Catalysis. *Angew. Chem., Int. Ed.* **2015**, *54*, 12664-12668. (d) Dong, Z.; Lu, G.; Wang, J.; Liu, P.; Dong, G. Modular ipso/ortho Difunctionalization of Aryl Bromides via Palladium/Norbornene Cooperative Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 8551-8562. (e) Zheng, H.; Zhu, Y.; Shi, Y. Palladium(0)-Catalyzed Heck Reaction/C-H Activation/Amination Sequence with Diaziridinone: A Facile Approach to Indolines. *Angew. Chem. Int. Ed.* **2014**, *53*, 11280-11284. (f) Wang, J.; Li, R.; Dong, Z.; Liu, P.; Dong, G. Complementary site-selectivity in arene functionalization enabled by overcoming the ortho constraint in palladium/norbornene catalysis. *Nature Chem.* **2018**, *10*, 866-872.
(20) (a) Wang, P.; Li, G.-C.; Jain, P.; Farmer, M. E.; He, J.; Shen, P.-X.; Yu, J.-Q. Ligand-Promoted meta-C–H Amination and Alkynylation. *J. Am. Chem. Soc.* **2016**, *138*, 14092-14099. (b) Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K. M.; Yu, J.-Q. Ligand-enabled meta-C–H activation using a transient mediator. *Nature* **2015**, *519*, 334. (c) Shen, P.-X.; Wang, X.-C.; Wang, P.; Zhu, R.-Y.; Yu, J.-Q. Ligand-Enabled Meta-C–H Alkylation and Arylation Using a Modified Norbornene. *J. Am. Chem. Soc.* **2015**, *137*, 11574-11577. (d) Shi, H.; Herron, A. N.; Shao, Y.; Shao, Q.; Yu, J.-Q. Enantioselective remote meta-C–H arylation and alkylation via a chiral transient mediator. *Nature* **2018**, *558*, 581-585. (e) Li, G.-C.; Wang, P.; Farmer, M. E.; Yu, J.-Q. Ligand-Enabled Auxiliary-Free meta-C–H Arylation of Phenylacetic Acids. *Angew. Chem. Int. Ed.* **2017**, *56*, 6874-6877. (f) Ding, Q.; Ye, S.; Cheng, G.; Wang, P.; Farmer, M. E.; Yu, J.-Q. Ligand-Enabled meta-Selective C–H Arylation of Nosyl-Protected Phenethylamines, Benzylamines, and 2-Aryl Anilines. *J. Am. Chem. Soc.* **2017**, *139*, 417-425.
(21) (a) Mariampillai, B.; Alliot, J.; Li, M.; Lautens, M. A Convergent Synthesis of Polysubstituted Aromatic Nitriles via Palladium-Catalyzed C–H Functionalization. *J. Am. Chem. Soc.* **2007**, *129*, 15372-15379. (b) Rudolph, A.; Rackelmann, N.; Lautens, M. Stereochemical and Mechanistic Investigations of a Palladium-Catalyzed Annulation of Secondary Alkyl Iodides. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485-1488. (c) Candito, D. A.; Lautens, M. Palladium-Catalyzed Domino Direct Arylation/N-Arylation: Convenient Synthesis of Phenanthridines. *Angew. Chem., Int. Ed.* **2009**, *48*, 6713-6716. (d) Gericke, K. M.; Chai, D. I.; Bieler, N.; Lautens, M. The Norbornene Shuttle: Multicomponent Domino Synthesis of Tetrasubstituted Helical Alkenes through Multiple C H Functionalization. *Angew. Chem. Int. Ed.* **2009**, *48*, 1447-1451. (e) Zhao, Y. B.; Mariampillai, B.; Candito, D. A.; Laleu, B.; Li, M.; Lautens, M. Exploiting the Divergent Reactivity of Aryl–Palladium Intermediates for the Rapid Assembly of Fluorene and Phenanthrene Derivatives. *Angew. Chem., Int. Ed.* **2009**, *48*, 1849-1852. (f) Thansandote, P.; Chong, E.; Feldmann, K. O.; Lautens, M. Palladium-Catalyzed Domino C–C/C–N Coupling Using a Norbornene Template: Synthesis of Substituted Benzomorpholines, Phenoxazines, and Dihydrodibenzoxazepines. *J. Org. Chem.* **2010**, *75*, 3495-3498. (g) Chai, D. I.; Thansandote, P.; Lautens, M. Mechanistic Studies of Pd-Catalyzed Regioselective Aryl C-H Bond Functionalization with Strained Alkenes: Origin of Regioselectivity. *Chem. - Eur. J.* **2011**, *17*, 8175-8188. (h) Jiao, L.; Bach, T. Palladium-Catalyzed Direct 2-Alkylation of Indoles by Norbornene-Mediated Regioselective Cascade C–H

Activation. *J. Am. Chem. Soc.* **2011**, *133*, 12990-12993. (i) Jiao, L.; Herdtweck, E.; Bach, T. Pd(II)-Catalyzed Regioselective 2-Alkylation of Indoles via a Norbornene-Mediated C–H Activation: Mechanism and Applications. *J. Am. Chem. Soc.* **2012**, *134*, 14563-14572. (j) Liu, H.; El-Salfiti, M.; Chai, D. I.; Auffret, J.; Lautens, M. Modular and Stereoselective Synthesis of Tetrasubstituted Helical Alkenes via a Palladium-Catalyzed Domino Reaction. *Org. Lett.* **2012**, *14*, 3648-3651. (k) Liu, H.; El-Salfiti, M.; Lautens, M. Expeditious Synthesis of Tetrasubstituted Helical Alkenes by a Cascade of Palladium-Catalyzed C-H Activations. *Angew. Chem. Int. Ed.* **2012**, *51*, 9846-9850. (l) Ye, J.; Lautens, M. Palladium-catalysed norbornene-mediated C–H functionalization of arenes. *Nat. Chem.* **2015**, *7*, 863-870. (m) Luo, B.; Gao, J. M.; Lautens, M. Palladium-Catalyzed Norbornene-Mediated Tandem Amination/Cyanation Reaction: A Method for the Synthesis of ortho-Aminated Benzonitriles. *Org. Lett.* **2016**, *18*, 4166-4169. (n) Zhang, B.-S.; Hua, H.-L.; Gao, L.-Y.; Liu, C.; Qiu, Y.-F.; Zhou, P.-X.; Zhou, Z.-Z.; Zhao, J.-H.; Liang, Y.-M. Palladium-catalyzed arene C–H activation/ketone C–H functionalization reaction: route to spirodihydroindenones. *Org. Chem. Front.* **2017**, *4*, 1376-1379. (o) Chen, S.; Liu, Z.-S.; Yang, T.; Hua, Y.; Zhou, Z.; Cheng, H.-G.; Zhou, Q. The Discovery of a Palladium(II)-Initiated Borono-Catellani Reaction. *Angew. Chem. Int. Ed.* **2018**, *57*, 7161-7165. (p) Cheng, H.-G.; Wu, C.; Chen, H.; Chen, R.; Qian, G.; Geng, Z.; Wei, Q.; Xia, Y.; Zhang, J.; Zhang, Y.; Zhou, Q. Epoxides as Alkylating Reagents for the Catellani Reaction. *Angew. Chem. Int. Ed.* **2018**, *57*, 3444-3448. (q) Liu, C.; Liang, Y.; Zheng, N.; Zhang, B.-S.; Feng, Y.; Bi, S.; Liang, Y.-M. Synthesis of indolines via a palladium/norbornene-catalyzed reaction of aziridines with aryl iodides. *Chem. Commun.* **2018**, *54*, 3407-3410. (i) Whyte, A.; Olson, M. E.; Lautens, M. Palladium-Catalyzed, Norbornene-Mediated, ortho-Amination ipso-Amidation: Sequential C–N Bond Formation. *Org. Lett.* **2018**, *20*, 345-348. (s) Wu, C.; Cheng, H.-G.; Chen, R.; Chen, H.; Liu, Z.-S.; Zhang, J.; Zhang, Y.; Zhu, Y.; Geng, Z.; Zhou, Q. Convergent syntheses of 2,3-dihydrobenzofurans via a Catellani strategy. *Org. Chem. Front.* **2018**, *5*, 2533-2536. (t) Zhang, B.-S.; Li, Y.; An, Y.; Zhang, Z.; Liu, C.; Wang, X.-G.; Liang, Y.-M. Carboxylate Ligand-Exchanged Amination/C(sp3)–H Arylation Reaction via Pd/Norbornene Cooperative Catalysis. *ACS Catal.* **2018**, *8*, 11827-11833.

(22) (a) Ahn, J. M.; Peters, J. C.; Fu, G. C. Design of a Photoredox Catalyst that Enables the Direct Synthesis of Carbamate-Protected Primary Amines via Photoinduced, Copper-Catalyzed N-Alkylation Reactions of Unactivated Secondary Halides. *J. Am. Chem. Soc.* **2017**, *139*, 18101-18106. (b) Matier, C. D.; Schwaben, J.; Peters, J. C.; Fu, G. C. Copper-Catalyzed Alkylation of Aliphatic Amines Induced by Visible Light. *J. Am. Chem. Soc.* **2017**, *139*, 17707-17710.

(23) Fu, W. C.; Wang, Z.; Chan, W. T. K.; Lin, Z.; Kwong, F. Y. 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.

(24) (a) Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. Structural Insights into Active Catalyst Structures and Oxidative Addition to (Biaryl)phosphine–Palladium Complexes via Density Functional Theory and Experimental Studies. *Organometallics* **2007**, *26*, 2183-2192. (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. Catalysts for Suzuki–Miyaura Coupling Processes: Scope and Studies of the Effect of Ligand Structure. *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696. (c) Maimone, T. J.; Milner, P. J.; Kinzel, T.; Zhang, Y.; Takase, M. K.; Buchwald, S. L. Evidence for in Situ Catalyst Modification during the Pd-Catalyzed Conversion of Aryl Triflates to Aryl Fluorides. *J. Am. Chem. Soc.* **2011**, *133*, 18106-18109.

(25) Without considering the zero-point energy (ZPE), the energy of the **TS2** is 1.3 kcal/mol higher than intermediate **D**. Taking the ZPE into account the barrier vanishes, and the energy of the **TS2** is 1.0 kcal/mol below the intermediate **D**.

(26) CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009

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