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Authors: Lu Bai, Jingjing Liu, Wenjie Hu, Kunyu Li, Yao-Yu Wang, and Xinjun Luan

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Palladium/Norbornene-Catalyzed C-H Alkylation/Alkyne Insertion/Indole Dearomatization Threefold Domino Reaction: Rapid Assembly of Spiroindolenine-Containing Pentacyclic Frameworks

Lu Bai[†], Jingjing Liu[†], Wenjie Hu, Kunyu Li, Yaoyu Wang, Xinjun Luan*

Abstract: Herein we report a highly chemoselective intermolecular annulation of indole-based biaryls with bromoalkyl alkynes by using palladium/norbornene (Pd/NBE) cooperative catalysis. This threefold domino process is realized through a sequence of Catellani-type C-H alkylation, alkyne insertion, and indole dearomatization, by forming two $C(sp^2)$ - $C(sp^3)$ and one $C(sp^2)$ - $C(sp^2)$ bonds in a single chemical operation, thus providing a diverse range of pentacyclic molecules containing a spiroindolenine fragment in good yields with excellent functional group tolerance. Preliminary mechanistic studies reveal that C-H bond cleavage is likely involved in the rate-determining step, and the indole dearomatization might take place through an olefin coordination/insertion and β -hydride elimination Heck-type pathway.

The rapid and controlled generation of complex and diverse molecular architectures from readily available starting materials in a minimum number of steps is a highly appealing goal in organic synthesis. One important strategy is the use of domino reactions, which allow for the sequential construction of various chemical bonds by a single-step manipulation.^[1] Among them, Pd/NBE-catalyzed reactions,^[2] which were originally discovered by Catellani^[3] and further developed by Lautens^[4] and others,^[5] represents a powerful approach for the expeditious synthesis of highly substituted arenes through vicinal bisfunctionalization of aryl iodides with various electrophiles and terminating reagents by using NBE as a transient mediator (Scheme 1a). Notably, a pre-existing R group, which remained intact in the transformation, was commonly indispensable for facilitating the NBE excursion to generate an arylpalladium A^{IV} from intermediate A^{III} . From the viewpoint of synthetic efficiency, it is highly desirable to decorate this often neglected moiety simultaneously, and the envisioned trisfunctionalization processes might be useful for building up some frameworks that are inaccessible by traditional methods. However, up to date, the progress in this area is very limited. To our knowledge, the only example concerning Pd/NBE-catalyzed trisfunctionalization was realized by the Lautens group, through an elegant threefold domino process, which was eventually terminated by a C-H vinylation of heterocyclic R group.^[6]

Transition-metal-catalyzed dearomatization reactions allow the direct conversion of easily accessible planar molecules to many synthetically valuable three-dimensional scaffolds.^[7-9] With our persistent enthusiasm on the exploration of cooperative C-H

Prof. Dr. X. Luan

[[†]] These authors contributed equally to this work.

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Scheme 1. Design plan for a new [Pd⁰]/NBE-catalyzed threefold domino reaction being terminated with indole dearomatization.

activation/arene dearomatization reactions,^[10] we endeavored to combine Catellani-type C-H functionalization with the disruption of π -system of arenes for enabling more efficient and economical transformations.^[11] Verv recently, we found that arvl iodides with an adjacent phenol species underwent spiroannulation with 2.5norbornadiene (NBD) and N-benzoyloxyamines (Scheme 1b).^[12] Remarkably, this Pd-catalyzed NBD-involved process rendered the ortho-C-H amination and subsequent dearomatization of the phenolic **R** group. This observation implied that key intermediate **B**^{III} favored the phenol dearomatization pathway to generate a NBD-embraced spiroindene, rather than giving rise to a A^{IV} -type of arvlpalladium species via NBD excursion. Presumably, if the rates of these two pathways are reversed, it might be possible to trap such NBD-free intermediate with an alkvne.^[8] In this context. we postulated a new Pd/NBE-catalyzed trisfunctionalization plan through a cascade of C-H alkylation, alkyne insertion and indole dearomatization, for the rapid assembly of attractive pentacyclic scaffolds containing a spiroindolenine fragment,^[13] by reacting ortho-indole substituted aryl iodides with tethered bromoalkyl alkynes that were designed by Lautens.^[4d-e,6] A brief description of our proposal, using 1a and 2a for illustrative purposes, is depicted in Scheme 1c. Besides the obvious risk of direct N-

^[*] L. Bai,^[†] J. Liu,^[†] W. Hu, K. Li, Prof. Dr. Y. Wang, Prof. Dr. X. Luan Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of the Ministry of Education, College of Chemistry & Materials Science, Northwest University, Xi'an, 710127 (China) E-mail: xluan@nwu.edu.cn

State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin, 300071 (China)

alkylation and inherent challenge in typical Catellani reactions,^[14] the prerequisites for successful execution of this proposal are that: 1) aryl/NBE palladacycle C^{II} must be selectively formed by avoiding the interruption of indole moiety;^[15] 2) NBE excursion of **C**^{III} should be more favorable than its intramolecular cyclizations; 3) intermediate $\mathbf{C}^{\mathbf{v}}$ has to undergo dearomative spiroannulation but not [4+2] annulation through a C-H bond vinylation.^[6] Herein, we wish to report our results on this subject.

Stimulated by the aforementioned challenges, we began the studies with 1a and 2a to explore the reaction conditions (Table 1). Initial attempts with PPh₃ and PCy₃ didn't give the anticipated product 3a, but N-alkylated cyclobutane adduct 5a was obtained in high yields (entries 1-2). To our delight, electron-rich P(2-furyl)₃ led to the formation of 3a in 52% yield, albeit with concomitant generation of byproduct 4a (entry 3). Base screening proved that K₃PO₄ was the better choice, providing **3a** as the only product in 67% yield (entry 6). Replacing Pd(OAc)₂ with several palladium precursors didn't show any superior results (entries 7-9). Further optimization revealed that no other solvent provided comparable efficiency as DMF (entries 10-13), but a THF/DMF mixed system could greatly enhance the process to yield 3a in 79% (entry 14). More gratifyingly, the reaction performance was further improved at lower temperature (65 °C) by using 50 mol% NBE (entry 15).

Table 1. Optimization of the reaction conditions.^[a]

1.0	H H H 1a 2a (f r equiv 1.5 ¢	[Pd] (5 Ligand (1 NBE (1.) Base (2. Ph Solvent R _a Br) 100 °C	mol%) 0 mol%) 0 equiv) 0 equiv) (0.1 M), c, 10 h	Ph 3a	⁺ (C)	4a (X 5a (X	= H) = R _a)
Entry	[Pd]	Ligand	Base	Solvent	Y 3a	ield (% 4a	5) ^[a]
1	Pd(OAc) ₂	PPh ₃	Cs_2CO_3	DMF	0	0	62
2	Pd(OAc) ₂	PCy ₃	Cs_2CO_3	DMF 🦯	0	0	89
3	Pd(OAc) ₂	P(2-furyl) ₃	Cs_2CO_3	DMF	52	21	0
4	Pd(OAc) ₂	P(2-furyl) ₃	Na ₂ CO ₃	DMF	59	0	0
5	Pd(OAc) ₂	P(2-furyl) ₃	K ₂ CO ₃	DMF	35	0	0
6	Pd(OAc) ₂	P(2-furyl) ₃	K ₃ PO ₄	DMF	67	0	0
7	PdCl ₂	P(2-furyl) ₃	K ₃ PO ₄	DMF	10	11	0
8	[Pd(allyl)Cl] ₂	P(2-furyl) ₃	K ₃ PO ₄	DMF	21	0	24
9	Pd ₂ (dba) ₃	P(2-furyl) ₃	K ₃ PO ₄	DMF	15	0	0
10	Pd(OAc) ₂	P(2-furyl) ₃	K₃PO₄	DMA	42	0	0
11	Pd(OAc) ₂	P(2-furyl) ₃	K₃PO₄	1,4-dioxane	9	69	0
12	Pd(OAc) ₂	P(2-furvl) ₃	K₃PO₄	THE	18	25	0
13	Pd(OAc) ₂	P(2-furvl) ₃	K ₃ PO ₄	DME	42	46	0
14 ^[b]	Pd(OAc) ₂	P(2-furyl) ₃	K ₃ PO ₄	THF/DMF	79	0	0
15 ^[b,c]	Pd(OAc) ₂	P(2-furyl) ₃	K ₃ PO ₄	THF/DMF	86	0	0
[a] Isolated yield. [b] THF/DMF = 4:1. [c] Run at 65 °C with 50 mol% NBE.							

With the optimal reaction conditions in hand, the scope with respect to the aryl iodides was first examined (Table 2). Overall, a broad range of indole-derived biaryls (1b-u) behaved very well in the domino reaction, affording the corresponding pentacyclic products 3b-u in 69-92% yields. Regarding the upper phenyl ring, it is tolerable with electron-donating groups (EDGs) such as methyl (1b,o), methoxy (1c), and methylenedioxy (1m) groups, and electron-withdrawing groups (EWGs) such as fluoro (1d,n), chloro (1e), trifluoromethyl (1f), trifluoromethoxy (1g), cyano (1h), nitro (1i), formyl (1j), acetyl (1j), and ester (1l) groups. Notably, C-H alkylation took place smoothly with the substrates (1m-n) bearing a substituent adjacent to the C-H activation site to give the desired products 1m-n in 70% and 82% yield, respectively. Moreover, the process proceeded smoothly with sterically congested substrates 1o-p, leading to the formation of 3o-p with crowded scaffolds in high yields. Gratifyingly, further studies demonstrated that the indole ring could be diversely substituted at different positions with various functional groups such as methoxy (1q), fluoro (1r), chloro (1s), ester (1t), and methyl (1u) groups, and the products 3q-u were obtained in 71-85% yields.

Table 2. Scope with respect to indole-derived aryl iodides.



3u 83%^[a] 3t 82%^{[a}

[a] 10 mol% Pd(OAc)₂ and 20 mol% P(2-furyl)₃ were used. [b] 100 mol% NBE was used.

To further survey the scope of this domino reaction, a variety of tethered bromoalkyl alkynes (2b-u) were evaluated (Table 3). The experimental results showed that the phenyl substituent on the alkyne terminus of 2a could be replaced with diversified aryls bearing an electron-donating methoxy group (2b), an EWG such as a fluoro (2c), chloro (2d), ester (2e), and nitro (2f) group, or a heterocyclic group such as N-Ts-3-indolyl (2g) and 2-thienyl (2h), and the desired products 3a'-g' were obtained in 63-85% yields. Notably, substrate 2i bearing a vinylic substituent behaved quite well to give compound 3h' in 90% yield. Moreover, a series of alkyl-substituted substrates containing a methyl (2j), allyl (2k), cyclopropyl (2I), or silyl ether groups were found to be suitable

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for the title transformation. Upon treatment with TBAF, 3I' underwent TBS deprotection followed by stereospecific alkoxide addition to furnish a fascinating hexacyclic framework 6. Much to our delight, substrate 2n being featured with an electrondeficient alkyne moiety underwent the insertion/dearomatization cascade efficiently to generate product 3m' in 76% yield. Moreover, the alkyne termini could be directly linked with a heteroatom such as silicon (20-p) and nitrogen (2q), and the corresponding reactions were achieved with extremely high efficiency. More importantly, substrate 2r, which contains a stereogenic center next to the alkyne fragment, was proven to be effective for the stereocontrol of our threefold domino process, affording 3q' as a diastereomeric mixture (4:1 dr). The relative stereochemistry of 3q'maior was confirmed by X-ray studies.[16] Finally, it is worth mentioning that the tether for linking the alkyl bromide and alkyne fragments could be extended with one more carbon, oxygen, or nitrogen, thus enabling the rapid construction of three types of unprecedented pentacyclic frameworks (3r'-t') bearing a seven-membered carbo- or heterocyclic ring unit.

Table 3. Scope with respect to bromoalkyl alkynes.



[a] 10 mol% Pd(OAc)₂ and 20 mol% P(2-furyl)₃ were used.

To gain more insights into the mechanism of this reaction, a series of exploratory experiments were carried out (Scheme 2). Parallel experiments with **1b** and $[D_6]$ -**1b** demonstrated a kinetic isotope effect ($k_H/k_D = 2.3$; Scheme 2a), suggesting that the C-H bond cleavage was likely involved in the rate-determining step.

Control experiment between **1a** and NBE led to the formation of **4a** in 5% yield, and the reaction of **1a** with alkyne **7** gave a spirocyclic product **8** in 91% yield (Scheme 2b). These

results implied that NBE possessed far better affinity than alkynes toward the Pd(II) center of intermediate C^{I} . Otherwise, such direct [3+2] spiroannulation byproduct like **8** would be preferentially formed in the Pd/NBE-catalyzed reactions of **1** with **2**. Treatment of **1a** with the alkyne **7** and alkyl bromide **9** under standard conditions afforded the anticipated product **10** in 76% yield, together with the generation of NBE-embraced **11**, and possible byproduct **8** was not detected at all (Scheme 2c). The success of this three-component trisfunctionalization reaction indicated that the di-*ortho*-substituted arylpalladium species C^{IV} favored the migrative insertion of alkynes in comparison with electron-rich NBE, which was due to the steric bulkiness of NBE. Moreover, this observation revealed that the use of tethered bromoalkyl alkynes **2** was crucial for the reaction with **1**, allowing preventing the formation of any undesired byproducts like **11**.

By not adding the base, the reaction of **1a** with **7** was carried out, and product **8** was isolated in 8% yield (Scheme 2d). This outcome revealed that **8** should not be generated through the deprotonation/tautomerization of indole moiety, and followed by the reductive elimination of a spirocyclic palladacycle. Most likely, this two-component process, and the titled threefold domino reaction, were all terminated by a dearomatizing Heck-type annulation through olefin coordination/insertion and β -hydride elimination. To testify our assumption, benzofuran derivative **12**, which couldn't be deprotonated by K₃PO₄, was examined, and the Heck product **13** was obtained in 68% yield (Scheme 2e).



Scheme 2. Mechanistic studies.

In summary, we have developed a new type of Pd/NBEcatalyzed threefold domino reaction, wherein *ortho*-indole aryl iodides and tethered bromoalkyl alkynes were used to build up spiroindolenine-containing pentacyclic scaffolds through controlled formation of three C-C bonds in a single step. Notably, this new protocol, using NBE as a transient mediator, was featured by terminating the trisfunctionalization domino process with indole dearomatization, and represents a rare example of transitionmetal-catalyzed intermolecular reactions for the rapid assembly of polycyclic frameworks from easily accessible starting materials.

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Keywords: C-H activation • dearomatization • norbornene • domino reactions • palladium

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A novel palladium/norbornene-catalyzed intermolecular annulation of ortho-indole substituted aryl iodides with tethered bromoalkyl alkynes has been developed for the rapid construction of diversified pentacyclic scaffolds containing a spiroindolenine fragment. This threefold domino process was realized through a sequence of C-H alkylation, alkyne insertion, and indole dearomatization.

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