

Letter

Synthesis of 3,4-Fused Tricyclic Indoles through Cascade Carbopalladation and C–H Amination: Development and Total Synthesis of Rucaparib

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ABSTRACT: 3,4- bioactive natural p the synthesis of 3	-Fused tricyclic indole scaffol roducts and pharmaceuticals. 3,4-fused tricyclic indoles h	Is are ubiquitous in A new protocol for as been developed \mathbb{R}^1

the synthesis of 3,4-fused tricyclic indoles has been developed through cascade carbopalladation and C–H amination with *N*,*N*-di-*tert*-butyldiaziridinone. The protocol allows access to a range of 3,4-fused tricyclic indoles, including those containing various linkers and fused with medium-sized rings. Rucaparib can be synthesized via this reaction, providing an advantageous synthetic method for the FDA-approved cancer medicine.



3,4-Fused tricyclic indoles are essential core structures of many bioactive natural products and pharmaceuticals and are attractive synthetic targets in the fields of medicinal chemistry and organic synthesis (Figure 1)¹ The synthesis of these





complex indole molecules is challenging and has been the subject of numerous synthetic studies.² Traditionally, 3,4-fused tricyclic indoles can be synthesized by the intramolecular cyclization of 4-substituted or 3,4-disubstituted indoles. However, the functionalization of the four-positions of indoles is challenging and usually requires multistep synthesis. Recently, the construction of 3,4-fused tricyclic indoles via indole ring formation has gained considerable interest. Compared with the traditional methods, this innovative approach avoids the laborious synthesis of four-substituted indole precursors and has great advantages. An elegant example is the method based on an intramolecular Fischer indole synthesis, which was developed by Cho and coworkers.³ In 2013, the groups of Boger and Jia reported the synthesis of

3,4-fused tricyclic indoles using alkyne-tethered ortho-iodoanilines via palladium-catalyzed intramolecular Larock indole synthesis.⁴ Replacing the alkyne moiety with an allene group can also give 3,4-fused tricyclic indoles.⁵ The intramolecular Larock indole syntheses require the presynthesis of multisubstituted haloanilines as starting materials. Notably, an innovative method through C-H alkenylation using anilines tethered to an alkyne at the meta position has been independently developed by the groups of Jia, Xu and Liu, Zhou and Li, and Nemoto.⁶ However, to activate more hindered C-H bonds, the reactions are restricted to indoles bearing an alkoxy group.^{2a} The group of Miura and Murakami disclosed an elegant dearomatizing annulation reaction from 1,2,3-triazole-tethered arenes.⁷ However, this method requires an additional oxidation reaction to form indole products and the presynthesis of 1,2,3-triazole-containing substrates. In all of these reactions, 3,4-fused tricyclic indoles are directly formed from the intramolecular cyclization of the substrates, and all of the substrates preinstalled with a nitrogen-containing group are used.8 Considerable efforts should still be devoted to developing efficient and general methods for the synthesis of 3,4-fused tricyclic indoles.

Over the past several decades, transition-metal-catalyzed C– H functionalization underwent explosive growth.⁹ C–H

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amination has also gained considerable interest and emerged as an innovative and powerful strategy for the formation of C-N bonds.¹⁰ In this context, N,N-di-tert-butyldiaziridinone represents a particularly intriguing C-H aminating reagent.¹¹ $\hat{N}_{,N}$ -Di-tert-butyldiaziridinone can diaminate C,C-palladacycles formed by palladium-catalyzed C-H activation, which provides an innovative method for the synthesis of Nheterocycles. We envisioned that a method for the construction of a 3,4-fused tricyclic indole skeleton could be developed via the C-H amination reaction with N.N-di-tertbutyldiaziridinone. It should be mentioned that the indole moieties of bioactive 3.4-fused tricvclic indoles are bridged with different ring sizes, and many compounds contain a medium-sized ring. The formation of medium-sized rings is often challenging due to entropic factors and transannular interactions.¹² The reaction for the synthesis of 3,4-fused tricyclic indoles via C-H amination with N,N-di-tertbutyldiaziridinone is a cascade process and involves several Pd(II) species during the catalytic cycle. Achieving selective cyclization and amination in different stages of the catalytic cycle is crucial for the development of the reaction and is expected to be challenging, in particular, in the formation of medium-sized rings.

Rucaparib is a poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor.¹³ It was approved by the FDA as Rubraca (rucaparib camsylate) for the treatment of ovarian cancer in 2016.¹⁴ Only several syntheses of rucaparib have been reported, and they generally follow two strategies (Figure 2): (1) The 3,4-fused



Figure 2. Strategies for the synthesis of rucaparib.

tricyclic indoles are constructed from 6-fluoro indole derivatives, and the 4-((methylamino)methyl)phenyl group is introduced at a late stage.^{1g,15} The synthesis of 6-fluoro indole derivatives requires multiple steps, and the installation of a functional group to the three- or four-positions of the indoles is often low-yielding. Furthermore, an additional brominating reaction is needed to introduce the 4-((methylamino)methyl)phenyl group. (2) Multisubstituted indole derivatives bearing a 4-((methylamino)methyl)phenyl group are first synthesized, and rucaparib is formed via the late-stage cyclization. However, the synthesis of multisubstituted indole derivatives requires quite a number of steps.^{13,16} It is still highly desirable to develop facile and efficient synthetic methods for rucaparib.

Herein we report a general synthetic protocol for 3,4-fused tricyclic indoles through palladium-catalyzed C–H amination with N,N-di-*tert*-butyldiaziridinone. The reaction was successfully applied to the synthesis of rucaparib, which represents an advantageous method for the synthesis of this cancer medicine.

We commenced the studies by investigating the reaction of model substrate 1a with *N*,*N*-di-*tert*-butyldiaziridinone (2). As shown in Table 1, 3,4-fused six-membered tricyclic indole 3a

Table 1. Survey of the Reaction Conditions

	1a (0.2 mmol)	Ph + + + N-1 2 (1.5 e	Pd(OAC) ₂ Cs ₂ CO ₃ (1 equi KOPiv (0.5 equi solvent (2 mL) 110 °C, 12 h	v) v) v) v) v v v v v v v v v v
entry	Pd(OAc) ₂ (mol %)	solvent	ligand (mol %)	yield (%) ^a
1	10	DMF		90 ^b
2	10	DMF		98 (96 ^c)
3	10	toluene		
4	10	THF		52
5	10	MeCN		38
6	10	DMA		90
7	5	DMF		78
8	5	DMF	$P(o-tol)_{3}(10)$	95
9	2	DMF	$P(o-tol)_3(4)$	91
10	1	DMF	$P(o-tol)_3(2)$	$56 (78\%^d)$ (SM = 41%)

^{*a*}Yields were determined by ¹H NMR analysis of the crude reaction mixture using CHCl₂CHCl₂ as the internal standard. ^{*b*}No KOPiv. ^cIsolated yield. ^{*d*}36 h.

was formed in 90% yield using 10 mol % of $Pd(OAc)_2$ as the catalyst and Cs_2CO_3 as the base (entry 1). The yield was improved to 98% by adding 0.5 equiv of KOPiv (entry 2). **3a** was not observed or was obtained in a lower yield when the reaction was carried out in other solvents (entries 3–6). Decreasing the amount of $Pd(OAc)_2$ led to a lower yield (entry 7). However, an excellent yield was obtained by using ligand $P(o\text{-tol})_3$ (entry 8). Notably, even 2 mol % of $Pd(OAc)_2$ gave a yield of 91% (entry 9), which indicates the high efficiency and practical utility of the protocol. The yield dramatically decreased when the catalyst loading was reduced to 1 mol % (entry 10). In this reaction, most of **1a** was recovered, and no other side products were observed. The yield was improved to 78% when the reaction time was prolonged to 36 h.

Having developed an efficient protocol for the construction of 3,4-fused tricyclic indoles, we then studied the substrate scope of the reaction. The compatibility of various iodoaryl groups was first investigated. As shown in Scheme 1, phenyl groups bearing an electron-donating substituent (methyl and methoxyl) were compatible (**3b** and **3c**). It should be noted that the yields decreased only slightly when 2 mol % of Pd(OAc)₂ was used. Although the presence of a withdrawing substituent (trifluoromethyl) led to a moderate yield, it could be enhanced to 85% by adding ligand $P(o-tol)_3$ (**3d**). The chloro and fluoro groups were well-tolerated, and the desired products were formed in good or excellent yield (**3e** and **3f**). Even the pyridine moiety-containing substrates were suitable, and the reaction provides a new method for the synthesis tricyclic 6-azaindoles (**3g–i**).

Next, the performance of diverse substituents on the alkynyl groups was studied. A range of phenyl groups bearing different substituents were first examined. As shown in Scheme 2, the phenyl groups bearing various functionalities at the para positions were compatible, and high yields could be achieved by choosing suitable conditions (3j-m). The meta- and ortho-

Scheme 1. Substrate Scope with the Respect to the Iodoaryl Groups



^aPd(OAc)₂ (10 mol %). ^bPd(OAc)₂ (10 mol %), P(o-tol)₃ (20 mol %). ^cPd(OAc)₂ (2 mol %), P(o-tol)₃ (4 mol %).





^aPd(OAc)₂ (10 mol %). ^bPd(OAc)₂ (10 mol %), P(o-tol)₃ (20 mol %). ^cPd(OAc)₂ (2 mol %), P(o-tol)₃ (4 mol %).

substituted phenyl groups also gave high yields for both electron-donating and -withdrawing substituents (3n-q). The naphthyl and thiophenyl groups were suitable, and the corresponding products were formed in a good or moderate yield (3r and 3s). The suitability of an alkyl group was also investigated (3t). Although the desired product was not generated in the case of a methyl group under the conditions without a ligand, it was obtained in a 76% yield by using P(*o*-tol)₃. The unsubstituted alkyne failed to form the desired product (3u).

The compatibility of different linkers was also investigated. As shown in Scheme 3, the amides bearing an alkyl or phenyl group were compatible, and the reactions were high-yielding (5a-c). The presence of a methyl group on the methylene carbon resulted in a yield of 80% (5d). An amide linker that links the iodobenzene and the alkyne in an opposite way gave a much lower yield (5e). It is notable that excellent yields were obtained for amine and ether linkages (5f and 5g). However,

Scheme 3. Substrate Scope with the Respect to the Linkers

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^{*a*}Pd(OAc)₂ (10 mol %); ^{*b*}Pd(OAc)₂ (10 mol %), P(*o*-tol)₃ (20 mol %). ^{*c*}Pd(OAc)₂ (2 mol %), P(*o*-tol)₃ (4 mol %).

the reaction was far less efficient in the presence of an ester linker (5h).

Many bioactive 3,4-fused tricyclic indoles contain a mediumsized ring. The construction of medium-sized rings still remains a challenge in organic synthesis. Notably, our reaction is applicable to the formation of medium-sized rings and therefore provides a facile method for the synthesis of indoleannulated medium-sized ring compounds (Scheme 4). A

Scheme 4. Substrate Scope with the Respect to the Ring Sizes



seven-membered indole product was formed in 88% yield under the standard conditions consisting of ligand $P(o-tol)_3$ (5i). An ether linkage was also compatible, albeit in a lower yield (5j). Eight- and even nine-membered rings could be constructed, and various linkers were tolerated (5k-o).

The synthesis of rucaparib started with the Sonogashira coupling of commercially available compounds 6 and 7. The reaction afforded compound 8 in high yield. The resulting compound 8 was converted to *p*-methoxybenzyl (PMB)-protected amine compound 9. The condensation of 9 and 10, which is cheap, yielded the key intermediate 11. 11 was subjected to the standard conditions to afford compound 12 in 87% yield. A yield of 61% was still obtained, even using 2 mol % of Pd(OAc)₂. Finally, treating 12 with trifluoroacetic acid

(TFA) provided rucaparib in 88% yield. Notably, the synthesis was carried out on a gram scale, which demonstrated the practical utility of this method (Scheme 5). This new method has advantages, including readily available starting materials, few steps, and a high overall yield.

Scheme 5. Synthesis of Rucaparib



^aPd(OAc)₂ (5 mol %), P(*o*-tol)₃ (10 mol %). ^bPd(OAc)₂ (2 mol %), P(*o*-tol)₃ (4 mol %).

A tentative mechanism is proposed for the tricyclic indoleforming reaction by using compound 1a as the model substrate (Scheme 6).¹¹ The reaction is initiated by the oxidative

Scheme 6. Plausible Mechanism



addition of **1a** to Pd(0), affording aryl Pd(II) species **A**. The subsequent intramolecular carbopalladation yields vinyl Pd(II) species **B**. The Pd(II) species cleaves the aryl C–H bonds to form *C*,*C*-palladacycle **C** as the key intermediate. The resulting *C*,*C*-palladacycle undergoes oxidative addition to *N*,*N*-di-*tert*-butyldiaziridinone to generate pallada(IV)cycle **D**. Intermediate **D** is converted into tricyclic indole product **3a** with the release of *tert*-butyl isocyanate (tBuNCO) and Pd(0).

In conclusion, we have developed a general protocol for the synthesis of 3,4-fused tricyclic indoles through palladiumcatalyzed C–H amination with N,N-di-*tert*-butyldiaziridinone. A wide range of 3,4-fused tricyclic indoles, including those containing various linkers and fused with medium-sized rings, can be synthesized by this new protocol. Notably, the reaction has been successfully applied to the synthesis of rucaparib, an FDA-approved cancer medicine, providing an advantageous synthetic method for it.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01513.

General information, general procedure for the synthesis of the substrates, general procedure for the synthesis of 3,4-fused tricyclic indoles, procedure for the synthesis of rucaparib, characterization of the substrates, characterization of the products, NMR spectra, and references-(PDF)

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Notes

The authors declare no competing financial interest.

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