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Enantioselective Synthesis of Indole-Fused Bicyclo[3.2.1]octanes via Palladium(II)-Catalyzed Cascade Reaction

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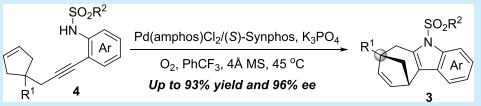
ABSTRACT: Indole-fused bicyclo[3.2.1]octanes are highly important structural units in natural products and biologically active compounds. However, there has been limited success in the enantioselective synthesis of these skeletons due to the complexity of the structure and the control of the enantioselectivity. Herein an enantioselective construction of indole-fused bicyclo[3.2.1]octanes bearing an all-carbon quaternary bridgehead stereocenter was developed via an aminopalladition-triggered Heck-type reaction. The protocol features mild conditions and good tolerance for a wide range of functional groups. The transformation can also be scaled up to demonstrate its practicability. The mechanistic studies reveal that the formation of an intermediate indol-3-yl palladium species via C−H activation should be ruled out.



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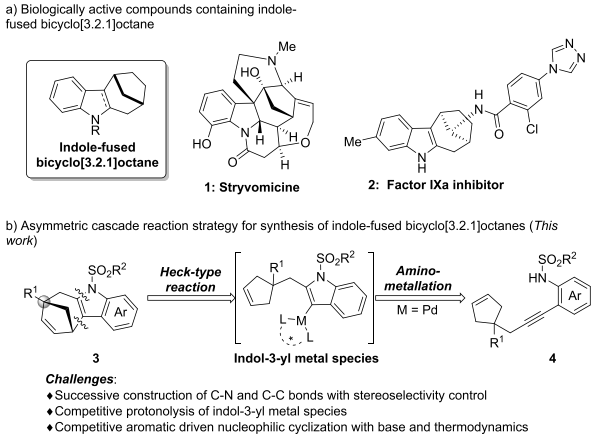
Polycyclic indole derivatives are commonly found in a number of biologically active compounds and natural products.[1] Among them, the indole-fused bicyclo[3.2.1]-octanes and their derivatives exhibit remarkable biological activities (Scheme 1a). For instance, Stryvomicine (**1**) was isolated from the seed of *Strychnos nux-vomica*, which is a traditional Chinese medicine and is widely used for the treatment of rheumatoid arthritis, swelling pain, trauma, bone fracture, facial nerve paralysis, myasthenia gravis, and polio-myelitis sequela.[2] Compound **2** is a potent selective Factor IXa inhibitor, and its IC_{50} is 54.26 nM.[3] Owing to their unique and diverse potential biological properties, considerable efforts have been undertaken to explore the synthesis of these skeletons in the past several decades.[4,5] However, the enantioselective catalytic construction of indole-fused bicyclo[3.2.1]octanes was flung into a dilemma due to the complexity of the structure and the control of the enantioselectivity. Therefore, the development of an efficient strategy to access chiral bicyclo[3.2.1]octanes skeletons from simple starting materials is of great significance.

Scheme 1. Enantioselective Synthesis of Indole-fused Bicyclo[3.2.1]octanes *via* an Asymmetric Cascade Reaction Strategy



The transition-metal-catalyzed cyclization/cross-coupling cascade reaction of 2-alkynyl aniline derivatives with nucleophiles or electrophiles is an attractive and practical pathway for the construction of 2,3-disubstituted indoles.[6] Mechanistically, the aminometalation of 2-alkynyl aniline derivatives generates the indol-3-yl metal species, which recently was employed for the construction of axially chiral indoles by the Kitagawa, Li, and Zhu groups.[7] Thus we envisioned that the indol-3-yl metal species might serve as a promising intermediate for the asymmetric Heck-type reaction for the rapid construction of chiral bicyclo[3.2.1]octanes containing an all-carbon quaternary bridgehead stereocenter (Scheme 1b).[8−11] However, several obvious challenges for this proposed cascade transformation need to be addressed. First, a transition-metal catalyst should allow the successive construction of C−N and C−C bonds with stereoselective control by nucleophilic cyclization and unactivated C═C double-bond insertion. Second, competitive protonolysis of the indol-3-yl metal species easily takes place, which might result in interrupting the unactivated C═C double-bond insertion.[6,12] Third, aromatic-driven nucleophilic cyclization could be

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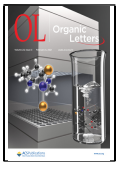

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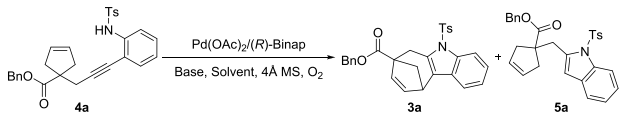
promoted by the base and thermodynamics,[13] which might not be of benefit to the asymmetric transition-metal-catalyzed cascade reaction. Herein we report the enantioselective synthesis of indole-fused bicyclo[3.2.1]octanes containing an all-carbon quaternary bridgehead stereocenter via the aminopalladition-triggered Heck-type reaction with excellent enantioselectivity.

Initially, *N*-sulfonyl-2-alkynylanilide **4a** was chosen as the model substrate to test our hypothesis (Table 1). In the presence of $Pd(OAc)_2$/(*R*)-Binap, Na_2CO_3, and O_2 as the oxidant in DCE at 50 °C, the cascade reaction occurred to give the desired product **3a** in 16% yield with 24% ee, albeit with inevitable protonolysis (16% yield of **5a**, entry 1). The assessment of the base revealed that K_3PO_4 is the best choice with respect to the yield and enantioselectivity. (See more details of the base in the Supporting Information.) The yield and enantioselectivity were slightly improved to 46% yield and 54% ee when the amount of K_3PO_4 was increased to 1.5 equiv (entry 8). The exploration of various solvents showed that the transformation is very sensitive to the reaction medium. The cascade reaction failed in DMF (entry 13). The formation of the side product **5a** was more favored when THF was employed as the solvent. Delightfully, $PhCF_3$ proved to be the most favorable solvent in view of enantioselectivity and reactivity.

Table 1. Screening of Bases and Solvents[a]

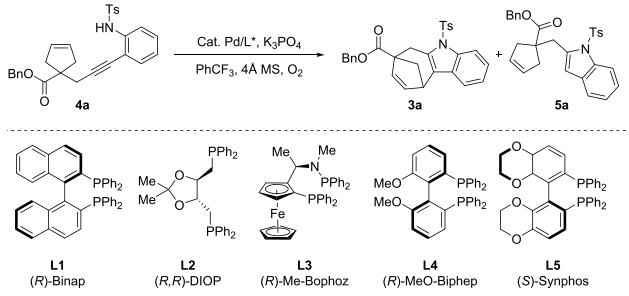


entry	base (*x* equiv)	solvent	**3a**/**5a** yield (%)[b]	ee (%)[c]
1	Na_2CO_3 (1.0)	DCE	16/16	24
2	K_2CO_3 (1.0)	DCE	26/10	50
3	Cs_2CO_3 (1.0)	DCE	29/11	48
4	Et_3N (1.0)	DCE	13/<5	48
5	^{t}BuOK (1.0)	DCE	41/22	46
6	^{t}BuONa (1.0)	DCE	28/21	48
7	K_3PO_4 (1.0)	DCE	38/21	50
8	K_3PO_4 (1.5)	DCE	46/23	54
9	K_3PO_4 (2.0)	DCE	47/24	50
10	K_3PO_4 (1.5)	THF	24/35	62
11	K_3PO_4 (1.5)	PhMe	27/11	62
12	K_3PO_4 (1.5)	PhH	35/13	64
13	K_3PO_4 (1.5)	DMF	<5/−	
14	**K_3PO_4 (1.5)**	**$PhCF_3$**	**64/21**	**74**

[a]**4a** (0.10 mmol), $Pd(OAc)_2$ (10 mmol %), (*R*)-Binap (11 mmol %), base (*x* equiv), solvent, 4 Å molecular sieve (100 mg), O_2 balloon, 50 °C, 20 h. [b]Isolated yield. [c]Determined by HPLC.

Aiming to further improve the enantioselectivity of reaction, a series of palladium precursors and chiral ligands were subsequently evaluated (Table 2). $Pd(amphos)Cl_2$ led to an obvious enhancement in the enantioselectivity, delivering the target product **3a** in 63% yield with 84% ee (entry 5). The effect of some commercially available bisphosphine ligands on the reactivity and enantioselectivity was investigated. It turned out that (*S*)-Synphos gave the best enantioselectivity with up to 90% yield (entry 9). When the reaction temperature was decreased and the reaction time was prolonged, 92% enantioselectivity and 75% yield were afforded (entry 10).

Table 2. Screening of Catalyst Precursors and Chiral Ligands[a]



entry	cat. Pd	L*	**3a**/**5a** yield (%)[b]	ee (%)[c]
1	$Pd(OAc)_2$	**L1**	64/21	74
2	$Pd(CF_3CO_2)_2$	**L1**	40/25	74
3	$PdCl_2(PPh_3)_2$	**L1**	76/11	64
4	$Pd(acac)_2$	**L1**	27/25	78
5	$Pd(amphos)Cl_2$	**L1**	63/7	84
6	$Pd(amphos)Cl_2$	**L2**	67/<5	6
7	$Pd(amphos)Cl_2$	**L3**	55/23	28
8	$Pd(amphos)Cl_2$	**L4**	74/7	84
9	$Pd(amphos)Cl_2$	**L5**	61/<5	90
10[d]	**$Pd(amphos)Cl_2$**	**L5**	**75/13**	**92**

[a]**4a** (0.10 mmol), Cat. Pd (10 mmol %), **L*** (11 mmol %), K_3PO_4 (1.5 equiv), $PhCF_3$, 4 Å molecular sieve (100 mg), O_2 balloon, 50 °C, 20 h. [b]Isolated yield. [c]Determined by HPLC. [d]45 °C, 48 h.

With the optimized conditions in hand, we turned our attention to investigate the substrate scope and generality of the current aminopalladition/Heck-type cascade reaction. The results are summarized in Scheme 2. As expected, various *N*-sulfonyl activating groups reacted smoothly, furnishing the indole-fused bicyclo[3.2.1]octanes containing all-carbon quaternary bridgehead stereocenter **3a**−**3d** in good yield with excellent enantioselectivity. However, replacement of the sulfonyl activating groups with a Boc or Ac group resulted in no reactivity. Excitingly, a series of *ortho*-alkynylanilines performed very well, and moderate to excellent enantioselectivities were obtained (**3h**−**3w**). Notably, halides such as fluoro and chloro were nicely tolerated, affording the corresponding products with good to excellent enantioselectivities. For example, 90% ee of **3l** and 87% ee of **3o** were observed, respectively. The electronic properties of *ortho*-alkynylanilines had a dramatic influence on the reactivity and enantioselectivity. When the electron-donating methoxyl (MeO) group was introduced to *ortho*-alkynylaniline, 94% ee and 82% yield were gained (**3j**). However, *ortho*-alkynylanilines bearing electron-withdrawing substituents, such as Ac, CF_3, and CO_2Me at the para position, furnished products with moderate enantioselectivity and reactivity (**3p**−**3r**). It is noteworthy that the effect of steric hindrance had only a marginal influence on the enantioselectivity. For instance, the transformation of **4u** and **4v** proceeded smoothly to provide 90% ee of **3u** and 91% ee of **3v**, respectively. The absolute configuration of the product (−)-**3k**, which can be increased to >99% ee by recrystallization with *n*-hexane/DCM, was unambiguously determined by X-ray crystallographic analysis.

Subsequently, the substrate scope of R^1 was explored. The all-carbon quaternary stereocenter possessing various functional groups, such as ester, amide, and ether, proceeded smoothly to deliver indole-fused bicyclo[3.2.1]octanes **3x**−**3ag** with good to excellent enantioselectivities. However, presum-

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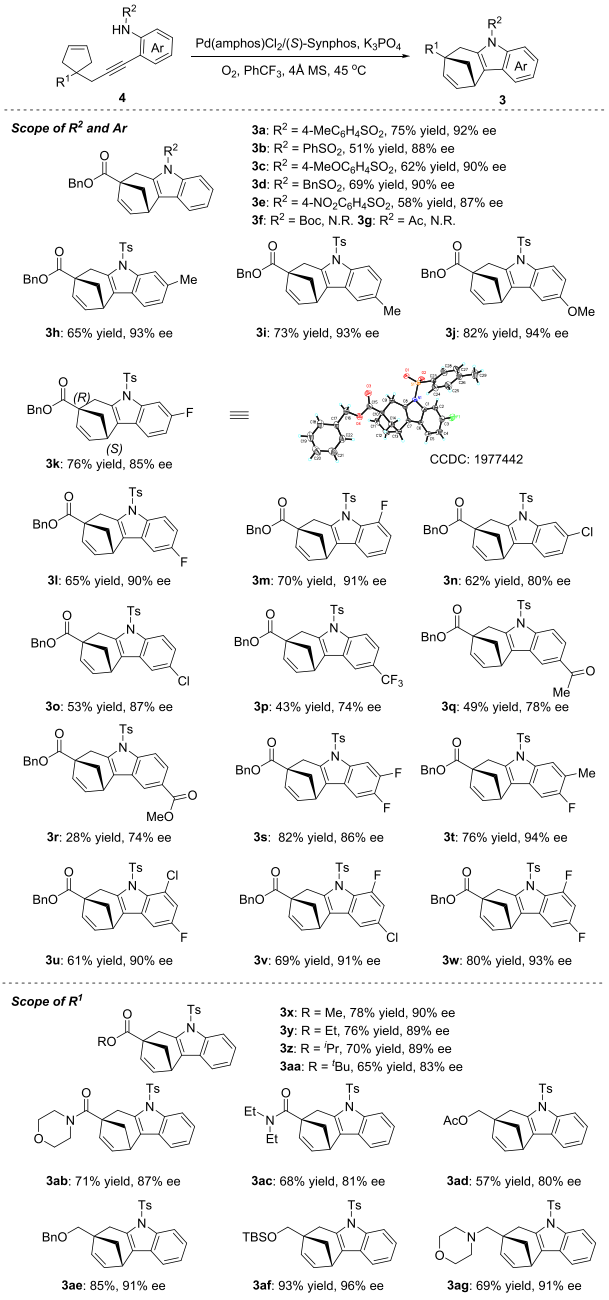
Scheme 2. Substrate Scope for Enantioselective Synthesis of Indole-Fused Bicyclo[3.2.1]octanes[a]

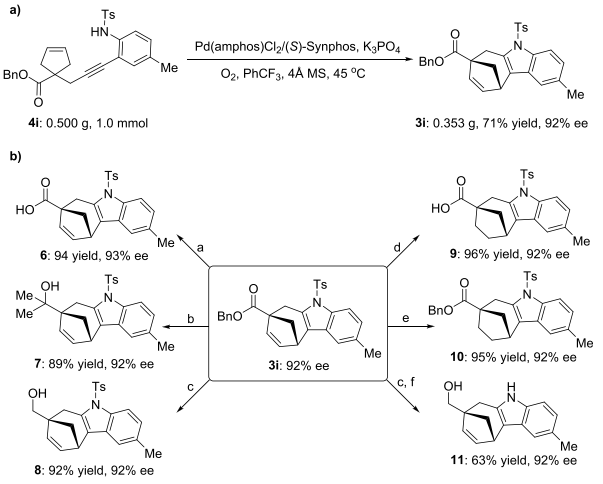


[a]Reaction conditions: **4** (0.10 mmol), Pd(amphos)Cl_2 (10 mmol %), (*S*)-Synphos (11 mmol %), K_3PO_4 (1.5 equiv), $PhCF_3$, 4 Å molecular sieve (100 mg), O_2 balloon, 45 °C. Isolated yield. The ee value was determined by HPLC.

ably as a result of steric hindrance, the substrate **3aa** containing *t*-butyl ester on the all-carbon quaternary stereocenter resulted in a diminished yield and ee value. Notably, the desired product **3af** was constructed in 93% yield with 96% ee.

To verify the practical utility of our protocol, a scale-up experiment was carried out, furnishing the desired product **3i** in 71% yield and with 92% ee (Scheme 3a). The reactivity and enantioselectivity were maintained in the scale-up reaction. Synthetic transformations of **3i** were then conducted (Scheme 3b). The hydrolysis of **3i** in the presence of K_2CO_3 afforded the acid **6** in 94% yield without the loss of enantiopurity.

Scheme 3. Scale-up Experiment and Synthetic Transformations of Indole-Fused Bicyclo[3.2.1]octanes 3i[a]



[a]Reaction conditions: (a) K_2CO_3, MeOH, 65 °C. (b) MeMgBr, THF, 0 °C to rt. (c) $LiAlH_4$, THF, 0 °C. (d) 10 wt % Pd/C, THF. (e) $RhCl(PPh_3)_3$, H_2, toluene, 80 °C. (f) KOH, EtOH, 120 °C.

Treatment of **3i** with MeMgBr delivered **7** in 89% yield with 92% ee. **3i** was treated with $LiAlH_4$ to give the alcohol **8** in the 92% yield with 92% ee. Additionally, **9** was obtained in the 90% yield *via* reduction and debenzylation. The C═C double bond of **3i** was efficiently hydrogenated with Wilkinson's catalyst, delivering compound **10** in 95% yield with 92% ee. Reduction of **3i** following deprotection of the Ts group with KOH in EtOH could produce **11** in the 63% yield, and excellent enantioselectivity was maintained.[14]

Some control experiments have been conducted to explore the reaction mechanism (Figure 1a,b). No desired product **3a** was observed when **5a** was employed for the reaction under standard conditions and even with 1.0 equiv palladium catalyst.

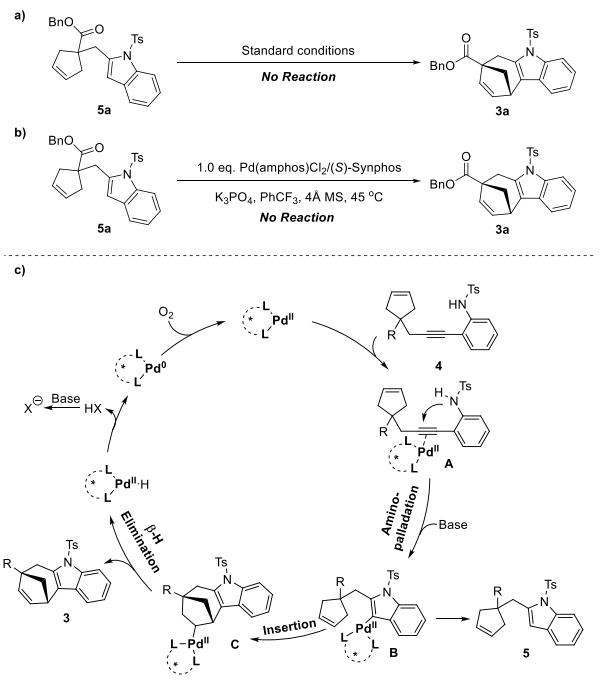


Figure 1. Control Experiments and Possible Mechanism.

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These results indicated that the indol-3-yl palladium species was not formed *via* C−H activation, and the protonolysis process was irreversible. According to the above results and previous literature,[6,8−11] a plausible mechanism is proposed in Figure 1c. Coordination of the palladium(II) catalyst with the triple bond of the *N*-sulfonyl-2-alkynylanilide **4** formed intermediate **A**, which underwent aminopalladation to generate the indol-3-yl palladium species **B**. Intramolecular C=C double-bond insertion of indol-3-yl palladium species **B** was followed by *β*-H elimination to furnish the desired product **3** and the Pd−H species. The palladium(II) catalyst was regenerated *via* reductive elimination and oxidation with O_2. Protonolysis of indol-3-yl palladium species **B** led to the byproduct **5**.

In summary, we have successfully developed an enantioselective construction of indole-fused bicyclo[3.2.1]-octanes containing an all-carbon quaternary bridgehead stereocenter with excellent enantioselectivity *via* an aminopalladition-triggered Heck-type reaction. The reaction features mild conditions and tolerates a wide range of functional groups. The practicability of this protocol can also be demonstrated with a scaled-up reaction and divergent derivatization. The mechanistic studies reveal that the formation of the intermediate indol-3-yl palladium species by C−H activation should be ruled out, and the protonolysis process was irreversible. The strategy documented in this Letter affords a new and efficient approach to synthetically valued chiral-indole-fused bicyclo[3.2.1]octane structures, which might be potentially useful for organic synthesis and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04030.

Experimental procedures, characterization data, and NMR spectra (PDF)

Accession Codes

CCDC 1977442 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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