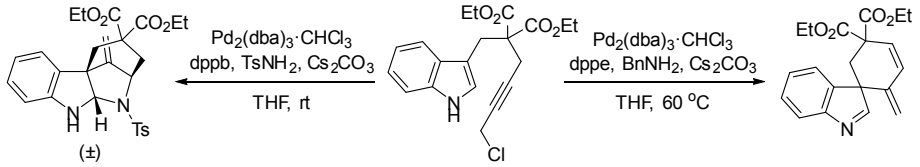
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Convenient synthesis of spiroindole derivatives via palladium-catalyzed cyclization of propargyl chlorides

Leave this area blank for abstract info.

Akira Iwata, Shinsuke Inuki, Shinya Oishi , Nobutaka Fujii, Hiroaki Ohno
Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan



Tetrahedron
journal homepage: www.elsevier.com

Convenient synthesis of spiroindole derivatives via palladium-catalyzed cyclization of propargyl chlorides

Akira Iwata , Shinsuke Inuki,† Shinya Oishi, Nobutaka Fujii*, Hiroaki Ohno*

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
palladium
spiroindole
cascade cyclization
catalytic asymmetric reaction

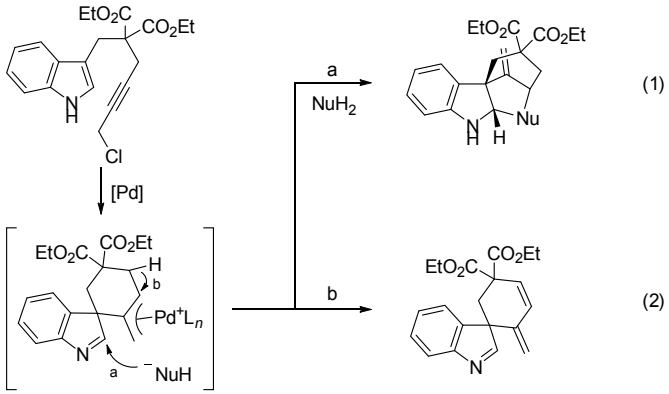
ABSTRACT

Herein, we report the palladium-catalyzed cyclization reactions of indoles bearing a propargyl chloride side chain at their 3-position. In the presence of an external nucleophile, such as a sulfonamide or malonate, indoles bearing a propargyl group at their 3-position gave fused tetracyclic spiroindolines preferentially. However, in the absence of an external nucleophile, the same substrates afforded spiroindoles. Our attempts to develop a catalytic asymmetric spirocyclization onto a propargylpalladium species are also presented in this paper.

1. Introduction

The palladium-catalyzed reactions of propargyl compounds provide efficient approaches for the formation of carbon-carbon and carbon-heteroatom bonds.[1] The pioneering work of Tsuji and co-workers revealed that double nucleophilic additions proceeded at the central and terminal carbons of the propargylic moiety when soft carbon- or oxo-nucleophiles were employed.[2] This chemistry is particularly useful for the construction of carbo- and heterocyclic frameworks, including furans,[3] cyclobutanes,[4] indenes,[5] cyclopentanones,[6] cyclic carbonates,[7] benzofurans,[8] and indoles,[9] especially when it is used in combination with an inter- or intramolecular nucleophilic addition reaction as the terminating step.

Spirocyclic compounds are currently attracting considerable interest in organic chemistry because of their unique molecular structure and diverse biological activities.[10] In particular, enantio-enriched spiroindoles and spiroindolines represent important structural motifs that can be found in a wide range of biologically active natural products and synthetic compounds.[11] As part of our ongoing efforts towards the construction of heterocyclic frameworks based on the palladium-catalyzed reactions of propargyl/allenic compounds, we recently became interested in the intramolecular nucleophilic addition reactions of indoles as a strategy for the synthesis of spiroindoles. It was envisaged that this strategy would provide facile access to tetracyclic spiroindolines when it was used in combination with the intermolecular nucleophilic cyclization of an external nucleophile (Scheme 1, eq. 1, path a). We also expected that running the same reaction without using an external nucleophile would promote β-hydride elimination (path b) to produce spiroindoles bearing a conjugated diene moiety (eq. 2).



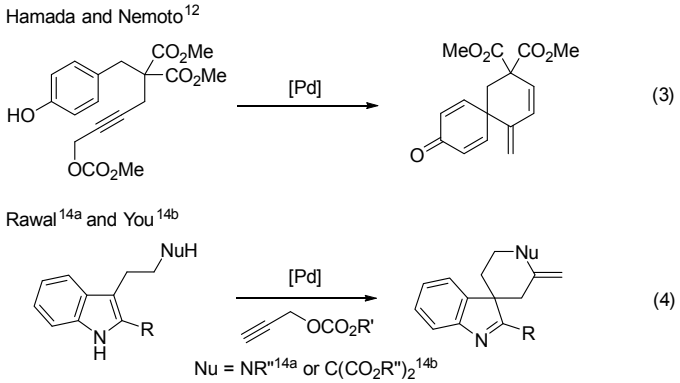
Scheme 1. Our concept: palladium-catalyzed spirocyclization of indole-based propargyl compounds

In 2013, Hamada and co-workers reported the development of a palladium-catalyzed intramolecular spirocyclization of phenol-based propargylic carbonates (Scheme 2, eq. 3).[12] When tryptamine-derived carbonates were used, this reaction produced spiroindoles bearing an azepine moiety. Immediately after our communication in 2014,[13] the groups of Rawal[14a] and You[14b] independently reported the intermolecular reactions of indole-

* Corresponding author. Tel.: +81-75-753-4571; fax: +81-75-753-4570; e-mail: hohno@pharm.kyoto-u.ac.jp

* Corresponding author. Tel.: +81-75-753-4551; fax: +81-75-753-4570; e-mail: nfujii@pharm.kyoto-u.ac.jp

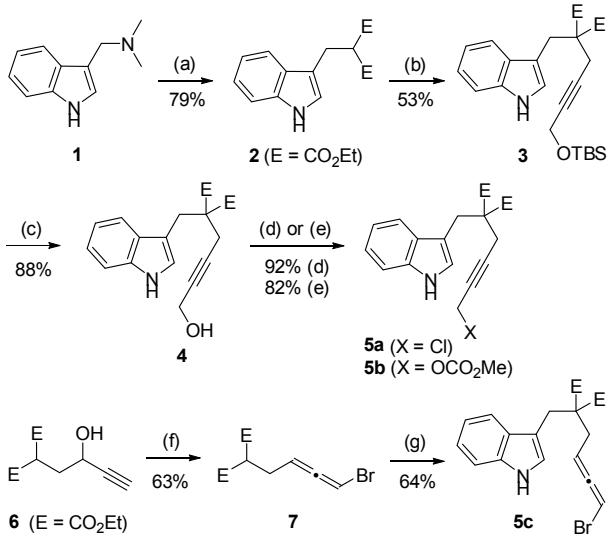
based dual nucleophiles and propargyl carbonates as general strategies for the synthesis of spiroindoles (eq. 4). In this paper, we report the full details of our recent investigations into construction of tetracyclic spiroindolines (eq. 1) and conjugated diene-type spiroindoles (eq. 2) via the palladium-catalyzed cyclization of propargyl chlorides. Our attempts to achieve a catalytic asymmetric spirocyclization onto a propargylpalladium species have also been presented.



Scheme 2. Related palladium-catalyzed spirocyclization reaction using propargyl compounds

2. Results and discussion

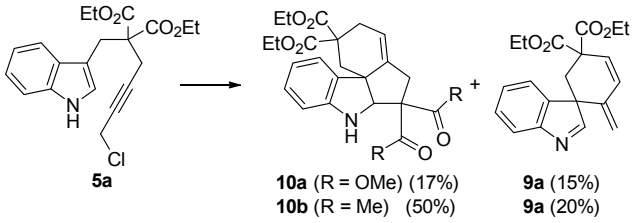
The route used for the preparation of substrates **5a**–**c** is shown in Scheme 3. In accordance with a literature procedure,[15] gramine (**1**) was converted to the corresponding malonate **2**. The subsequent alkylation of **2** followed by a desilylation reaction afforded propargyl alcohol **4**. Substrates **5a** and **5b** were obtained by the reaction of **4** with NCS/PPh_3 or $ClCO_2Me$/pyridine, respectively. Bromoallene **5c** was prepared from propargyl alcohol **6** using an established procedure for the formation of bromoallenes.[16] The treatment of **6** with TrisCl (Tris = 2,4,6-triisopropylbenzenesulfonyl) and DMAP gave the corresponding sulfonate, which was converted to bromoallene **7** by treatment with $CuBr{\cdot}SMe_2$ in the presence of LiBr. Finally, the introduction of the indole unit to **7** was achieved by its reaction with gramine (**1**) in the presence of ethyl propiolate to give bromoallene **5c**. The other substrates were also prepared in the same manner (see Supplementary material).



Scheme 3. Preparation of substrates **5a**–**c**. (a) diethyl malonate, ethyl propiolate, Et_2O, rt; (b) $BrCH_2C{\equiv}CCH_2OTBS$, NaH, THF, 0 °C to rt; (c) TBAF, THF, 0 °C; (d) NCS, PPh_3, CH_2Cl_2, rt; (e) $ClCO_2Me$, pyridine, CH_2Cl_2, 0 °C; (f) TrisCl, DMAP, CH_2Cl_2, then $CuBr{\cdot}SMe_2$, LiBr, THF, 50 °C; (g) **1**, ethyl propiolate, Et_2O, rt.

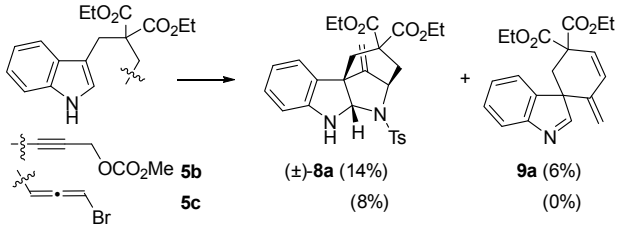
Our studies began with a series of screening experiments to identify the optimal reaction conditions using propargyl chloride **5a** as a model substrate (Table 1). The reaction of **5a** with 5 mol % $Pd(PPh_3)_4$, $TsNH_2$ and Cs_2CO_3 in THF gave spiroindole **9a**, the β-hydride elimination product, in only 20% yield (entry 1). When the reaction was conducted in the presence of 5 mol % $Pd(dba)_2$ and the bidentate ligand 1,1′-bis(diphenylphosphino)ferrocene (dppf), the desired reaction proceeded smoothly to afford the tetracyclic spiroindoline **8a** in 47% yield (entry 2). A variety of different inorganic bases (entries 3–5), ligands (entries 6–10) and solvents (entries 11–13) were also screened against the reaction, and the results revealed that the use of 1,4-bis(diphenylphosphino)butane (dppb) as the ligand with Cs_2CO_3 as the base in THF gave the best results, with compound **8a** being isolated in *ca*. 72% yield (entry 9). However, the main problem with these conditions was found to be poor reproducibility. Operating under the assumption that the poor reproducibility of these conditions was related to the purity of $Pd(dba)_2$, we investigated the use of $Pd_2(dba)_3{\cdot}CHCl_3$ following its recrystallization from $CHCl_3$.[17] This change afforded the desired product **8a** in 72% yield reproducibly (entry 14).

With the optimized conditions in hand, we proceeded to examine the performance of the reaction in the presence of a variety of different nucleophiles. The results are summarized in Table 1 (entries 15–19) and Scheme 4. The reaction with sulfonamides (e.g., $PhSO_2NH_2$, $MtsNH_2$, $NsNH_2$, and $MsNH_2$) gave the corresponding tetracyclic spiroindolines **8b**–**e** in moderate yields (entries 15–18). In contrast, benzylamine was found to be inert as the external nucleophile, with the β-hydride elimination product **9a** being isolated as the major product (entry 19). Interestingly, the use of dimethyl malonate as the nucleophile resulted in the formation of the regioisomeric spiroindoline **10a** (17%) and spiroindole **9a** (15%) as shown in Scheme 4. The use of acetyl acetone, which is a more acidic carbon nucleophile than dimethyl malonate, led to an increase in the yield of spiroindoline **10b** (50%), along with spiroindole **9a** (20%).



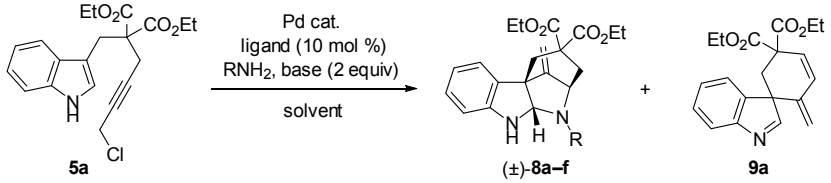
Scheme 4. Reaction with carbon nucleophiles. Reaction conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), dppb (10 mol %), Cs_2CO_3 and $CH_2(COR)_2$ in THF at rt.

It is well known that bromoallenes are the synthetic equivalents of propargyl compounds including chlorides and carbonates in palladium-catalyzed transformations.[18] With this in mind, we examined the reactions of propargyl carbonate **5b** and bromoallene **5c** (Scheme 5). Unfortunately, these reactions gave the desired spiroindoline **8a** in only 8–14% yield. These results therefore demonstrated that substrates of this type are less effective for this reaction than propargyl chloride **5a**.



Scheme 5. Reaction of carbonate **5b** and bromoallene **5c**. Reaction conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), dppb (10 mol %), $TsNH_2$ and Cs_2CO_3 in THF at rt.

Table 1. Optimization of the reaction conditions and the reaction with various nitrogen nucleophiles.



entry	Pd (mol %)	ligand	RNH_2 (equiv)	Base	solvent (M)	temp (°C)	time (h)	% yield[a] (product) 8	9a
1	$Pd(PPh_3)_4$ (5)	(PPh_3)	$TsNH_2$ (1)	Cs_2CO_3	THF (0.1)	60	24	0	20
2	$Pd(dba)_2$ (5)	dppf[b]	$TsNH_2$ (1)	Cs_2CO_3	THF (0.1)	50	0.5	47 (**8a**)	5
3	$Pd(dba)_2$ (5)	dppf	$TsNH_2$ (1)	K_2CO_3	THF (0.1)	50	3	15 (**8a**)	6
4	$Pd(dba)_2$ (5)	dppf	$TsNH_2$ (1)	$CaCO_3$	THF (0.1)	60	24	0	0
5	$Pd(dba)_2$ (5)	dppf	$TsNH_2$ (1)	$NaHCO_3$	THF (0.1)	60	24	0	0
6	$Pd(dba)_2$ (5)	dppm[c]	$TsNH_2$ (1)	Cs_2CO_3	THF (0.1)	60	24	0	17
7	$Pd(dba)_2$ (5)	dppe[d]	$TsNH_2$ (1)	Cs_2CO_3	THF (0.1)	60	7	22 (**8a**)	62
8	$Pd(dba)_2$ (5)	dppp[e]	$TsNH_2$ (1)	Cs_2CO_3	THF (0.1)	50	1	29 (**8a**)	6
9	$Pd(dba)_2$ (5)	dppb[f]	$TsNH_2$ (1)	Cs_2CO_3	THF (0.1)	rt	2.5	*ca.* 72 (**8a**)	3
10	$Pd(dba)_2$ (5)	dpppe[g]	$TsNH_2$ (1)	Cs_2CO_3	THF (0.1)	50	5	37 (**8a**)	2
11	$Pd(dba)_2$ (5)	dppb	$TsNH_2$ (1)	Cs_2CO_3	dioxane (0.1)	70	20	*ca.* 13 (**8a**)	3
12	$Pd(dba)_2$ (5)	dppb	$TsNH_2$ (1)	Cs_2CO_3	DMF (0.1)	rt	2.5	*ca.* 59 (**8a**)	1
13	$Pd(dba)_2$ (5)	dppb	$TsNH_2$ (1)	Cs_2CO_3	CH_3CN (0.1)	40	2	*ca.* 54 (**8a**)	1
14	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)	dppb	$TsNH_2$ (1.5)	Cs_2CO_3	THF (0.067)	rt	3	72 (**8a**)	5
15	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)	dppb	$PhSO_2NH_2$ (1.5)	Cs_2CO_3	THF (0.067)	rt	5	64 (**8b**)	6
16	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)	dppb	$MtsNH_2$[h] (1.5)	Cs_2CO_3	THF (0.067)	rt	3.5	55 (**8c**)	9
17	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)	dppb	$NsNH_2$ (1.5)	Cs_2CO_3	THF (0.067)	60	2	43 (**8d**)	15
18	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)	dppb	$MsNH_2$ (1.5)	Cs_2CO_3	THF (0.067)	60	24	68 (**8e**)	10
19	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)	dppb	$BnNH_2$ (1.5)	Cs_2CO_3	THF (0.067)	60	7	0 (**8f**)	54

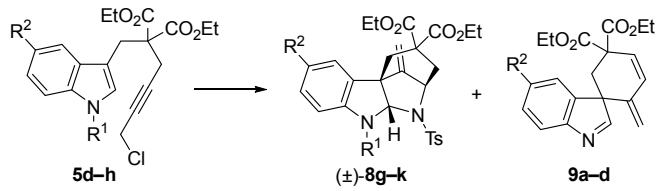
[a] Isolated yields. [b] 1,1'-bis(diphenylphosphino)ferrocene [c] bis(diphenylphosphino)methane. [d] 1,2-bis(diphenylphosphino)ethane. [e] 1,3-bis(diphenylphosphino)propane. [f] 1,4-bis(diphenylphosphino)butane. [g] 1,5-bis(diphenylphosphino)pentane. [h] Mts = 2,4,6-trimethylbenzenesulfonyl.

We next examined the scope and limitations of the reaction using a series of different indole substrates (Table 2). *N*-Substituted indoles **5d** and **5e** did not produce the spirocyclic products (entries 1 and 2). In contrast, indoles bearing an electron-withdrawing fluorine group (**5f**) or electron-donating methoxy group (**5h**) at their 5-position reacted smoothly under the optimized conditions to give the desired products **8i** and **8k** in good yields (entries 3 and 5). However, when compound **5g** bearing a bromine group at the 5-position of the indole was used as a substrate, a slightly lower yield (43%) of spiroindoline **8j** was observed. The lower yield observed in this case was attributed to side reaction(s) involving the aryl bromide moiety of the substrate, as well as the aryl bromide of the product **8j**.

We then turned our attention to the selective synthesis of the β-elimination product **9** (Table 3). It was envisaged that **9** could be efficiently produced under the same reaction conditions in the absence of an external nucleophile. This assumption was based on the results of our previous reaction, where the use of 1,2-bis(diphenylphosphino)ethane (dppe) as a ligand afforded spiroindole **9a** as the major product in 62% yield (Table 1, entry 7). Contrary to our expectation, the treatment of **5a** with $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %) and dppe (10 mol %) in the

presence of Cs_2CO_3 (2 equiv) at 70 °C afforded the desired product **9a** in only 7% yield (Table 3, entry 1). Based on this disappointing result, we carefully examined the reaction parameters and screened a series of bases against the reaction (entries 2–6), including Cs_2CO_3, Et_3N, $(i\text{-Pr})_2NEt$ (DIPEA) and $BnNH_2$ at 50–55 °C. Among them, a combination of $BnNH_2$ and Cs_2CO_3 gave a better result (33%, entry 6) than the reaction using Cs_2CO_3 alone (entry 1). Furthermore, the reaction temperature had a significant impact on the yield of **9a**. For example, the reaction reached completion within 3 h at a slightly elevated temperature (60 °C) to afford the desired product in 68% yield (Table 3, entry 7). Lowering the loading of $BnNH_2$ (entry 8, 45%) or increasing the loading of the catalyst (entry 9, 64%) did not improve the yield of **9a**. It is noteworthy that the reaction involving the use of $BnNH_2$ as the only base afforded only a trace amount of **9a** (entry 10). Under the optimized conditions, substituted indoles **5f** and **5h** afforded spiroindoles **9b** and **9d**, respectively, in moderate to good yields (entries 11 and 13). Furthermore, the brominated substrate **5g** reacted under these conditions to **9c**, albeit in a lower yield (40%, entry 12).

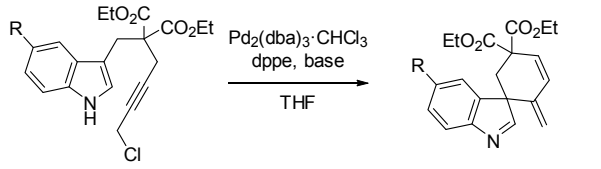
Table 2. Reaction of various indoles.[a]



entry	subst.	R^1	R^2	temp (°C)	time (h)	% yield (product)[b] 8	9
1	**5d**	Boc	H	60	24	0 (**8g**)	0 (**9a**)
2	**5e**	Me	H	60	24	0 (**8h**)	0 (**9a**)
3	**5f**	H	F	rt	3	71 (**8i**)	5 (**9b**)
4	**5g**	H	Br	60	3	43 (**8j**)	6 (**9c**)
5	**5h**	H	OMe	rt	2.5	71 (**8k**)	20 (**9d**)

[a] Reactions were carried out using propargyl chlorides **5d**–**h** with $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), dppb (10 mol %), Cs_2CO_3 (2 equiv) and $TsNH_2$ (1.5 equiv) in THF (0.067 M). [b] Isolated yields.

Table 3 Synthesis of spiroindoles **9a–d.**



5a (R = H), **5f** (R = F)
5g (R = Br), **5h** (R = OMe)

9a (R = H), **9b** (R = F)
9c (R = Br), **9d** (R = OMe)

entry	subst.	[Pd]/dppe (mol %)	base (equiv)	temp (°C)	time (h)	% yield[a] (product)
1	**5a**	5/10	Cs_2CO_3 (2)	70	4	7 (**9a**)
2	**5a**	5/10	Et_3N (2)	55	24	3 (**9a**)
3	**5a**	5/10	DIPEA (2)	55	24	4 (**9a**)
4	**5a**	5/10	Et_3N (1.5)/ Cs_2CO_3 (2)	55	24	11 (**9a**)
5	**5a**	5/10	DIPEA (1.5)/ Cs_2CO_3 (2)	55	20	21 (**9a**)
6	**5a**	5/10	$BnNH_2$ (1.5)/ Cs_2CO_3 (2)	55	24	33 (**9a**)
7	**5a**	5/10	$BnNH_2$ (1.5)/ Cs_2CO_3 (2)	60	3	68 (**9a**)
8	**5a**	5/10	$BnNH_2$ (0.2)/ Cs_2CO_3 (2)	60	4	45 (**9a**)
9	**5a**	10/20	$BnNH_2$ (1.5)/ Cs_2CO_3 (2)	60	3	64 (**9a**)
10	**5a**	10/20	$BnNH_2$ (2)	60	24	trace (**9a**)
11	**5f**	5/10	$BnNH_2$ (1.5)/ Cs_2CO_3 (2)	60	3	56 (**9b**)
12	**5g**	5/10	$BnNH_2$ (1.5)/ Cs_2CO_3 (2)	60	3	40 (**9c**)
13	**5h**	5/10	$BnNH_2$ (1.5)/ Cs_2CO_3 (2)	60	3	74 (**9d**)

[a] Isolated yields.

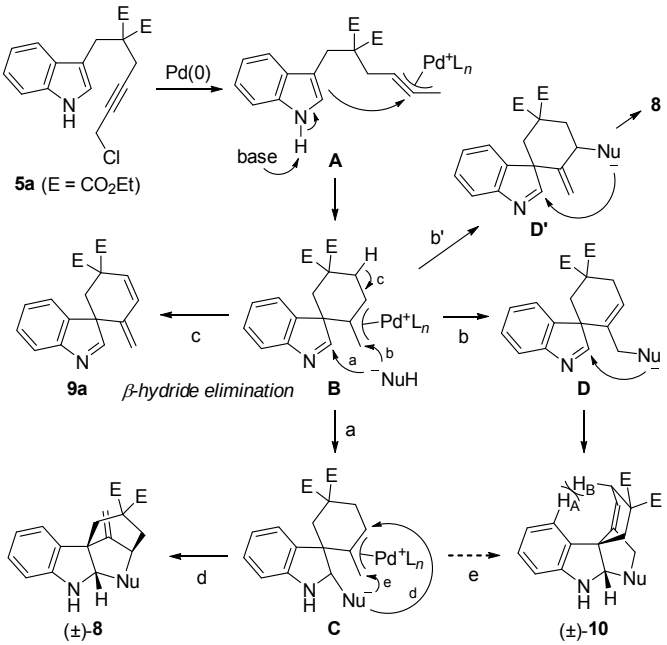


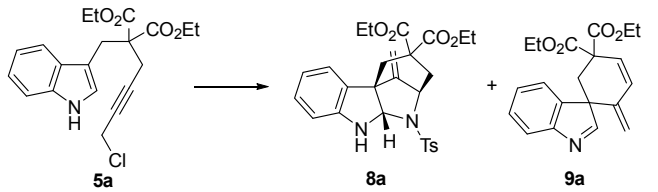
Figure 1. Proposed mechanism for palladium-catalyzed cascade cyclization.

A plausible mechanism for the cascade cyclization is shown in Figure 1. Briefly, propargyl chloride would initially react with a palladium catalyst to give the η^3-propargylpalladium complex **A**.[1c,18] Intramolecular nucleophilic addition of the indole to the central carbon atom of the η^3-propargylpalladium **A** would give η^3-allylpalladium complex **B**.[19] Deprotonation at the indole nitrogen would be necessary for this step, considering that the *N*-substituted substrates **5d** and **5e** did not react under the optimized reaction conditions (Table 2, entries 1 and 2). The tetracyclic spiroindolines **8** and **10** would then be formed by the intermolecular nucleophilic attack of the external nucleophile via path a and/or b. Path a represents the first intermolecular nucleophilic attack on the imine carbon, which would be followed by the allylic substitution reaction of intermediate **C**. Depending on which carbons of the allylic moiety in **C** participated in the cyclization (path d vs. e), the regioisomeric products **8** and **10** would be formed. Path b would occur to give intermediate **D** if the intermolecular allylic substitution reaction dominated over the addition of the nucleophile to the imine, with spiroindoline **10** being formed as the major product. In this step, the occurrence of an intermolecular reaction at the more hindered carbon (path b') would be another possible pathway. In contrast,

β-hydride elimination from **B** would produce diene **9a** (path c). When a sulfonamide was used as the external nucleophile, tetracyclic spiroindoline **8** was obtained without producing any of the regioisomeric spiroindoline **10**. This regioselectivity was most likely affected by steric hindrance during the reactions involved in path a, in that the product **10** as well as the transition state from **C** to **10** would be destabilized by unfavorable steric interactions between the indole proton at the 4-position (H_A) and the flagpole hydrogen (H_B) of the cyclohexene moiety. In contrast, the reaction using carbon nucleophile would favor the formation of regioisomer **10** (Scheme 4). This can be explained by considering both the sterically congested and soft characteristics of the carbon nucleophiles. Thus, the sterically hindered imine carbon (having a quaternary carbon at the neighboring position) would induce the nucleophilic attack of the soft carbon nucleophiles at the η^3-allylpalladium moiety of **B** to form **10** via intermediate **D** (path b).[20]

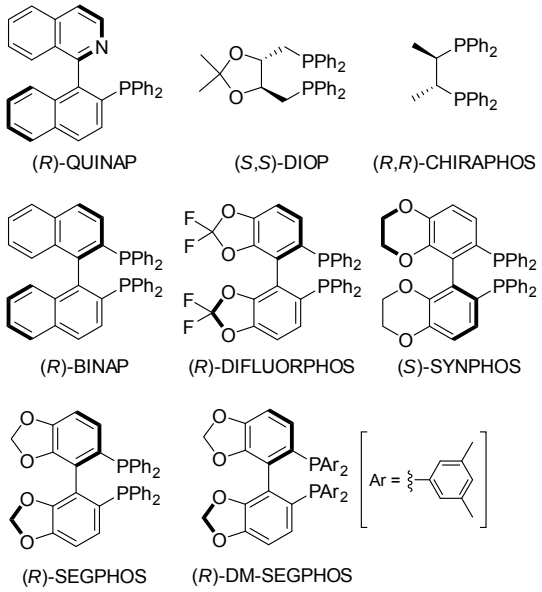
Finally, we attempted to carry out a catalytic asymmetric version of the current reaction. To the best of our knowledge, only two catalytic asymmetric reactions have been reported to date for the propargylpalladium chemistry. Rawal et al.[14a] reported an asymmetric version of the aforementioned intermolecular spirocyclization of a tryptamine-derived substrate (Scheme 2, eq 4) and obtained the spiroindole (Nu = NR) in 16% ee using (*R*)-BINAP. You et al.[14b] found that (*R*)-SEGPHOS showed more efficient asymmetric induction, affording the corresponding spiroindole [Nu = $C(CO_2Et)_2$] in 52% ee. The enantio-determining step in these reactions would be the allylic substitution step, where the chiral spirocenter would be formed by the nucleophilic reaction of the indole moiety. We screened a series of chiral ligands against β-hydride elimination reaction to produce spiroindole **9a** (Table 4, entries 1–8). When (*R*)-SEGPHOS and (*R*)-DM-SEGPHOS were used, these reactions produced spiroindole **9a** with better enantioselectivities (51–53% ee, entries 6 and 7), although the yields of **9a** were unsatisfactory (12–24%). We thus proceeded to examine the synthesis of tetracyclic spiroindoline **8a** using (*R*)-SEGPHOS and (*R*)-DM-SEGPHOS. Fortunately, the palladium-catalyzed reaction of **5a** with $TsNH_2$ in the presence of H_2O (1 equiv) using (*R*)-SEGPHOS gave the tetracyclic spiroindoline **8a** (38% yield) and spiroindole **9a** (15% yield) with moderate enantioselectivities (65–71% ee, entry 10). It should be noted that the addition of H_2O to the reaction was necessary for a high level of reproducibility. This result therefore highlights the great potential of a propargylpalladium complex in terms of its use in catalytic asymmetric reactions.

Table 4. Optimization of the catalytic asymmetric reaction conditions. [a,b]



entry	chiral ligand	other reagent	time (h)	% yield[c] (% ee)[d]	
				8a	**9a**
1	(*R*)-QUINAP	$BnNH_2$	5	-	trace
2	(*S*,*S*)-DIOP	$BnNH_2$	3.5	-	mixture
3	(*R*)-CHIRAPHOS	$BnNH_2$	7	-	13 (13)
4	(*R*)-BINAP	$BnNH_2$	4	-	22 (34)
5	(*S*)-SYNPHOS	$BnNH_2$	6	-	*ca.* 34% (40)
6	(*R*)-SEGPHOS	$BnNH_2$	6	-	12 (53)
7	(*R*)-DM-SEGPHOS	$BnNH_2$	4	-	24 (51)
8	(*R*)-DIFLUORPHOS	$BnNH_2$	24	-	5.5 (34)
9	(*R*)-SEGPHOS	$TsNH_2$	24	24 (56)	14 (73)
10	(*R*)-SEGPHOS	$TsNH_2$, H_2O [e]	14	38 (65)	15 (71)
11	(*R*)-DM-SEGPHOS	$TsNH_2$, H_2O [e]	20	16 (30)	4 (77)

[a] Reactions were carried out using propargyl chloride **5a** with $Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol %), chiral ligand (10 mol %), Cs_2CO_3 (2 equiv) and other reagent (1.5 equiv) in THF (0.067 M). [b] One of the enantiomers of **8a** is shown in the Scheme. [c] Isolated yields. [d] Determined by HPLC analysis (Chiralcel IC-3) [e] Reaction was carried out with addition of H_2O (1 equiv).



3. Conclusion

In conclusion, we have developed the palladium-catalyzed spirocyclization of propargyl chlorides using an external nucleophile for the divergent synthesis of tetracyclic spiroindolines. When this reaction was conducted in the absence of an appropriate external nucleophile, it gave the corresponding spiroindoles through β-hydride elimination. The regioselectivity of this reaction was found to be dependent on the external nucleophiles employed in the reaction. We have also investigated an asymmetric version of this reaction to produce spiroindole derivatives in 65–71% ee. This methodology would provide a novel approach to biologically active spiroindole derivatives.

4. Experimental

General Methods.

All reactions under argon atmosphere were performed using syringe-septum cap techniques and all glassware was dried in an oven at 80 °C for 2 h prior to use. For flash chromatography, silica gel (Wakosil C-200E: Wako Pure Chemical Industries, Ltd) or NH_2 silica gel (Chromatorex NH-DM1020: Fuji Silysia Chemical Ltd.) was employed. Thin layer chromatography was

performed on Merck TLC silica gel 60 F_{254} or Wako NH_2 silica gel 60 F_{254} plate (layer thickness 0.25 mm), which were developed using standard visualizing agents: UV fluorescence (254 nm) and anisaldehyde with heating. Melting points were measured by a hot stage melting point apparatus (uncorrected). ^{1}H NMR spectra were recorded using a JEOL AL-400 or JEOL ECA-500 spectrometer, and chemical shifts are reported in δ (ppm) relative to TMS as internal standard. ^{13}C NMR spectra were recorded using a JEOL AL-400 or JEOL ECA-500 spectrometer and referenced to the residual solvent signal. ^{1}H NMR spectra are tabulated as follows: chemical shift, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s). Exact mass (HRMS) spectra were recorded on a JMS-HX/HX 110A mass spectrometer. Infrared (IR) spectra were obtained on a JASCO FT/IR-4100 FT-IR spectrometer with JASCO ATR PRO410-S.

General procedure for the synthesis of tetracyclic spiroindolines (8).

To a stirred mixture of **5a** (30 mg, 0.080 mmol) and $TsNH_2$ (20.5 mg, 0.12 mmol) in THF were added $Pd_2(dba)_3{\cdot}CHCl_3$ (2.1 mg, 3.9 μmol, 2.5 mol %), dppb (3.4 mg, 8.0 μmol, 10 mol %), and Cs_2CO_3 (52 mg, 0.16 mmol) at room temperature under argon. The mixture was stirred for 3 h at this temperature, and H_2O was added to the mixture. The whole was extracted with EtOAc. The extract was washed with H_2O, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over NH_2 silica gel with *n*-hexane–EtOAc (8:1) to give **8a** (29.3 mg, 72% yield) and **9a** (1.4 mg, 5.2% yield).

General procedure for the synthesis of spiroindoles (9).

To a stirred mixture of **5a** (30 mg, 0.080 mmol) and $BnNH_2$ (13 μL, 0.12 mmol) in THF were added $Pd_2(dba)_3{\cdot}CHCl_3$ (2.1 mg, 3.9 μmol, 2.5 mol %), dppe (3.2 mg, 8.0 μmol, 10 mol %), and Cs_2CO_3 (52 mg, 0.16 mmol) at 60 °C under argon. The mixture was stirred for 3 h at this temperature, and H_2O was added to the mixture. The whole was extracted with EtOAc. The extract was washed with H_2O, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (9:1 to 8:1) to give **9a** (18.5 mg, 68% yield).

Asymmetric synthesis of spiroindoline (8a) and spiroindole (9a).

To a stirred mixture of **5a** (30 mg, 0.080 mmol), $TsNH_2$ (20.5 mg, 0.12 mmol) and H_2O (1.4μL, 0.080) in THF were added $Pd_2(dba)_3{\cdot}CHCl_3$ (2.1 mg, 3.9 μmol, 2.5 mol %), (*R*)-SEGPHOS (4.9 mg, 8.0 μmol, 10 mol %), and Cs_2CO_3 (52 mg, 0.16 mmol) at 60 °C under argon. The mixture was stirred for 14 h at this temperature, and H_2O was added to the mixture. The whole was extracted with EtOAc. The extract was washed with H_2O, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over NH_2 silica gel with *n*-hexane–EtOAc (10:1 to 8:1) to give **8a** (15.7 mg, 38% yield, 65% ee [HPLC, Chiralcel-IC-3 column eluting with 65:35 *n*-hexane/*i*-PrOH at 0.75 mL/min, t_1 = 17.98 min (major enantiomer), t_2 = 26.74 min (minor enantiomer)]} and **9a** {4.1 mg, 15% yield and 71% ee [HPLC, Chiralcel-IC-3 column eluting with 65:35 *n*-hexane/*i*-PrOH at 0.75 mL/min, t_1 = 16.03 min (major enantiomer), t_2 = 39.26 min (minor enantiomer)]}.

Diethyl 2-[(1*H*-indol-3-yl)methyl]-2-(4-chlorobut-2-yn-1-yl)malonate (5a).
Brown oil; IR (neat): 3409 (NH), 2242 (C≡C), 1729 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.3 Hz, 6H), 2.83 (t, *J* = 2.2 Hz, 2H), 3.57 (s, 2H), 4.10-4.25 (m, 6H), 7.03 (d, *J* = 2.4 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.32 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.66 (dd, *J* = 8.0, 1.0 Hz, 1H), 8.08 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 23.1, 27.3, 30.8, 58.2, 61.7 (2C), 78.3, 82.9, 109.6, 111.0, 118.9, 119.5, 122.0, 123.4, 128.1, 135.8, 170.1 (2C). HRMS (FAB) calcd $C_{20}H_{21}ClNO_4$: $[M - H]^-$, 374.1165; found: $[M - H]^-$, 374.1168.

Diethyl 11-methylene-1-tosyl-2,3,10,10a-tetrahydro-1*H*-2,5a-methanoazepino[2,3-*b*]indole-4,4(5*H*)-dicarboxylate (8a).
Colorless solid; mp 164–165 °C; IR (neat): 3361 (NH), 1729 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 2.38 (s, 3H), 2.40 (d, *J* = 13.7 Hz, 1H), 2.48 (d, *J* = 13.7 Hz, 1H), 3.22 (d, *J* = 13.7 Hz, 2H), 4.09-4.10 (m, 1H), 4.13-4.39 (m, 4H), 4.44 (s, 1H), 4.66 (d, *J* = 4.1 Hz, 1H), 4.76 (s, 1H), 6.05 (d, *J* = 4.6 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.82 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.07-7.15 (m, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.86 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 21.4, 37.7, 39.9, 52.3, 57.7, 61.3, 62.1, 62.6, 84.0, 103.4, 110.7, 119.3, 122.9, 127.4 (3C), 129.0, 129.6 (2C), 137.6, 143.2, 148.8, 151.7, 170.9, 171.3. HRMS (FAB) calcd $C_{27}H_{30}N_2O_6S$: $[M^+]$, 510.1825; found: $[M^+]$, 510.1832.

Diethyl 2-methylenespiro[cyclohexane-1,3'-indol]-3-ene-5,5-dicarboxylate (9a).
Yellow oil; IR (neat): 1732 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22-1.28 (m, 6H), 2.37 (d, *J* = 14.3 Hz, 1H), 2.72 (d, *J* = 14.3 Hz, 1H), 4.16-4.30 (m, 4H), 4.56 (s, 1H), 4.87 (s, 1H), 6.18 (d, *J* = 10.3 Hz, 1H), 6.57 (d, *J* = 10.3 Hz, 1H), 7.27-7.35 (m, 2H), 7.37-7.43 (m, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.95 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 35.0, 55.5, 60.8, 62.3 (2C), 114.8, 121.5, 122.9, 125.4, 126.5, 128.5, 131.6, 137.6, 141.3, 155.4, 169.8, 170.1, 173.9. HRMS (FAB) calcd $C_{20}H_{22}NO_4$: $[M + H]^+$, 340.1549; found: $[M + H]^+$, 340.1555.

2,2-Diethyl 6,6-dimethyl 3,5,6a,7-tetrahydro-1*H*-indeno[1,7a-*b*]indole-2,2,6,6-tetracarboxylate (10a).
Yellow oil; IR (neat): 1735 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.2 Hz, 3H), 1.23-1.28 (m, 3H), 2.53 (d, *J* = 14.9 Hz, 1H), 2.66-2.90 (m, 5H), 3.68 (s, 3H), 3.73 (s, 3H), 4.00-4.34 (m, 5H), 4.76 (s, 1H), 5.70-5.76 (m, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 6.67 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.99 (dd, *J* = 8.0, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 13.9, 29.6, 29.7, 38.6, 39.9, 52.6, 52.9, 53.9, 54.7, 61.5, 65.6., 74.2, 109.4, 118.0, 119.4, 123.6, 128.2, 135.0, 140.9, 149.6, 169.3, 170.6, 171.0, 171.8. HRMS (FAB) calcd $C_{25}H_{29}NO_8$: $[M^+]$, 471.1893; found: $[M^+]$, 471.1901.

Diethyl 6,6-diacetyl 5,6,6a,7-tetrahydro-1*H*-indeno[1,7a-*b*]indole-2,2(3*H*)-dicarboxylate (10b).
Yellow oil; IR (neat): 3406 (NH), 1728 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 2.01 (s, 3H), 2.18 (s, 3H), 2.37 (d, *J* = 14.7 Hz, 1H), 2.64-2.73 (m, 3H), 2.84-2.91 (m, 2H), 4.04-4.20 (m, 4H), 4.43 (br s, 1H), 4.83

(s, 1H), 5.70-5.75 (m, 1H), 6.55 (d, J = 8.0 Hz, 1H), 6.70 (dd, J = 8.0, 8.0 Hz, 1H), 6.91 (dd, J = 8.0, 1.1 Hz, 1H), 7.00 (ddd, J = 8.0, 8.0, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 13.9, 26.3, 28.8, 29.5, 36.3, 40.4, 54.2, 55.0, 61.6 (2C), 73.3., 79.5, 110.2, 117.6, 119.8, 123.4, 128.3, 136.0, 141.1, 149.4, 170.8, 171.7, 203.1, 204.8. HRMS (FAB) calcd $C_{25}H_{29}NO_6$: [M^+], 439.1995; found: [M^+], 439.2000.

Acknowledgement

This work was supported by a Grant-in-Aid for the Encouragement of Young Scientists (A) from JSPS, Japan; Platform for Drug Design, Discovery, and Development from MEXT, Japan; research Grants from Takeda Science Foundation. A.I. and S.I. are grateful for Research Fellowships from the Japan Society for the Promotion of Science (JSPS) for Young Scientists.

References and Foot notes

† Current address: *Department of Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama, Kanagama 223-8522, Japan*

1. For reviews, see: (a) Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2589. (b) Tsuji, J. *Palladium Reagents and Catalysts, New Perspectives for the 21st Century*; Willey: UK, Chichester, 2004. pp 431. (c) Yoshida, M. *Heterocycles* **2013**, *87*, 1835.
2. Tsuji, J.; Watanabe, H.; Minami, I.; Shimizu, I. *J. Am. Chem. Soc*. **1985**, *107*, 2196.
3. (a) Minami, I.; Yuhara, M.; Watanabe, H.; Tsuji, J. *J. Organomet. Chem*. **1987**, *334*, 225. (b) Minami, I.; Yuhara, M.; Tsuji, J. *Tetrahedron Lett.* **1987**, *28*, 629.
4. Yoshida, M.; Ohno, S.; Namba, K. *Angew. Chem., Int. Ed*. **2013**, *52*, 13597.
5. (a) Duan, X.-H.; Guo, L.-N.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2006**, *8*, 5777. (b) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2007**, *72*, 1538. (c) Bi, H.-P.; Guo, L.-N.; Gou, F.-R.; Duan, X.-H.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2008**, *73*, 4713.
6. (a) Yoshida, M.; Nemoto, H.; Ihara, M. *Tetrahedron Lett*. **1999**, *40*, 8583. (b) Yoshida, M.; Komatsuzaki, Y.; Nemoto, H.; Ihara, M. *Org. Biomol. Chem.* **2004**, *2*, 3099.
7. (a) Yoshida, M.; Ihara, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 616. (b) Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. *J. Am. Chem. Soc*. **2003**, *125*, 4874. (c) Yoshida, M.; Fujita, M.; Ihara, M. *Org. Lett.* **2003**, *5*, 3325.
8. (a) Yoshida, M.; Morishita, Y.; Fujita, M.; Ihara, M. *Tetrahedron Lett*. **2004**, *45*, 1861. (b) Yoshida, M.; Morishita, Y.; Fujita, M.; Ihara, M. *Tetrahedron* **2005**, *61*, 4381.
9. (a) Ambrogio, I.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2006**, *8*, 2083. (b) Cacchi, S.; Giancarlo, F.; Eleonora, F. *Synlett* **2009**, 1817.
10. Calliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed*. **2007**, *46*, 8748.
11. (a) Liu, C.-T.; Wang, Q.-W.; Wang, C.-H. *J. Am. Chem. Soc*. **1981**, *103*, 4634. (b) Verbitski, S. M.; Mayne, C. L.; Davis, R. A.; Concepcion, G. P.; Ireland, C. M. *J. Org. Chem.* **2002**, *67*, 7124. (c) Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355. (d) Jadulco, R.; Edrada, R.; Ebel, R.; Berg, A.; Schaumann, K.; Wray, V.; Steube, K.; Proksch, P. *J. Nat. Prod.* **2004**, *67*, 78. (e) Neuss, N.; Neuss, M. N. In *The Alkaloids*; Brossi, A.; Suffness, M., Eds.; Academic: San Diego, 1990; Vol. 37, pp 229.
12. Nemoto, T.; Zhao, T.; Yokosaka, T.; Suzuki, Y.; Wu, R.; Hamada, Y. *Angew. Chem., Int. Ed*. **2013**, *52*, 2217.
13. A portion of this study has been reported as a preliminary communication: Iwata, A.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, N. *Chem. Commun*. **2014**, *50*, 298.
14. (a) Montgomery, T. D.; Nibbs, A. E.; Zhu, Y.; Rawal, V. H. *Org. Lett*. **2014**, *16*, 3480. (b) Gao, R.-D.; Liu, C.; Dai, L-X.; Zhang, W.; You, S.-L. *Org. Lett*. **2014**, *16*, 3919.
15. Jones, D. T.; Artman, G. D.; Williams, R. M. *Tetrahedron Lett.* **2007**, *48*, 1291.
16. (a) Montury, M.; Goré, J. *Synth. Commun*. **1980**, *10*, 873. (b) Elsevier, C. J.; Meijer, J.; Tadema, G.; Stehouwer, P. M.; Bos, H. J. T.; Vermeer, P. *J. Org. Chem*. **1982**, *47*, 2194.
17. $Pd_2(dba)_3 \cdot CHCl_3$ is one of the most efficient palladium(0) sources, see: Zalesskiy, S. S.; Ananikov, V. P. *Organometallics* **2012**, *31*, 2302.
18. (a) Ohno, H.; Hamaguchi, H.; Ohata, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1749. (b) Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T. *J. Am. Chem. Soc*. **2004**, *126*, 8744. For selected related works reported by our group, see: (c) Ohno, H.; Okano, A.; Kosaka, S.; Tsukamoto, K.; Ohata, M.; Ishihara, K.; Maeda, H.; Tanaka, T.; Fujii, N. *Org. Lett*. **2008**, *10*, 1171. (d) Inuki, S.; Yoshimitsu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett*. **2009**, *11*, 4478. (e) Okano, A.; Oishi, S.; Tanaka, T.; Fujii, N.; Ohno, H. *J. Org. Chem*. **2010**, *75*, 3396. (f) Yoshimitsu, Y.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett*. **2013**, *15*, 3046.
19. For a recent review on related catalytic dearomatization reactions, see: Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem. Int. Ed*. **2012**, *51*, 12662.
20. At present, formation of **10** through intermediate **C** (path e) cannot be completely excluded. We performed an additional experiment with a separately prepared propargyl tosylamide (S_N2 adduct from **5a**) to confirm that this reaction does not proceed via the first S_N2 reaction. In addition, the tetracyclic spiroindolines **8a** was not obtained from the elimination product **9a** under the reaction conditions.

Supplementary Material

Supplementary material was provided by the authors including further optimization of the reaction conditions, experimental procedures and characterization data for all new compounds.