Synthetic Methods

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Palladium-Catalyzed Tandem Cyclization of Bromoenynes through Aromatic C–H Bond Functionalization**

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Transition-metal-catalyzed cyclization of dienes, diynes, and enynes has received considerable attention in recent years.[1] In contrast, cyclization of this class of compounds through functionalization of a C–H bond of an aromatic ring has scarcely been investigated. We anticipated that tandem cyclization of enynes of type **1** (Scheme 1) could serve as a useful synthetic method for direct construction of tricyclic products such as **4** through the use of a nonfunctionalized aryl group.

Recent investigations in palladium chemistry has revealed that functionalization of a C–H bond of an aromatic group is highly effective for the construction of fused aromatic rings.[2–6] Although tandem cyclization involving C–H bond functionalization that generates two,[7] three,[8] or four carbon–carbon bonds[9] in a one-pot manner and leads to

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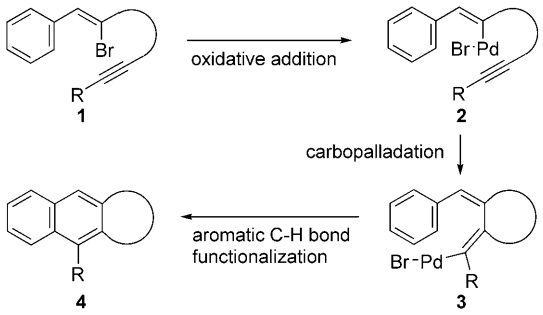
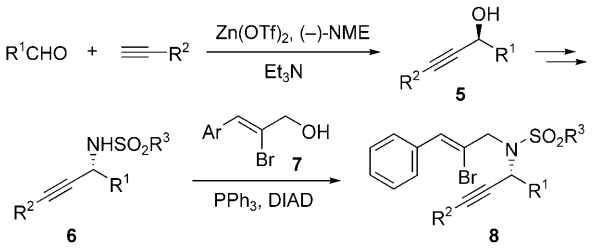


Scheme 1. Palladium-catalyzed tandem cyclization of bromoenynes.

monocyclized products is well documented, the tandem reaction involving a biscyclization process is extremely rare. Grigg et al. reported that an aryl halide bearing a carbon–carbon multiple bond and an additional aryl group undergoes bis- or triscyclization on treatment with a palladium(0) catalyst.[10] More recently, the palladium(0)-catalyzed tandem cyclization of alkyne-substituted phenyl iodide to form condensed aromatic rings[11] and the tandem biscyclization of allenenes with aryl halides[12] were also reported. However, to the best of our knowledge, there has been no report on the successful C–H functionalization of halogenated enynes. Herein we describe a tandem biscyclization of bromoenynes through intramolecular carbopalladation and functionalization of an aromatic C–H bond in the presence of a palladium catalyst.

Benzoisoindole is an important structural motif in medicinal chemistry and exists in many pharmaceutically useful compounds.[13] With a view to synthesizing nitrogen heterocycles, including benzoisoindole derivatives, we prepared enynes **8** as shown in Scheme 2. The chiral propargyl amine

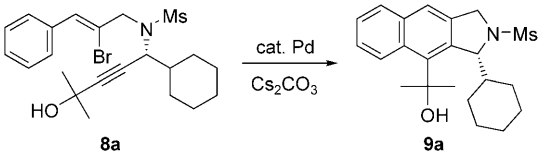


Scheme 2. Synthesis of bromoenynes through the procedure developed by Carreira and co-workers.

derivatives **6** could be prepared with high enantiomeric excess through the asymmetric alkynylation of aldehydes in the presence of zinc triflate and *N*-methylephedrine (NME) developed by Carreira and co-workers,[14] followed by amination of the resulting propargyl alcohols. In some cases, racemic propargylamines which were readily prepared by the reaction of lithium acetylide with aldehydes followed by amination, were used. Condensation of propargyl amines **6** with 3-aryl-2-bromoprop-2-en-1-ols **7** under Mitsunobu conditions gave the desired brominated enynes **8**.

With the requisite brominated enynes in hand, we next investigated the tandem cyclization of bromoenynes under various reaction conditions. After considerable experimentation, we found that bromoenyne **8a** yielded the desired cyclized product **9a** in the presence of a palladium catalyst and Cs_2CO_3 in EtOH (Table 1).[15] Other bases such as

Table 1: Optimization of reaction conditions using bromoenyne **8a**.[a]



Entry	Catalyst (mol%)	Solvent	*T*	*t* [h]	Yield [%][b]
1	$[Pd(PPh_3)_4]$ (6)	EtOH	reflux	1	26
2	$[Pd_2(dba)_3]\cdot CHCl_3$ (2)	EtOH	reflux	5	59
3	$[Pd(dppf)_2Cl_2]$ (2)	EtOH	reflux	3.5	38
4	$Pd(OAc)_2$ (6)	EtOH	reflux	2.5	74
5	$Pd(OAc)_2$ (2)	EtOH	reflux	7	64
6	$Pd(OAc)_2$ (2)	DMF	100 °C	21	35
7	$Pd(OAc)_2$ (2)	dioxane	reflux	21	27

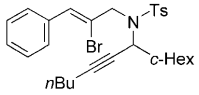
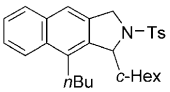
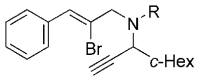
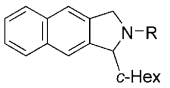
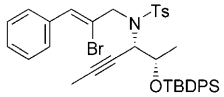
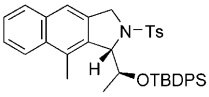
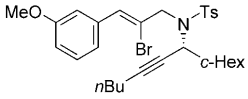
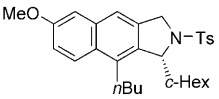
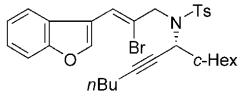
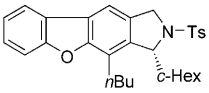
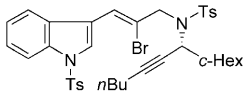
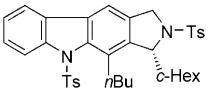
[a] Reactions were carried out with Cs_2CO_3 (2 equiv). [b] Yields of isolated products. dba = dibenzylideneacetone, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, Ms = methylsulfonyl.

NaOAc were ineffective. Of the palladium catalysts investigated (entries 1–4), palladium acetate most effectively catalyzed the desired conversion (74%, entry 4). Decreased loading of the catalyst (2 mol%) slightly lowered the yield of the tricyclic product **9a** (64%, entry 5). EtOH proved to be a better solvent than DMF or dioxane for the tandem cyclization (entries 6 and 7).

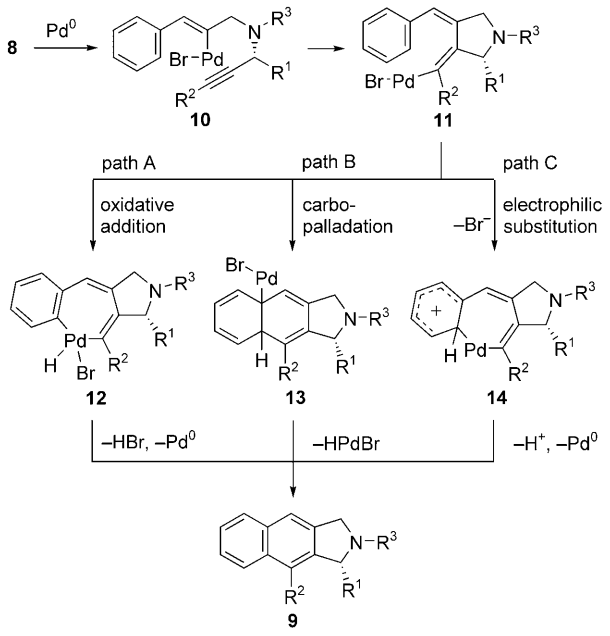
Next we investigated the tandem cyclization of various bromoenynes in the presence of palladium acetate and cesium carbonate in EtOH (Table 2). The cyclization of tosylamide **8b** having an *n*-butyl group on the alkyne terminus gave the desired benzoisoindole **9b** in 79% yield (entry 1). Bromoenyne **8c** (entry 2) and **8d** (entry 3), each with a terminal alkyne, yielded **9c** and **9d**, respectively, in moderate yields (46 and 56%, respectively). The reaction of lactate-derived enyne **8e** with a protected hydroxy group led to functionalized benzoisoindole **9e** (entry 4), although the yield was relatively low. It is noteworthy that bromoenynes having a heteroaromatic ring can also be used for the tandem cyclization involving the functionalization of the aromatic C–H bond. For example, treatment of enyne **8g** bearing a benzofuranyl group with a catalytic amount of palladium acetate and cesium carbonate yielded tetracyclic product **9g** in a shorter reaction time (1 h, entry 6). A similar result was obtained with *N*-tosylindole derivative **8h** in DMF (entry 7).[16]

As shown in Scheme 3, this tandem cyclization could proceed through the oxidative addition of bromoenyne **8** to palladium(0), carbopalladation onto the carbon–carbon triple bond of the intermediate **10**, and functionalization of an aromatic C–H bond of **11**. The final arylation step would be promoted through 1) intramolecular oxidative addition of an aromatic C–H bond to palladium(II) (path A),[2] 2) carbopalladation onto the aryl group in **11** and the subsequent β-hydride elimination (path B),[3] or 3) electrophilic attack by the palladium(II) intermediate **11** to the aromatic carbon atom

Table 2: Tandem cyclization of bromoenynes **8**.[a]

Entry	Substrate		*t* [h]	Product		Yield [%][b]
1		**8b**	6		**9b**	79
						
2		**8c** (R = Ms)	6		**9c** (R = Ms)	46
3		**8d** (R = Ts)	2		**9d** (R = Ts)	56
4[c]		**8e**	24		**9e**	39
5		**8f**	5		**9f**	57
6		**8g**	1		**9g**	59
7[d]		**8h**	18		**9h**	51

[a] Reactions were carried out with $Pd(OAc)_2$ (2 mol%) and Cs_2CO_3 (2 equiv) in EtOH. [b] Yields of isolated products. [c] An increased amount of $Pd(OAc)_2$ (4 mol%) was used. [d] DMF was used as the solvent. Ts = toluene-4-sulfonnyl, *c*-Hex = cyclohexyl.



Scheme 3. Possible reaction pathways for functionalization of the C–H bond.

followed by deprotonation and reductive elimination (path C).[4] It is difficult to say at present which is the most favorable reaction course, as is also the case in related palladium-catalyzed functionalizations of aromatic C–H bonds.[5]

In conclusion, we have developed a novel tandem cyclization of bromoenynes for the synthesis of tri- and tetracyclic heterocycles. This study has demonstrated for the first time that enynes can undergo a tandem cyclization involving functionalization of C–H bonds of benzene or heteroaromatic rings, such as benzofuran and indole, in the presence of a palladium catalyst. This tandem cyclization in which two carbon–carbon bonds are formed is synthetically useful since complex heterocyclic skeletons can be constructed directly from readily prepared enynes.

Experimental Section

General procedure for condensation of propargylamine derivatives **6** with 3-aryl-2-bromoprop-2-en-1-ols **7**: Diisopropyl azodicarboxylate (DIAD; 2.2 equiv) was added dropwise to a stirred mixture of **6** (1 equiv), **7** (2.2 equiv), and PPh_3 (2.2 equiv) in THF at 0 °C. The mixture was stirred for 4 h at room temperature and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with an eluent of *n*-hexane/EtOAc to give **8**.

General procedure for the palladium-catalyzed cyclization of bromoenynes **8** (Table 1, entry 5): A mixture of **8a** (124 mg, 0.265 mmol), Cs_2CO_3 (173 mg, 0.531 mmol), and $Pd(OAc)_2$ (1.2 mg, 0.0531 mmol; 2 mol%) in EtOH (1.5 mL) was heated under reflux for 7 h. After cooling the mixture, saturated NH_4Cl was added. The mixture was then extracted with EtOAc and dried over $MgSO_4$. Concentration under reduced pressure gave an oily residue, which was purified by column chromatography on silica gel with *n*-hexane/EtOAc (10:1) to give **9a** (65.7 mg, 64% yield) along with an unidentified minor product (2.5 mg, 3% yield). **9a**: colorless oil; $[\alpha]_D^{28} = +31.4$ ($c = 0.62$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3545$ (OH), 1336

(NSO_2), 1153 cm^{-1} (NSO_2); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.90$–1.28 (m, 5H), 1.58–1.85 (m, 6H), 1.96 (s, 3H; CMe), 2.03 (s, 3H; CMe), 2.55 (s, 3H; SO_2Me), 4.65 (dd, $J = 16.8$, 1.2 Hz, 1H; NCH_aH_b), 4.80 (dd, $J = 16.8$, 1.2 Hz, 1H; NCH_aH_b), 5.97 (d, $J = 1.2$ Hz, 1H; 1-H), 7.42–7.50 (m, 2H; Ar), 7.61 (s, 1H; Ar), 7.79–7.82 (m, 1H; Ar), 8.25 ppm (dd, $J = 9.9$, 2.7 Hz, 1H; Ar); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta = 26.2$, 26.3, 26.7 (2C), 31.4, 32.6, 34.2 (2C), 47.0, 53.4, 71.9, 75.2, 120.8, 125.0, 125.1, 126.5, 129.0, 130.3, 134.6, 136.4, 137.3, 139.0 ppm; MS (FAB): *m/z* (%): 388 ($[M+H^+]$) (53), 154 (100); HRMS (FAB): calcd for $C_{22}H_{30}NO_3S$ $[M+H^+]$: 388.1946; found: 388.1948.

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[16] The reaction in EtOH led to cleavage of the tosyl group on the nitrogen atom without formation of the desired tetracyclic product **9h**.

