COMMUNICATIONS doi.org/10.1002/adsc.202100763 Advanced Synthesis & Catalysis

Pd-Catalyzed Cyclization of Alkynyl Norbornene Derivatives for the Synthesis of Benzofused Heteroarenes

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Manuscript received: June 19, 2021; Revised manuscript received: August 13, 2021;
Version of record online: ■■, ■■

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202100763

Abstract: Modular approaches, which allow a systematic variation of heteroaromatic cores and substituents, are crucial for the development of heteroaromatic drug candidates and organic functional materials. A new strategy involving the cyclization of heteroarenes tethered with alkynes through a norbornene bridge was developed. The precursors were readily prepared by a three-component coupling process of heteroaryl halides, norbornadiene, and terminal alkynes. The Pd catalytic system derived from $Pd(OAc)_2$ and 2-(pyrazol-1-yl) pyridine transformed a variety of five-membered heteroarenes to the corresponding benzofused products, including (di)benzothiophene, indazole, carbazole, indole, and benzofuran, with aryl and alkyl substituents at the C4(C7) position. During the cyclization process, the norbornene ring underwent a retro-Diels-Alder reaction, serving as an acetylene synthon. This approach was used to synthesize naphthalene derivatives from electron-rich arenes, demonstrating its versatility in the annulation of (hetero)aromatic rings.

Keywords: Palladium; Norbornene; Alkynes; Heterocycles; Cyclization; C–H functionalization

The 5,6-fused bicyclic heteroaromatic ring system represents an indispensable subclass of heterocycles in the development of biologically active compounds and organic functional materials.[1] The position and type of substituents are modulated to provide the desired biological and physicochemical properties, using the heterocyclic system as the core. In particular, biologically active compounds with C4(C7)-substituted fused bicyclic rings (Figure 1) are important drug candidates against schizophrenia,[2] autoimmune diseases,[3] cancers,[4] and pulmonary diseases.[5] Therefore, strategies that are broadly applicable to the synthesis of a series of 5,6-fused bicycles, including benzothiophene, benzofuran, indole, and indazole, are highly desirable for examining the isostere effect of heterocycles.[6] The installation of functional groups at the parent cores is one approach that affords functionalized 5,6-benzofused heteroarenes.[7] Recently, this approach has been greatly facilitated by transition metal-catalyzed C–H functionalization.[8] Although the C–H bonds of the five-membered rings have been selectively transformed to C–C and C-heteroatom bonds,[9] remote C–H functionalization reactions at the aryl rings mostly rely on directing group-assisted approaches.[10] Alternatively, to produce C4(C7)-substituted benzofused heteroarenes, cyclization has been performed with alkyne-tethered heteroarenes using Au and Ag catalysts (Figure 2A).[11] However, the cyclization precursors are prepared by the addition of alkyne group donors to carbonyl group-containing heteroarenes, which typically require additional steps during preparation.

To produce C4(C7)-substituted benzofused heteroarenes, we envisioned a strategy involving norbornadiene (NBD). Recently, we demonstrated that the incorporation of NBD as an acetylene synthon led to the benzannulation of five-membered heteroarenes through a Pd-catalyzed cyclization followed by a retro-Diels-Alder reaction (Figure 2B, top).[12] In addition to the Pd-catalyzed 1:2 coupling reaction between heteroaryl halides and NBD, a 2:1 coupling reaction was developed to synthesize polycyclic heteroaromatic systems (Figure 2B, middle).[13] Consequently, it was considered that C4(C7)-substituted benzofused heteroarenes could arise from alkynyl norbornene derivatives, through a simultaneous retro-Diels-Alder reaction of the norbornene ring, which results in π-

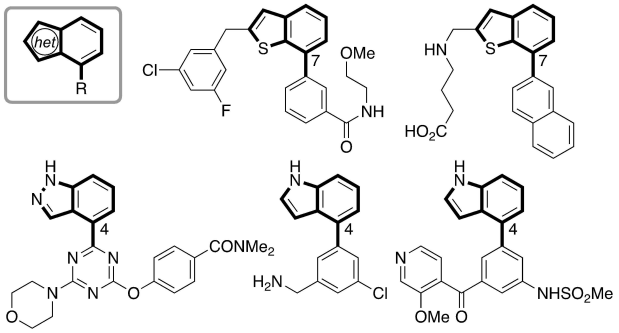


Figure 1. Biologically active compounds with C4(C7)-substituted benzofused heteroarenes.

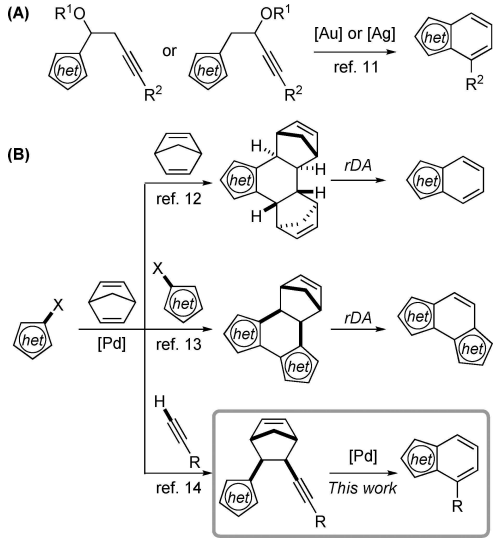
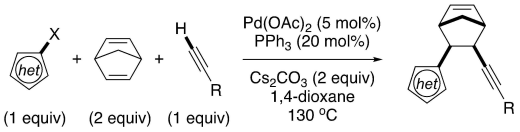


Figure 2. Strategies for preparing substituted 5,6-benzofused heteroarenes.

conjugated structures (Figure 2B, bottom). This approach provides increased accessibility to the cyclization precursors prepared by Pd-catalyzed three-component reactions, using readily available heteroaryl halides, NBD, and terminal alkynes in one step (Scheme 1).[14] In the key cyclization process, the alkyne substituent was transferred to the C4(C7) substituent, while a variety of five-membered heteroarenes were incorporated into the 5,6-fused bicyclic system.

A slightly modified three-component coupling[14] procedure readily afforded the alkynyl norbornene, **1 a**,

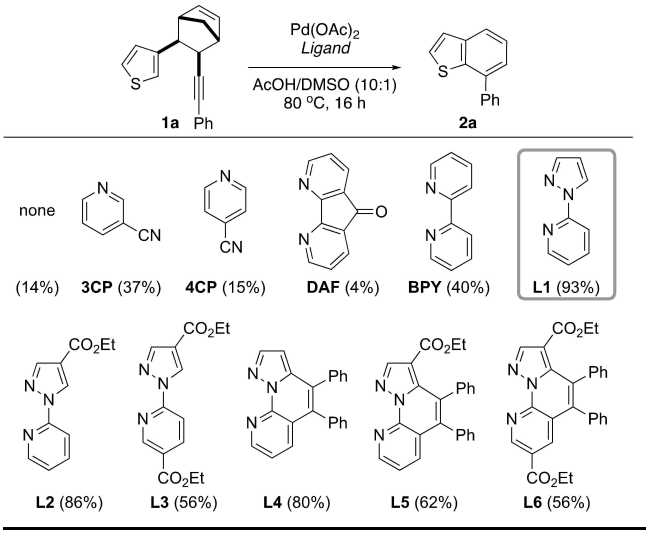


Scheme 1. Preparation of cyclization precursors.

allowing the examination of various catalytic systems for the cyclization (Table 1). To facilitate the intramolecular reaction, a large volume of solvents was employed, which however could be reduced for other substrates (vide infra). Au and Ag catalytic systems, which are useful in the electrophilic cyclization of alkynyl heteroarenes with a flexible linker, afforded a trace amount of the cyclization product, **2 a** (see Supporting Information).[11] Based on our previous study on the development of new nitrogen bidentate ligands that provide electrophilic Pd catalysts,[15] we examined a series of nitrogen ligands with $Pd(OAc)_2$. $Pd(OAc)_2$ alone afforded a low yield, and the addition of 3- and 4-cyano pyridines (**3CP** and **4CP**, respectively) did not significantly improve the yield. In contrast to the low reactivity of 4,5-diazafluorenone (**DAF**) and 2,2′-bipyridine (**BPY**), 2-(pyrazol-1-yl) pyridine (**L1**) generated a high yield.[16] The **L2** and **L3** ligands, which are more electron-deficient than **L1**, afforded lower yields than that of **L1**. In addition, conformationally rigid tricyclic ligands, **L4**–**L6**, were inferior to their conformationally flexible counterparts, **L1**–**L3**.

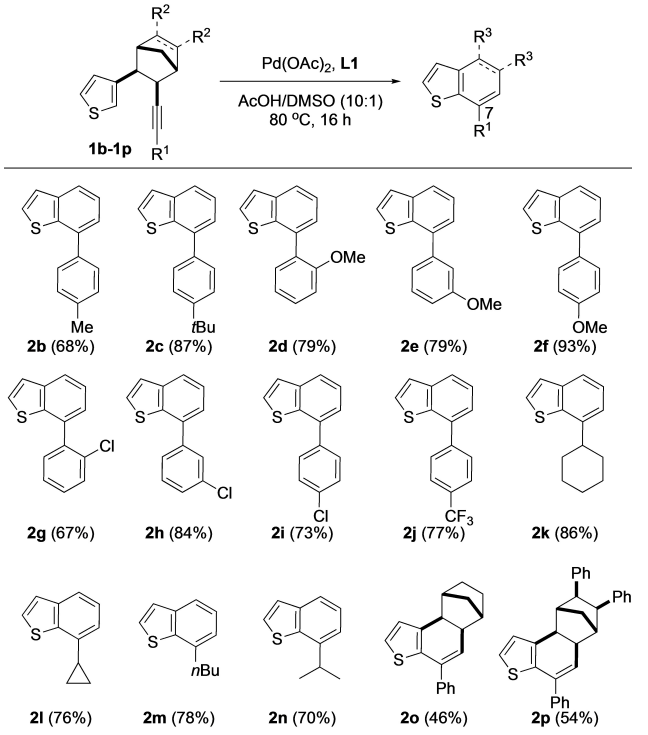
The scope of alkynes was investigated (Table 2), using **L1** as the optimal ligand. Aryl groups substituted with alkyl, methoxy, chloro, and trifluoromethyl groups afforded 7-aryl benzothiophenes in good yields (**2 b**–**2 j**). Notably, the position of the substituents on the aryl ring did not affect the cyclization, as demonstrated in the reactions of *o*-, *m*-, and *p*-chloroarene derivatives as well as anisole-containing ones (**2 d**–**2 i**). Furthermore, this cyclization approach

Table 1. Ligand effect on the Pd-catalyzed cyclization of the alkynyl norbornene, **1 a**.[a]



[a] Reaction conditions: **1 a** (0.40 mmol), $Pd(OAc)_2$ (0.010 mmol), ligand (0.010 mmol), AcOH (16 mL), DMSO (1.6 mL), 80 °C, and 16 h. Isolated yields.

Table 2. Scope of alkynes.[a]



[a] Reaction conditions: alkynyl thiophene (0.40 mmol), $Pd(OAc)_2$ (0.010 mmol), **L1** (0.010 mmol), AcOH (16 mL), DMSO (1.6 mL), 80 °C, and 16 h. Isolated yields.

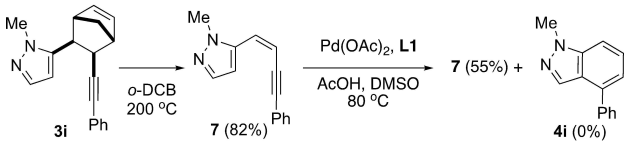
afforded 7-alkyl benzothiophenes (**2k**–**2n**), which are often difficult to prepare by the conventional cross-coupling reactions of 7-halobenzothiophenes. In addition, cyclization reactions of norbornane derivatives were performed to produce nonplanar heterocycles, **2o** and **2p**, without retro-Diels-Alder reactions because of the absence of the olefin in the bridged bicyclic rings.

Next, the scope of heteroarenes was investigated by varying their substituents and types (Table 3). The methyl substituent of the thiophene ring was tolerated in the cyclization reactions (entries 1 and 2). When thiophene was attached to the norbornene unit proximal to the sulfur atom, the obtained yields were low (entries 3 and 4). These results indicate that the nucleophilic site of heteroarenes is favored during cyclization because the α-carbon atom proximal to the sulfur atom in thiophene is a more electron-rich position than the β-carbon atom. However, the presence of an electron-withdrawing group on the thiophene ring created a marginal impact (entries 5 and 6). Product **4e** generated crystals that are suitable for X-ray analysis, confirming its structure.[17] Besides thiophene, both regioisomers of benzothiophene derivatives were transformed to cyclization products, **4g** and **4h** (entries 7 and 8). Furthermore, pyrazole derivatives, which have not been used in electrophilic cyclization reactions, were successfully converted to the corresponding indazoles (entries 9 and 10). The low yield of **4j**, compared to that of the regioisomer **4i**, is attributed to the electronic effect observed in the cyclization of thiophenes, which was not overcome by increasing the amounts of the catalyst and ligand. This is because the pyrazole C4 position is more nucleophilic than the C5 position. Indole, pyrrole, and furan derivatives underwent cyclization reactions to afford the corresponding carbazole **4k**, indole **4l**, and benzofuran **4m**, respectively (entries 11–13). For the model substrate **1a** that is susceptible to intermolecular reactions, a large volume of solvents was required (Table S1). However, reducing the amount of solvents did not generate a significant impact on yields with substrates that are less likely to undergo dimerization than monosubstituted thiophene **1a**, as demonstrated in the reactions of benzothiophene **3g** and disubstituted pyrrole **3l**.

The cyclization reaction was used to synthesize naphthalene derivatives using aryl norbornene compounds (Table 4). Similar to heteroarenes, electron-rich arenes with available nucleophilic sites were amenable to the synthesis of functionalized naphthalenes. For example, alkynyl dimethoxybenzene, **5a**, afforded an excellent yield of **6a** (entry 1). However, when two nucleophilic sites were present, regioisomers were formed, and the less hindered regioisomers, such as **6b** and **6c**, were preferred (entries 2 and 3). The xylyl and tolyl norbornenes, **5d** and **5e**, produced inferior results, presumably because they are less electron-rich than arenes with methoxy and dimethylamino groups (entries 4 and 5).

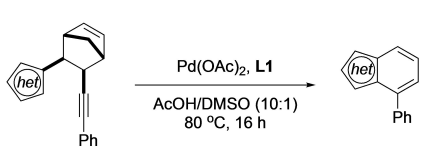
The effect of the rigid, nonconjugated structure enabled by the norbornene bridge was investigated, using a bridged bicyclic ring-free structure. Heating the cyclization precursor, **3i**, afforded the corresponding (*Z*)-enyne, **7**, by a retro-Diels-Alder reaction (Scheme 2). In contrast to the norbornene precursors, **7** did not produce the desired cyclization product, illustrating the advantage of the norbornene bridge that puts the heterocycle and the alkyne close together compared to the π-conjugated planar system of **7** (Figure S2).

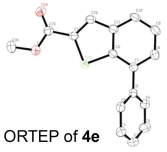
Based on previous studies, a plausible reaction mechanism is proposed (Figure 3).[18] The coordination of substrate **1a** to Pd catalyst **I** activates the alkyne π-system, facilitating the electrophilic cyclization of

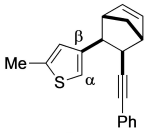
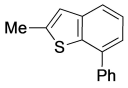
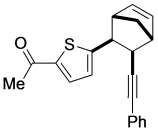
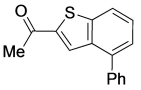
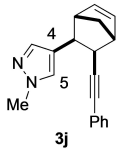
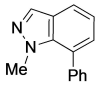
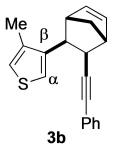
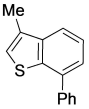
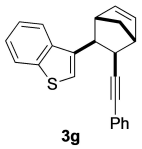
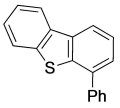
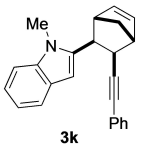
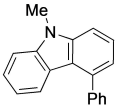
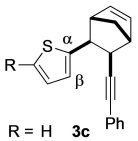
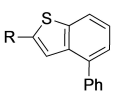
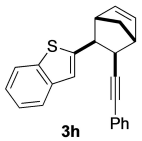
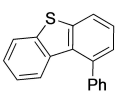
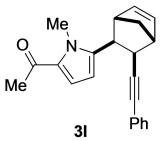
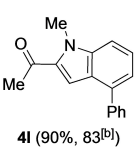
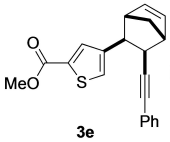
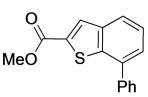
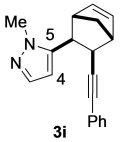
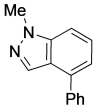
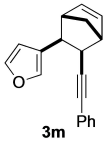


Scheme 2. Retro-Diels-Alder reaction followed by cyclization.

Table 3. Scope of heteroarenes.[a]





entry	reactant	product	entry	reactant	product	entry	reactant	product
1			6			10		
	3a	**4a** (75%)		**3f**	**4f** (55%)		**3j**	**4j** (22%, 26%[b,c])
2			7			11		
	3b	**4b** (84%)		**3g**	**4g** (71%, 66%[b])		**3k**	**4k** (86%)
3 4	 R = H **3c** Me **3d**	 **4c** (34%) **4d** (59%)	8			12		
				3h	**4h** (73%)		**3l**	**4l** (90%, 83[b])
5			9			13		
	3e	**4e** (73%)		**3i**	**4i** (16%, 86%[b,c])		**3m**	**4m** (58%)

[a] Reaction conditions: alkynyl heteroarene (0.40 mmol), $Pd(OAc)_2$ (0.010 mmol), **L1** (0.010 mmol), AcOH (16 mL), DMSO (1.6 mL), 80 °C, and 16 h. Isolated yields.
[b] AcOH (4.0 mL) and DMSO (0.40 mL).[c] $Pd(OAc)_2$ (0.020 mmol), **L1** (0.020 mmol), and 100 °C. ORTEP diagram of **4e** with anisotropic displacement parameters at 50% probability.

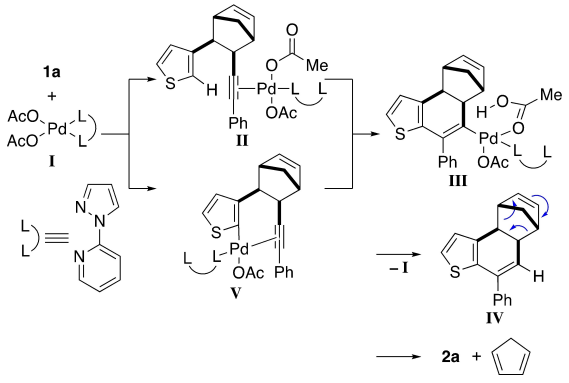
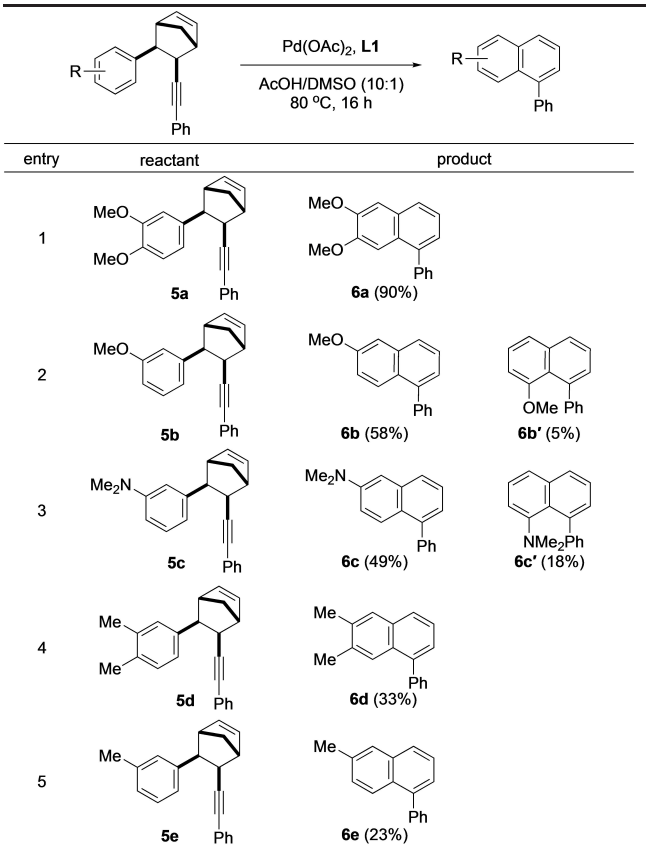


Figure 3. Proposed mechanism.

complex **II** through a concerted mechanism for the cleavage of the C–H bond, the formation of the C–C bond, and the palladation at the alkyne, which is supported by a preliminary DFT calculation (Figure S3). The protodepalladation of **III** affords **IV** while regenerating the Pd(II) complex, **I**. A subsequent retro-Diels-Alder reaction of **IV** produces product **2a**. Alternatively, electrophilic concerted metalation-deprotonation (*e*CMD) of the heteroaromatic ring using the Pd(II) complex, **I**, first occurs to produce **V**;[19] a subsequent migratory insertion in the alkyne and protonation may generate the product. In both cases, the use of the pyrazolopyridine ligand could be beneficial to generate a vacant coordination site by facile dissociation of the weakly coordinating pyrazole part, yet flexibly provide the stabilization effect as a bidentate ligand. However, the formation of a considerable amount of more sterically hindered isomers, **6b′** and **6c′**, in the cyclization of **5b** and **5c**, respectively (Table 4, entries 2 and 3), is in favor of the former mechanism because the metalation is prohibited by the steric hindrance from adjacent substituents.[15]

In conclusion, we developed Pd-catalyzed cyclization reactions of alkynyl (hetero)arenes for the synthesis of benzofused (hetero)cyclic compounds. The norbornene bridge spacing between the (hetero)aryl ring and alkynyl group facilitates the cyclization

Table 4. Scope of arenes.[a]



[a] Reaction conditions: alkynyl arene (0.40 mmol), $Pd(OAc)_2$ (0.010 mmol), **L1** (0.010 mmol), AcOH (16 mL), DMSO (1.6 mL), 80 °C, and 16 h. Isolated yields.

reaction using the Pd catalytic system while functioning as an acetylene synthon. This modular strategy allows access to a wide range of benzofused heteroarenes with various substituents, systematically. Selective cyclization was achieved using Pd catalysts, which contained pyrazolopyridine ligands, and further applications of this catalytic system will be reported in due course.

Experimental Section

Representative procedure for cyclization. $Pd(OAc)_2$ (2.2 mg, 0.010 mmol) and **L1** (1.5 mg, 0.010 mmol) were added to the solution of a substrate (0.40 mmol), AcOH (16 mL), and DMSO (1.6 mL) in a 40 mL-glass vial. This mixture was stirred in a preheated reaction block at 80 °C for 16 h. Afterward, the reaction mixture was cooled to 25 °C, treated with toluene (30 mL), and concentrated under reduced pressure to evaporate the AcOH. The residue was purified by flash column chromatography to obtain the desired product.

Acknowledgements

This research was supported by the National Research Foundation of Korea (NRF-2019R1A2C1007852 and NRF-2019R1A4A1028007).

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