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Palladium(II)-catalyzed Intermolecular Cascade Cyclization of Methylenecyclopropanes with Aromatic Alkynes: Construction of Spirocyclic Compounds Containing Indene and 1,2-Dihydronaphthalene Moieties

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Abstract: A palladium(II)-catalyzed intermolecular cascade cyclization of methylenecyclopropanes with aromatic alkynes is reported in this paper. The reaction involves a migratory insertion of alkyne, an intramolecular Heck-type reaction, and β-H elimination, providing a series of spirocyclic compounds containing indene and 1,2-dihydronaphthalene moieties in moderate to excellent yields upon heating.

Keywords: palladium catalysis; methylenecyclopropane; cyclization

Palladium catalysis is a central method in carbon-carbon and carbon-heteroatom bond formation to rapidly assemble molecular complexity.[1] During recent years, cascade reactions have attracted a substantial amount of attention from organic chemists, as a means to achieve multiple bond-forming to lead to carbo- and heterocyclic frameworks in one pot, giving complicated organic molecules.[2] With well understood multistep catalytic cycles, palladium-catalyzed cross-coupling reactions provide a promising basis for the design of cascade reactions.[3] In addition, it is also well known that they have a good tolerance towards a range of functional groups. In these palladium-catalyzed cross-coupling reactions, the Heck reaction, also known as the Mizoroki-Heck reaction, disclosed independently by Heck and Mizoroki,[4] is one of the most convenient and powerful methods for carbon-carbon double bond formation in the synthesis of functionalized organic molecules, natural products, pharmaceuticals, agrochemicals, and functional materials.[5]

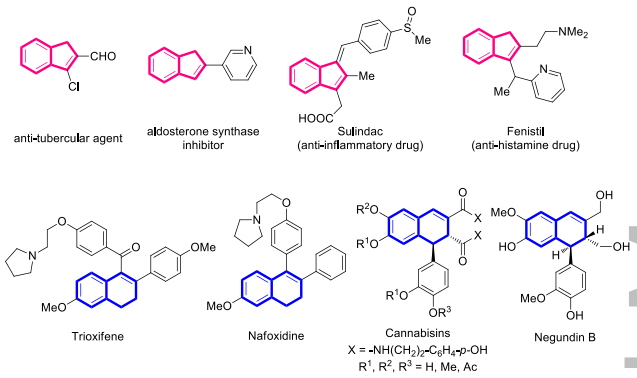
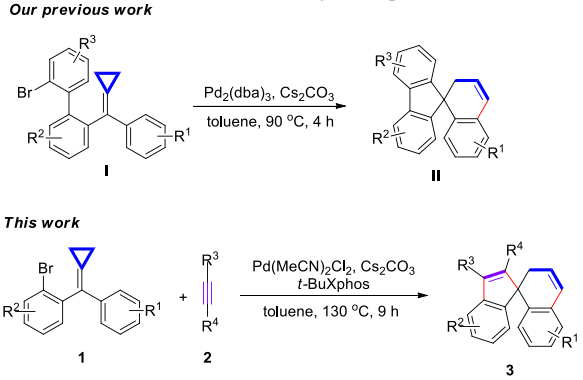


Figure 1. Representative natural products and drug molecules containing indene or 1,2-dihydronaphthalene core unit.

Indene scaffolds as a vital class of organic compounds are used in many synthetic and pharmaceutical fields. During recent years, substituted indene derivatives, such as anti-tubercular agents,[6] aldosterone synthase inhibitors,[7] anti-inflammatory drugs,[8] and anti-histamine drugs,[9] have been reported in medicinal chemistry. Furthermore, 1,2-dihydronaphthalene moieties exist in various natural products which have potent and therapeutic values for medical chemistry, including trioxifenes,[10] nafoxidenes,[11] cannabisins,[12] and negundin B[13] (Figure 1). Thus, it is significant to develop new approaches for the rapid construction of indene and 1,2-dihydronaphthalene moieties.



Scheme 1. Previous work and this work.

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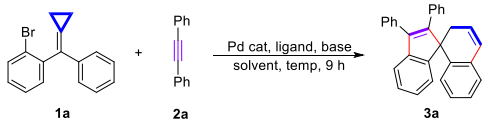
Methylenecyclopropanes (MCPs), containing a highly strained cyclopropane ring with an exo-methylene moiety,[14] are readily accessible and highly reactive molecules which are frequently utilized as building blocks for the synthesis of natural products and medicine precursors in organic synthesis.[15] MCPs can undergo diverse ring-opening reactions due to a thermodynamic driving force derived from the release of the cyclopropane ring strain under transition metal catalysis[16] and Lewis acid catalysis.[17] In the past decades, transition-metal-catalyzed reactions of MCPs have been extensively investigated because of their unique structural features and electronic properties. In 2018, we disclosed a novel palladium-catalyzed intramolecular cascade cyclization of MCPs **I**, affording spirocyclic compounds **II** containing fluorene and 1,2-dihydronaphthalene moieties in good yields (Scheme 1, our previous work).[18] This transformation proceeded through an intramolecular Heck-type reaction and a β-H elimination, affording products having three aromatic moieties. On the basis of our previous work, we envisaged that the use of more easily available ortho-bromine tethered MCPs **1** could also afford spirocyclic skeletons bearing an indene and a 1,2-dihydronaphthalene moieties through an intermolecular cascade cyclization with aromatic alkynes under palladium catalysis (Scheme 1, this work).

Table 1. Optimization of the reaction conditions for the synthesis of **3a**.

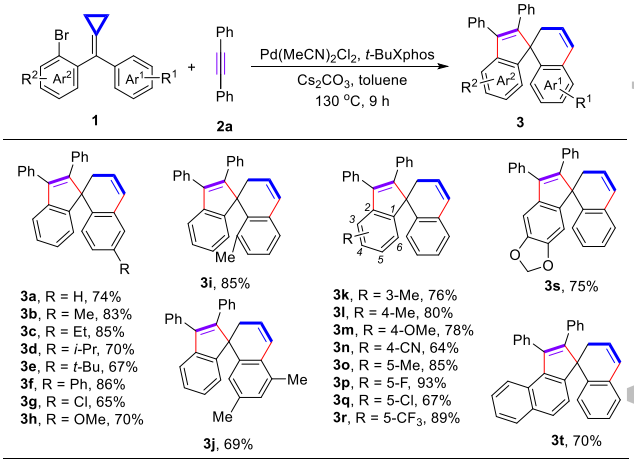


1a **2a** **3a**

entry	catalyst	ligand	base	solvent	temp (°C)	yield (%)[a]
1	$Pd(PPh_3)_4$	Ph_3P	Cs_2CO_3	toluene	100	33
2	$Pd(TFA)_2$	Ph_3P	Cs_2CO_3	toluene	100	31
3	$Pd(OAc)_2$	Ph_3P	Cs_2CO_3	toluene	100	complex
4	$[Pd(allyl)Cl]_2$	Ph_3P	Cs_2CO_3	toluene	100	complex
5	$Pd(PPh_3)_2Cl_2$	Ph_3P	Cs_2CO_3	toluene	100	complex
6	$Pd_2(dba)_3$	Ph_3P	Cs_2CO_3	toluene	100	NR
7	$Pd(PhCN)_2Cl_2$	Ph_3P	Cs_2CO_3	toluene	100	38
8	$Pd(MeCN)_2Cl_2$	Ph_3P	Cs_2CO_3	toluene	100	40
9	$Pd(MeCN)_2Cl_2$	$(4\text{-}FC_6H_4)_3P$	Cs_2CO_3	toluene	100	24
10	$Pd(MeCN)_2Cl_2$	$(4\text{-}MeOC_6H_4)_3P$	Cs_2CO_3	toluene	100	32
11	$Pd(MeCN)_2Cl_2$	*t*-Bu_3P	Cs_2CO_3	toluene	100	18
12	$Pd(MeCN)_2Cl_2$	dppp	Cs_2CO_3	toluene	100	46
13	$Pd(MeCN)_2Cl_2$	dppf	Cs_2CO_3	toluene	100	50
14	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	Cs_2CO_3	toluene	100	55
15	$Pd(MeCN)_2Cl_2$	1,10-phen	Cs_2CO_3	toluene	100	NR
16	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	K_2CO_3	toluene	100	NR
17	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	Na_2CO_3	toluene	100	NR
18	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	K_3PO_4	toluene	100	35
19	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	Na_3PO_4	toluene	100	NR
20	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	Na_2HPO_4	toluene	100	NR
21	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	NaTFA	toluene	100	NR
22	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	CsOAc	toluene	100	NR
23	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	DMAP	toluene	100	NR
24	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	Cs_2CO_3	PhCl	100	18
25	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	Cs_2CO_3	PhOMe	100	complex
26	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	Cs_2CO_3	dioxane	100	complex
27	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	Cs_2CO_3	DMF	100	complex
28	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	Cs_2CO_3	DME	100	complex
29	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	Cs_2CO_3	$PhCF_3$	100	complex
30	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	Cs_2CO_3	DCE	100	NR
31	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	Cs_2CO_3	toluene	110	65
32	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	Cs_2CO_3	toluene	120	74
33	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	Cs_2CO_3	toluene	130	76
34	$Pd(MeCN)_2Cl_2$	*t*-BuXphos	Cs_2CO_3	toluene	140	70

Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), catalyst (10.0 mol %), ligand (10.0 mol %), base (0.2 mmol), solvent (1.0 mL). [a] Yields are determined by 1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. NR denotes no reaction.

To examine the feasibility of this hypothesis, we utilized *ortho*-bromodiphenylmethylenecyclopropane **1a** as a model substrate to react with 1,2-diphenylacetylene **2a** in the presence of palladium catalyst, ligand, and base. The screening results are summarized in Table 1. Initially, we examined various palladium catalysts (10 mol%), such as $Pd(PPh_3)_4$, $Pd(TFA)_2$, $Pd(OAc)_2$, $[Pd(allyl)Cl]_2$, $Pd(PPh_3)_2Cl_2$, $Pd_2(dba)_3$, $Pd(PhCN)_2Cl_2$, and $Pd(MeCN)_2Cl_2$, in the presence of Ph_3P (10.0 mol%) and Cs_2CO_3 (2.0 equiv) in toluene at 100 °C within 9 hours (Table 1, entries 1-8). We found that $Pd(MeCN)_2Cl_2$ was an effective catalyst, delivering the desired product **3a** in 40% yield (Table 1, entry 8). Next, the examination of various phosphorus- and nitrogen-containing ligands including $(4\text{-}FC_6H_4)_3P$, $(4\text{-}MeOC_6H_4)_3P$, *t*-Bu_3P, 1,3-bis(diphenylphosphino)propane (dppp), 1,1'-bis(diphenylphosphino)ferrocene (dppf), *t*-BuXphos, and 1,10-phenanthroline in this reaction revealed that *t*-BuXphos was very eligible and the yield of **3a** could be improved to 55% (Table 1, entries 9-15). After exploring catalysts and ligands, the base effects were investigated utilizing K_2CO_3, Na_2CO_3, K_3PO_4, Na_3PO_4, Na_2HPO_4, NaTFA, CsOAc, and 4-dimethylaminopyridine (DMAP) under the standard conditions (Table 1, entries 16-23). The desired product **3a** was afforded in 35% yield when K_3PO_4 was used as a base in this transformation (Table 1, entry 18) and no reaction occurred when K_2CO_3, Na_2CO_3, Na_3PO_4, Na_2HPO_4, NaTFA, CsOAc, and DMAP were used under identical conditions (Table 1, entries 16-17 and 19-23). Then, the solvent effects were examined with chlorobenzene (PhCl), anisole (PhOMe), dioxane, N,N-dimethylformamide (DMF), 1,2-dimethoxyethane (DME), benzotrifluoride ($PhCF_3$), and 1,2-dichloroethane (DCE) under the standard conditions (Table 1, entries 24-30). We observed that the desired product **3a** was given in 18% yield in PhCl (Table 1, entry 24), and a complex mixture was formed in PhOMe, dioxane, DMF, and DME (Table 1, entries 25-29) and this transformation did not take place in DCE under the standard conditions (Table 1, entry 30). Finally, we screened the reaction temperature at 110, 120, 130, and 140 °C, respectively (Table 1, entries 31-34) and found that the reaction should be carried out at 130 °C, giving **3a** in 76% yield (Table 1, entry 33). Therefore, the optimization of the reaction conditions was identified that the reaction should be carried out using $Pd(MeCN)_2Cl_2$ (10.0 mol%) as the catalyst in the presence of *t*-BuXphos (10.0 mol%) and Cs_2CO_3 (2.0 equiv) in toluene at 130 °C within 9 hours.



[a] Reactions were carried out by use of **1** (0.2 mmol), **2a** (0.4 mmol), and Cs_2CO_3 (0.4 mmol) in toluene (2.0 mL) with $Pd(MeCN)_2Cl_2$ (10.0 mol%), *t*-BuXphos (10.0 mol%) at 130 °C within 9 hours, isolated yields.

Scheme 2. Substrate scope for synthesis of **3a-3t**.[a]

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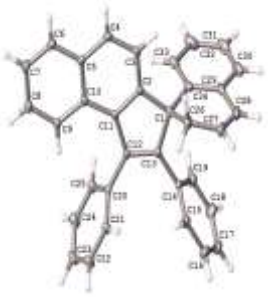
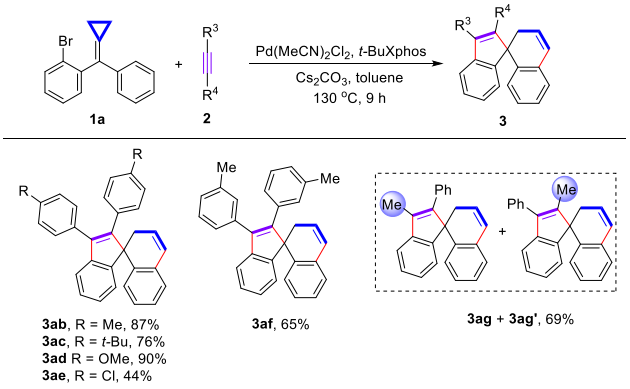


Figure 2. X-ray crystal structure of **3t**.

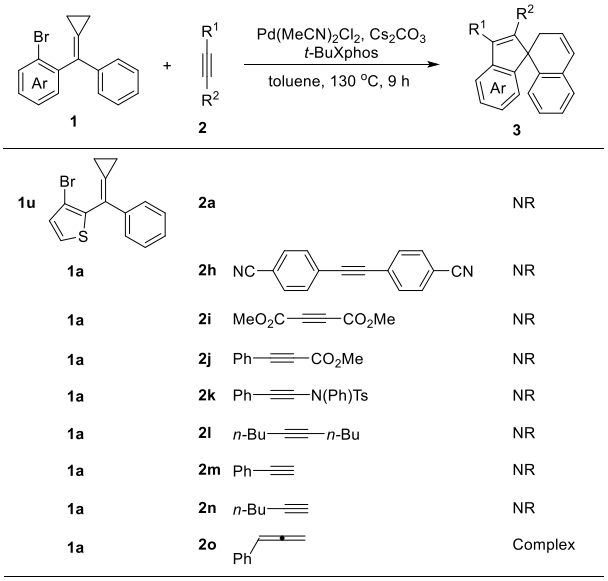
With the optimal conditions in hand, we next investigated the substrate scope of this palladium-catalyzed intermolecular cascade cyclization of MCPs **1** with alkynes (Scheme 2). First, the substituent R^1 on the aromatic Ar^1 ring was examined. A series of alkyl groups, phenyl group, Cl and MeO substituents were introduced at the *para*-position of the Ar^1 ring and we found that the desired products **3b-3j** could be afforded in moderate to good yields ranging from 65% to 86%. When a methyl group was introduced at the *ortho*-position of the aromatic Ar^1 ring, the reaction proceeded smoothly to furnish the desired product **3i** in 85% yield. The corresponding product **3j** was given in 69% yield when dimethyl was introduced at the *meta*-position of the aromatic Ar^1 ring. Next, we examined the substituent R^2 on the aromatic ring Ar^2. Regardless of whether electron-withdrawing or -donating groups were introduced on the aromatic Ar^2 ring, the desired products **3k-3r** could be provided in moderate to excellent yields. The substrates **1k-1m** and **1o** with electron-donating methyl group and MeO group at 3-, 4- or 5-position of aromatic Ar^2 ring afforded the corresponding products **3k**, **3l**, **3m**, and **3o** in 76%, 80%, 78%, and 85% yields, respectively. The substrates **1n** and **1p-1r** with electron-withdrawing CN, F, Cl, and CF_3 on the aromatic Ar^2 ring offered the corresponding products **3n**, **3p**, **3q**, and **3r** in 64%, 93%, 67%, and 89% yields, respectively. To our delight, substrate **1s** containing a benzo[d][1,3]dioxole heterocycle gave the desired product **3s** in 75% yield. As for substrate **1t** containing a naphthyl moiety, the reaction also proceeded smoothly to furnish the desired product **3t** in 70% yield. The structure of **3t** has been unambiguously assigned by X-ray diffraction.[19] The corresponding ORTEP drawing is shown in Figure 2 and its CIF data are presented in the Supporting Information. These results indicated that the electronic property of MCPs **1** has no significant effects on the reaction outcomes.



[a] Reactions were carried out by use of **1a** (0.2 mmol), **2** (0.4 mmol), and Cs_2CO_3 (0.4 mmol) in toluene (2.0 mL) with $Pd(MeCN)_2Cl_2$ (10.0 mol%), *t*-BuXphos (10.0 mol%) at 130 °C within 9 hours, isolated yields.

Scheme 3. Substrate scope for synthesis of **3ab-3ag**.[a]

To further investigate the scope of this reaction, we prepared other alkynyl substrates **2b-2g** and used them in the reaction with MCP **1a**. The experimental results are shown in Scheme 3. Introducing electron-donating groups, such as methyl, tert-butyl, and MeO groups, on the aromatic ring of alkynes **2** smoothly afforded the corresponding products **3ab**, **3ac**, **3ad**, and **3af** in 87%, 76%, 90%, and 65% yields, respectively. A noticeably low yield of **3ae** was given when electron-withdrawing Cl atom was introduced on the aromatic ring of alkyne **2**. Moreover, using 1-phenylpropyne as a substrate also produced the corresponding products **3ag** and **3ag'** in 69% total yield as a regioisomeric mixture (6:1).

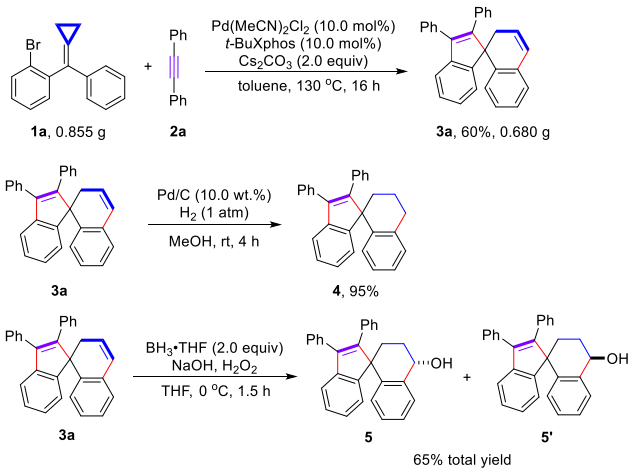


[a] Reactions were carried out by use of **1** (0.2 mmol), **2** (0.4 mmol), and Cs_2CO_3 (0.4 mmol) in toluene (2.0 mL) with $Pd(MeCN)_2Cl_2$ (10.0 mol%), *t*-BuXphos (10.0 mol%) at 130 °C within 9 hours.

Scheme 4. Other attempts of the reaction.[a]

We also investigated some other substrates and the results are shown in Scheme 4. Substrate **1u**, containing a thienyl moiety, did not undergo the reaction to give the corresponding product under the standard conditions. It should be noted that the reaction could not occur when alkynes **2h-2k** contained strongly electron-withdrawing groups; when disubstituted aliphatic alkyne **2l**, monosubstituted aromatic alkyne **2m**, and monosubstituted aliphatic alkynes **2n** were used in this reaction, the reactions could not take place either. Furthermore, a complex mixture was afforded when substrate **2o** having an allene moiety was utilized as the reactant in the reaction (Scheme 4).

To further illuminate the synthetic utility of this transformation, the reaction on a 0.855 g scale of **1a** with **2a** under the standard conditions was conducted, affording **3a** in 60% yield (0.680 g) (Scheme 5). Furthermore, the hydrogenation of **3a** in methanol furnished the corresponding tetrahydronaphthalene product **4** in 95% yield in the presence of Pd/C under H_2 atmosphere. The hydroboration of **3a** was performed with addition of borane-tetrahydrofuran solution, affording a diastereoisomer mixture **5** and **5'** in 65% total yield in 2:1 ratio after being quenched by NaOH and H_2O_2.



Scheme 5. Gram-scale synthesis and further transformation of **3a**.

Compared with our previous report,[18] an additional migratory insertion of alkyne was presented in this reaction. Following by an intramolecular Heck-type reaction, β-H elimination, cyclopropane ring-opening, and final cyclization provided a series of spirocyclic compounds containing indene and 1,2-dihydronaphthalene moieties (see Scheme S6 in SI).

In summary, a facile palladium(II)-catalyzed intermolecular cascade cyclization of MCPs **1** with aromatic alkynes **2** has been developed, providing spirocyclic compounds bearing indene and 1,2-dihydronaphthalene moieties in moderate to excellent yields. This work further enriched the chemical transformations of MCPs under palladium catalysis from intramolecular manner to intermolecular manner. Further investigations on expanding the scope of this reaction toward the synthesis of a variety of novel and potentially useful spirocyclic compounds containing other functional moieties are underway in our laboratory.

Experimental Section

General Procedure for Synthesis of 3

To a flame-dried sealing tubes were added the methylenecyclopropanes **1** (0.20 mmol, 1.0 equiv), alkynes **2** (0.40 mmol, 2.0 equiv), $Pd(MeCN)_2Cl_2$ (0.02 mmol, 0.1 equiv), *t*-BuXphos (0.02 mmol, 0.1 equiv) and cesium carbonate (0.40 mmol, 2.0 equiv), and the flask was evacuated and backfilled with Ar for 3 times. Toluene (2.0 mL) was added to this flask *via* a syringe under Ar. The reaction mixture was stirred for 9 hours at 130 °C. Appropriate amount of silica gel was added to the reaction mixture and the solvent was removed under vacuum pump at low temperature. Then, the crude product was purified by a silica gel chromatography (PE) to get the desired products **3** in 44-93% yields.

Acknowledgements

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Updates

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