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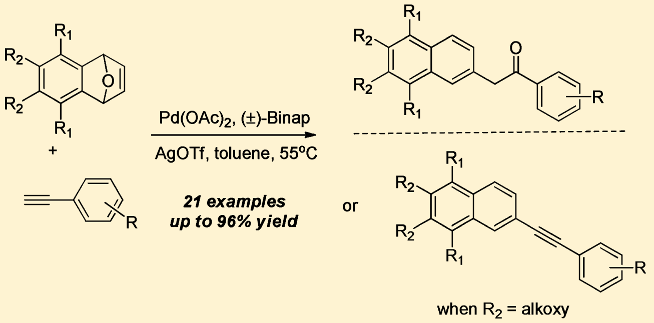
Palladium/Silver-Cocatalyzed Tandem Reactions of Oxabenzonorbornadienes with Substituted Arylacetylenes: A Simple Method for the Preparation of 1,2-Diarylethanones and 1,2-Diarylacetylenes

Jingchao Chen,[†,§] Shanshan Liu,[†,§] Yongyun Zhou,[†] Sifeng Li,[†] Chengyuan Lin,[‡] Zhaoxiang Bian,[‡] and Baomin Fan*,[†]

[†]YMU-HKBU Joint Laboratory of Traditional Natural Medicine, Yunnan Minzu University, Kunming 650500, Yunnan, China
[‡]School of Chinese Medicine, Hong Kong Baptist University, Hong Kong, China

Ⓢ *Supporting Information*

ABSTRACT: The effective synthesis of 1,2-diarylethanones was achieved using palladium(II) acetate [Pd(OAc)$_2$] and silver triflate (AgOTf) as cocatalysts from various oxabenzonorbornadiene derivatives and substituted arylacetylenes via tandem reactions under mild conditions. Exploration of the oxabenzonorbornadiene substrates showed that the 1,2-diarylacetylenes were obtained from adjacent alkoxy substituted oxabenzonorbornadiene derivatives. Preliminary mechanistic studies indicate that the AgOTf served as an indispensable catalyst, and the mechanism of the tandem reaction was proposed.



■ INTRODUCTION

The reactions of norbornadiene derivatives with terminal alkynes are quite versatile and can be regarded as an obvious evidence for the diversity of organic reactions. Various norbornadienes and terminal alkynes can undergo ring-opening reactions,[1] addition reactions,[2] [2 + 1] cycloaddition reactions,[3] [2 + 2] cycloaddition reactions,[4] and other reactions[5] to afford cyclic products using transition-metal catalysts or Lewis acids.[6] On the other hand, Lewis acids can play an important role as additives in the transition-metal-catalyzed reactions of norbornadiene derivatives, which had been demonstrated by the pioneering work of Lautens'[7] group. This methodology was also proved to be effective in the nickel-catalyzed ring-opening reaction of oxa/azabenzonorbornadienes with terminal alkynes by Cheng's[8] group. It is quite interesting and necessary to explore the utility of the combination of transition-metal catalysts and Lewis acids in the catalytic reactions of norbornadiene derivatives, especially those with terminal alkynes. Recently, by employing copper(I) triflate, our group has established an efficient palladium/copper cocatalytic system for asymmetric ring-opening reaction of azabenzonorbornadienes with terminal alkynes.[9] By switching the Lewis acid from copper(I) triflate to silver triflate and fine-tuning the reaction conditions, we realized the highly enantioselective ring-opening reaction of oxabenzonorbornadienes with terminal alkynes.[10] During the course of our investigation, 1,2-diphenylethanone was separated as a byproduct and attracted our attention, since it possesses a common skeleton that demonstrates particular biological activities, including protein tyrosine phosphatase inhibitory activity and antimicrobial activity.[11] As an extension of our previous work, we further studied the generation of 1,2-diphenylethanones. Herein, we report the palladium/silver-cocatalyzed tandem reactions of oxabenzonorbornadienes with arylacetylenes. Furthermore, 1,2-diarylacetylenes, widely used as polymers and liquid crystals materials,[12] could be smoothly produced according to the electronic property of the substitutional groups on the phenyl ring of oxabenzonorbornadienes.

■ RESULTS AND DISCUSSION

Initial trials were carried out by testing phosphine ligands for the tandem reaction of oxabenzonorbornadiene with phenylacetylene. As shown in Table 1, the tandem reaction of oxabenzonorbornadiene **1a** with phenylacetylene **2a** (3 equiv) in the presence of AgOTf and Pd complexes generated by palladium(II) acetate [Pd(OAc)$_2$] and phosphine ligands was studied. The result indicated that (*rac*)-Binap, xantphos, and DPEphos gave good yields (62–79% yields, entries 1–3), whereas DPPF, DPPB, and PPh$_3$ were inefficient in this reaction (entries 4–6). It could be observed that (*rac*)-Binap resulted in the best yield. Other palladium precatalysts in combination with (*rac*)-Binap were also investigated. Most of palladium precursors could promote the reaction to give

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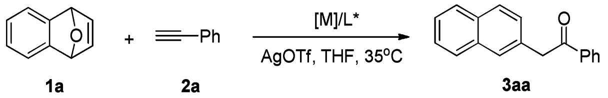
Table 1. Ligand and Palladium Screening for Palladium-Catalyzed Tandem Reaction of Oxabenzonorbornadienes and Phenylacetylene[a]



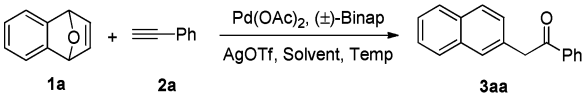
entry	[M]	ligand	time (h)	yield[b] (%)
1	$Pd(OAc)_2$	(±)-Binap	22	79
2	$Pd(OAc)_2$	xantphos	27	75
3	$Pd(OAc)_2$	DPEphos	4	62
4	$Pd(OAc)_2$	Dppf	48	trace
5	$Pd(OAc)_2$	Dppb	48	trace
6	$Pd(OAc)_2$	PPh_3	48	trace
7	$Pd(acac)_2$	(±)-Binap	22	78
8	$PdBr_2$	(±)-Binap	36	63
9	$(CF_3CO_2)_2Pd$	(±)-Binap	5	54
10	$Pd(C_5HF_6O_2)_2$	(±)-Binap	22	67
11	$PdCl_2$	(±)-Binap	36	65
12	PdI_2	(±)-Binap	17	71
13	$C_6H_{10}Pd_2Cl_2$	(±)-Binap	46	27

[a] Reaction conditions: **2a** (0.9 mmol), **2a**:**1a**:[Pd]:ligand:[Ag] (3:1:0.05:0.06:0.1) in THF (2 mL) at 35 °C under argon for indicated period of time. [b] Isolated yield by column chromatography. $Pd(C_5HF_6O_2)_2$ = palladium(II) hexafluoroacetylacetonate. $C_6H_{10}Pd_2Cl_2$ = allyl-palladium(II) chloride dimer.

acceptable yields (54−78% yields, entries 7−12) under the same conditions, but $C_6H_{10}Pd_2Cl_2$ showed lower catalytic activity (27% yield, entry 13). Thus, $Pd(OAc)_2$ was found to be the most effective palladium precursor.

Therefore, $Pd(OAc)_2$ and (*rac*)-Binap were selected to investigate solvent and temperature effects (Table 2). Among the test solvents, DME, dioxane, and toluene were more effective (79−86% yields, entries 3−6) than DCE and DCM (entries 1 and 2) in the present reaction. Toluene was the most suitable solvent (entry 6). The dosage of the ligand had a strong effect on the yield. For example, using 3 mol % (*rac*)-Binap obtained 92% yield within 2 h (entry 7). However, by increasing (*rac*)-Binap to 9 mol %, the product yield decreased to 70% (entry 8). The temperature experiments indicated that the reaction temperature of 55 °C was optimal (entries 9−11).

Table 2. Optimization of Reaction Conditions[a]

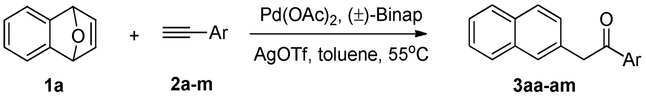


entry	solvent	temp (°C)	time (h)	yield[b] (%)
1	DCE	35	2	complex
2	DCM	35	2	complex
3	DME	35	2	81
4	THF	35	22	79
5	dioxane	35	2	79
6	toluene	35	2	86
7[c]	toluene	35	2	92
8[d]	toluene	35	1.5	70
9[c]	toluene	rt	17	93
10[c]	toluene	55	1	96
11[c]	toluene	75	0.5	87

[a] Reaction conditions: **2a** (0.9 mmol), **2a**:**1a**:[Pd]:Binap:[Ag] (3:1:0.05:0.03:0.1), in solvent (2 mL) under argon for indicated period of time. [b] Isolated yield by column chromatography. [c] 3 mol % (±)-Binap was used. [d] 9 mol % (±)-Binap was used.

The results of the tandem reactions of a variety of terminal alkynes **2a−m** and oxabenzonorbornadiene **1a** in the presence of $Pd(OAc)_2$ (5% mol)/AgOTf (10% mol) and (*rac*)-Binap (3% mol) in toluene at 55 °C are summarized in Table 3.

Table 3. Pd-Catalyzed Reactions of 1a with Various Terminal Alkynes[a]



entry	Ar	2	time (h)	yield[b] (%)
1	Ph	**2a**	1	96
2	$4\text{-}MeOC_6H_4$	**2b**	1	91
3	$2\text{-}MeOC_6H_4$	**2c**	1	90
4	$3\text{-}MeOC_6H_4$	**2d**	1	96
5	$3,5\text{-di-}MeOC_6H_3$	**2e**	0.3	92
6	$4\text{-}FC_6H_4$	**2f**	0.5	95
7	$4\text{-}PhOC_6H_4$	**2g**	1	95
8	$4\text{-}CF_3OC_6H_4$	**2h**	0.5	90
9	$4\text{-}BrC_6H_4$	**2i**	1	96
10	$4\text{-}MeC_6H_4$	**2j**	1	92
11	$4\text{-}OHCH_2C_6H_4$	**2k**	1	90
12	$4\text{-}CF_3C_6H_4$	**2l**	0.5	93
13	$4\text{-}CNC_6H_4$	**2m**	13	94

[a] Reaction conditions: **2a** (0.6 mmol), **2a**:**1a**:[Pd]:Binap:[Ag] (3:1:0.05:0.03:0.1), in toluene (2 mL) at 55 °C under argon for indicated period of time. [b] Isolated yield by column chromatography.

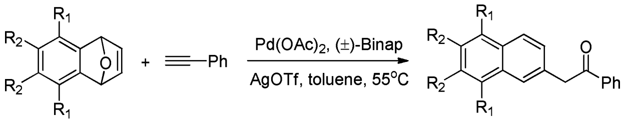
Generally, all of the terminal aromatic alkynes reacted with **1a** smoothly to provide the corresponding products in excellent yields (entries 1−13). Arylacetylenes with substituents of different electronic properties were suitable to give the corresponding products. In particular, the terminal alkyne with $-CH_2OH$ on the aromatic ring also afforded a high yield (entry 11).

To extend the scope of substrates, substituted oxabenzonorbornadiene derivatives **1a−f** were examined (Table 4). Except for **1b**, which bears an electron-donating group and gave a moderate yield (entry 2), the tandem reactions of most oxabenzonorbornadienes with phenylacetylene **2a** proceeded smoothly to afford the corresponding products in good yields (entries 1, 3−6).

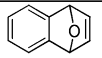
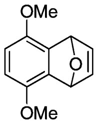
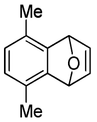
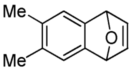
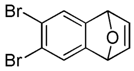
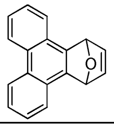
Further investigation of this tandem reaction was performed by testing additional oxabenzonorbornadiene derivatives with adjacent alkoxy substituted on the phenyl ring (Table 5). Interestingly, we could obtain another kind of product in good yields when we employed adjacent alkoxy substituted oxabenzonorbornadiene derivatives **1g−i** as substrates to react with phenylacetylene **2a**.

In order to investigate the reaction mechanism, we have prepared a possible reaction intermediate **4**[10] and subjected it to the synthesis of **3ab** (Table 6). It was found that this transformation did not proceed without catalyst (entry 1). However, when a mixture of $Pd(OAc)_2$, (±)-Binap, and AgOTf was used as catalyst, the ketone product **3ab** was obtained in high yield (entry 2). However, no desired product **3ab** was detected in the absence of AgOTf when $Pd(OAc)_2$ and (±)-Binap were used (entry 3). Interestingly, the transformation proceeded smoothly when AgOTf was used alone

Table 4. Pd-Catalyzed Tandem Reactions of Substituted Oxabenzonorbornadienes with Phenylacetylene 2a^{a}

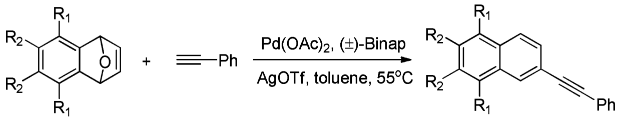


1a-f **2a** **3aa-fa**

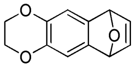
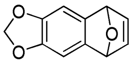
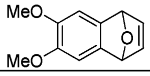
entry	oxabenzo-norbornadienes	time(h)	yield(%)^{b}
1	 **1a**	1	96
2	 **1b**	0.5	56
3	 **1c**	3	93
4	 **1d**	3	91
5	 **1e**	0.5	89
6	 **1f**	5	83

^{a}Reaction conditions: **2a** (0.6 mmol), **2a**:**1a**:[Pd]:Binap:[Ag] (3:1:0.05:0.03:0.1), in toluene (2 mL) at 55 °C under argon for indicated period of time. ^{b}Isolated yield by column chromatography.

Table 5. Reaction of Adjacent Alkoxy Substituted Oxabenzonorbornadienes and 2a under Pd/Ag Catalytic Conditions^{a}

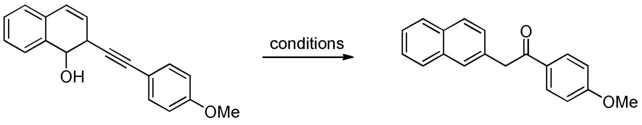


1g-i **2a** **3ga-ia**

entry	oxabenzo-norbornadienes	time(h)	yield^{b} (%)
1	 **1g**	1	90
2	 **1h**	0.5	77
3	 **1i**	0.5	85

^{a}Reaction conditions: **2a** (0.6 mmol), **2a**:**1a**:[Pd]:Binap:[Ag] (3:1:0.05:0.03:0.1), in toluene (2 mL) at 55 °C under argon for indicated period of time. ^{b}Isolated yield by column chromatography.

Table 6. Study of the Transformation from 4 to 3ab^{a}



4 **3ab**

entry	conditions	temp (°C)	time (h)	yield^{e} (%)
1		70	60	NR
2^{b}	Pd(OAc)$_2$/(±)-Binap, AgOTf	35	3	93
3^{c}	Pd(OAc)$_2$/(±)-Binap	70	60	complex
4^{d}	AgOTf	55	2	98

^{a}Reactions were carried out in toluene (2 mL) under argon. ^{b}5 mol % Pd(OAc)$_2$, 3 mol % Binap, and 10 mol % AgOTf were used. ^{c}5 mol % Pd(OAc)$_2$ and 3 mol % Binap were used. ^{d}15 mol % AgOTf was used. ^{e}Isolated yield by column chromatography.

(entry 4). Therefore, this result suggested that AgOTf served as an indispensable catalyst in the present transformation.

On the basis of the above experiments, a plausible mechanism for this novel tandem reaction is shown in Figure 1. The arylacetylene reacts with the complex of Pd(OAc)$_2$ and (±)-Binap to produce palladium acetylide species **B**, which coordinates with silver-activated oxabenzonorbornadiene to afford **D**. By the migratory insertion of an arylethynyl group to the carbon−carbon double bond, the intermediate **E** is formed. Following β-hydrogen elimination, the C−O bond is broken, producing the intermediate **F**. After a simple cation exchange, **G** is afforded as a byproduct, which is observed in the beginning of this tandem reaction.

Next, with adjacent alkoxy substitutions on oxabenzonorbornadiene, a relatively favorable intermediate **H** is generated from **F** by the leaving of the hydroxyl group (Path A). Then, the corresponding proton elimination affords the 1,2-diarylacetylene **I**. However, in most cases, **F** is transferred to the silver intermediate **K** by intramolecular nucleophilic addition (Path B). The following proton elimination and cation exchange afford the 1,2-diarylethanone **M**.

CONCLUSION

We describe the effective synthesis of 1,2-diarylethanones from the oxabenzonorbornadiene derivatives and substituted arylacetylenes using Pd(OAc)$_2$ and AgOTf as cocatalyst. 1,2-Diarylacetylene derivatives were also obtained from adjacent alkoxy substituted oxabenzonorbornadiene derivatives. On the basis of the mechanism study, a plausible reaction pathway that generates both 1,2-diarylethanones and 1,2-diarylacetylenes was proposed.

EXPERIMENTAL SECTION

General Method. The reactions and manipulations were performed under an atmosphere of argon using standard Schlenk techniques and drybox (Mikrouna, Supper 1220/750). Anhydrous toluene, DME, THF, and dioxane were distilled from sodium benzophenone ketyl prior to use. Anhydrous toluene was distilled from calcium hydride and stored under argon. Absolute MeOH and isopropyl alcohol were distilled from magnesium and stored under argon. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker-Avance 400 MHz spectrometer, and $CDCl_3$ was used as solvent. Chemical shifts (δ) were reported in ppm with tetramethylsilane as internal standard, and J values were given in Hz. High-resolution mass spectra (HRMS) were performed on a VG Autospec-3000 spectrometer. Column chromatography was performed with silica gel (200−300 mesh).

Typical Procedure for Palladium/Silver-Cocatalyzed Tandem Reactions of Oxabenzonorbornadienes with Terminal Alkynes. Pd(OAc)$_2$ (3.4 mg, 0.015 mmol), (±)-Binap (5.6 mg, 0.009 mmol), and 1.0 mL of toluene were added to a Schlenk tube under an argon atmosphere. The resulting solution was stirred at room temperature for 30 min. Then, a solution of CF_3SO_3Ag (7.7 mg, 0.03 mmol) was added, and the mixture was stirred for an additional 10 min. After the addition of oxabenzonorbornadiene **1a** (43.2 mg, 0.3 mmol) in toluene (1.0 mL), the mixture was stirred for an additional

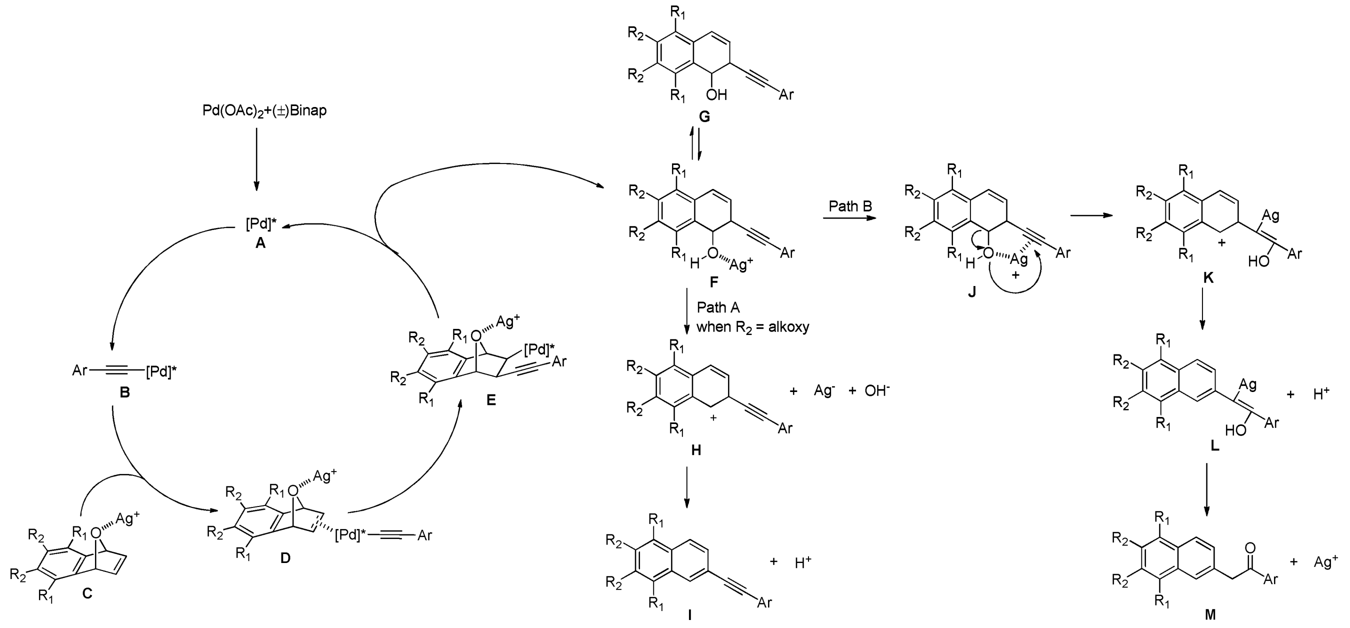


Figure 1. Mechanism for palladium/silver-cocatalyzed tandem reaction of oxabenzonorbornadiene and terminal alkyne.

10 min. After the last addition of terminal alkyne **2a** (100 μL, 0.9 mmol), the mixture was stirred at 55 °C under an argon atmosphere with TLC monitoring until achieving the complete consumption of **1a**. After vacuum evaporation of the solvent, the residue was purified by silica gel column chromatography to provide the desired product **3aa** (73.1 mg, 96% yield).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.5b00551.

Preparation method of oxabenzonorbornadienes, characterization data, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: FanBM@ynni.edu.cn.

Author Contributions

§These authors contributed equally.

Notes

The authors declare no competing financial interest.

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