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Pd(II)-Catalyzed Synthesis of Alkylidene Phthalides via a Decarbonylative Annulation Reaction

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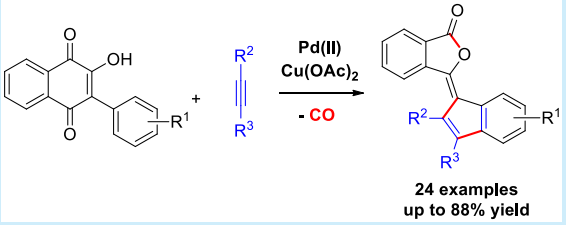
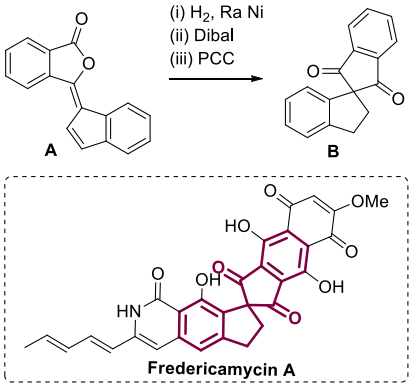
Supporting Information

ABSTRACT: An unprecedented Pd(II)-catalyzed decarbonylative C−H/C−C activation and annulation reaction, which proceeds via intramolecular cyclization, is reported. This reaction of hydroxynaphthoquinones with disubstituted alkynes provides good yields of substituted alkylidene phthalides, which are the key intermediates for the synthesis of bioactive natural products.



Alkylidene butyrolactones are the key scaffold of various biologically active natural products and synthetic compounds.[1] They are the key intermediates for the synthesis of many important heterocyclic, carbocyclic, and alicyclic compounds.[2] For example, alkylidene phthalide **A** (Scheme 1)[3]

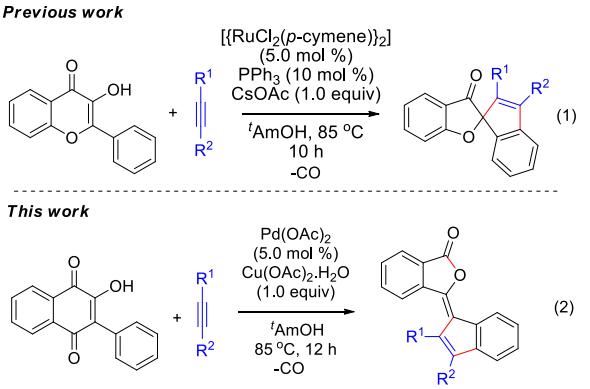
Scheme 1. Synthesis of the Spirocyclic Scaffold of Fredericamycin A



is the key intermediate for the synthesis of antitumor antibiotic Fredericamycin A (Scheme 1), which was isolated from *Streptomyces griseus*.[4] This ylidene lactone **A** could be easily transformed to the key spirocyclic scaffold **B** of Fredericamycin A via reduction and oxidation reactions (Scheme 1).[3]

In recent years, the transition metal-catalyzed decarbonylative activation of inert C−H/C−C bonds and alkyne annulation reactions have provided a new direction for the efficient construction of various heterocyclic compounds. These metal-catalyzed decarbonylative annulation reactions are mainly limited to four- and five-membered ring systems.[5] Very recently, we reported a Ru(II)-catalyzed decarbonylative annulation reaction, through C−H/C−C activation of six-membered 3-hydroxy-2-phenyl-chromones with alkynes for the synthesis of spiro benzofuranones (Scheme 2, eq 1).[6] Herein,

Scheme 2. Decarbonylative Annulation Reactions



as a continuation of our work on metal-catalyzed novel organic reactions,[7] we describe an unprecedented decarbonylative C−H/C−C activation and annulation reaction, which proceeds via one additional intramolecular cyclization reaction step, for the synthesis of alkylidene phthalides (Scheme 2, eq 2). These alkylidene phthalides are typically synthesized by the acylation reaction of an indene anion with dimethyl phthalate, followed by cyclization of the resulting ester to lactone under acidic conditions.[3] Furthermore, Balme and co-workers reported a four-step palladium-catalyzed bis-cyclization reaction for the synthesis of alkylidene phthalide.[8]

Initially, the decarbonylative annulation reaction of **1a** was studied with alkyne **2a** in the presence of various transition

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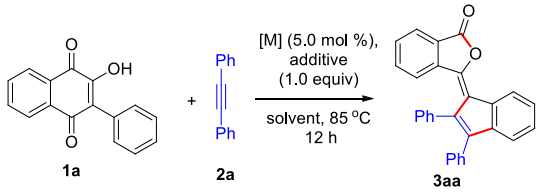
metal catalysts (Table 1). Among the catalysts screened for this reaction (entries 1–4), $Pd(OAc)_2$ provided the highest yield of

Table 1. Optimization of the Reaction Conditions for 3aa[a]

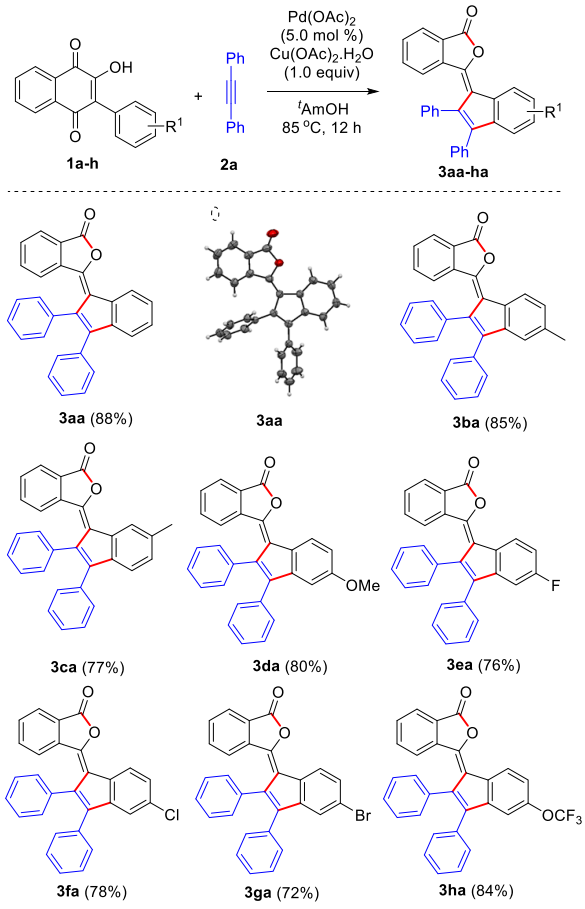


entry	catalyst	additive	solvent	3aa (%)[b]
1	$RuCl_3{\cdot}xH_2O$	$Cu(OAc)_2{\cdot}H_2O$	MeCN	0
2	$[\{RuCl_2(p\text{-cymene})\}_2]$	$Cu(OAc)_2{\cdot}H_2O$	MeCN	19
3	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	MeCN	16
4	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	MeCN	70
5	$Pd(OAc)_2$	CsOAc	MeCN	54
6	$Pd(OAc)_2$	AgOAc	MeCN	41
7	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	toluene	51
8	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	H_2O	42
9	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	^{t}AmOH	88
10[c]	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	MeOH	56

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst (5.0 mol %), additive (0.2 mmol), and solvent (5.0 mL) at 85 °C under air for 12 h, unless otherwise mentioned. [b]Isolated yields. [c]Reaction performed at 64 °C.

3aa in the presence of additive $Cu(OAc)_2{\cdot}H_2O$ (entry 4). Screening of some other commonly used additives such as CsOAc and AgOAc could not improve the yield of annulated product **3aa**. However, screening of some other aprotic and protic solvents (entries 7–10) revealed ^{t}AmOH as the best solvent for performing this reaction (entry 9). These optimized reaction conditions were first applied for the annulation reaction of hydroxynaphthoquinones **1b–h** with alkyne **2a**. As shown in Scheme 3, 2-phenyl-3-hydroxynaphthoquinones that have different electron-donating and electron-withdrawing substituents such as Me, OMe, F, Cl, and OCF_3 on the 2-phenyl ring of **1** afforded good yields of corresponding products **3ba–fa** and **3ha**. The annulation reaction of **1c** with **2a** highly regioselectively afforded **3ca**. Furthermore, hydroxynaphthoquinone possessing a sensitive bromo functional group (**1g**) tolerates the reaction conditions well to provide **3ga** in good yield. However, the annulation reaction of heterocycle-substituted hydroxynaphthoquinones such as 2-(furan-2-yl)-3-hydroxynaphthalene-1,4-dione and 2-hydroxy-3-(thiophen-2-yl)naphthalene-1,4-one with **2a** under the optimized reaction conditions could not afford the desired products. Next, the scope of the reaction with some of the alkynes **2b–n** was studied with **1a**. As shown in Scheme 4, diaryl-substituted alkynes possessing electron-donating and -withdrawing substituents on the phenyl ring (**2b–d**) turned out to be good substrates for this reaction to afford compounds **3ab–ad**. The unsymmetrical diaryl-substituted alkynes **2e–h** provided inseparable mixture of isomers **3ae–ah**, respectively, with **1a**. Dialkyl-substituted alkynes **2i** and **2j** were also found to be good substrates for this reaction to provide **3ai** and **3aj**, respectively, with **1a** in good yields. The annulation reactions of alkynes **2k–m** substituted with an aryl and an alkyl group with **1a** highly regioselectively afforded **3ak–am**, respectively. Similarly, phenylpropiolate **2n** was also found to be a good substrate for this reaction that afforded **3an**, regioselectively.

Scheme 3. Scope of Hydroxynaphthoquinones 1a–h[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.2 mmol), Pd catalyst (5.0 mol %), and $Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv) in ^{t}AmOH (5.0 mL) heated at 85 °C for 12 h under air.

Then, the scope of the reaction was tested with diynes **2o** and **2p** with **1a**. As shown in Scheme 5, both tested alkynes **2o** and **2p** provided good yields of phthalides **3ao** and **3ap**, respectively, and these reactions were highly regioselective. Interestingly, the annulation reaction of silylalkynes **2q–s** with **1a** also afforded the same alkyne-containing phthalides **3ao–ap** and similar phthalide **3aq**, albeit in low yields (Scheme 5). However, under the standard reaction conditions, the reaction of **1a** with trimethyl(thiophen-3-ylethynyl)silane could not afford the corresponding phthalide. The terminal alkynes were not found to be suitable substrates for this annulation reaction. As in the previous studies of the metal-catalyzed alkyne annulation reactions, the regioselectivity of the unsymmetrical diaryl-substituted alkynes is difficult to predict, which usually provides a mixture of isomers.[9] However, the annulation reaction of unsymmetrical alkynes, substituted with an aryl and an alkyl group, affords highly regioselective products. These products are regioselective because of the preferential binding of the metal with the electron rich center of the unsymmetrical alkynes.[9] The structures of the compounds were determined with the help of spectroscopic studies and finally confirmed by single X-ray crystallographic studies of compound **3aa**.[10]

The competitive experiment performed between alkynes possessing an electron-donating group (**2b**) and an electron-withdrawing group (**2d**) with **1a** showed a faster rate of reaction of **2b** [1.7:1 **3ab**:**3ad** (Scheme SI-3)]. Another

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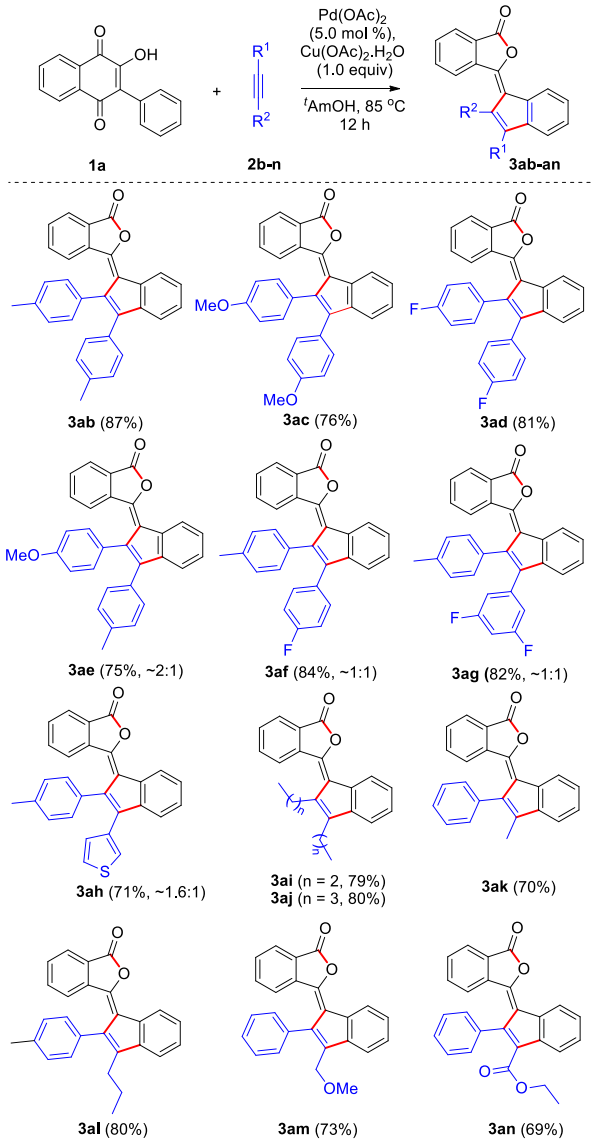
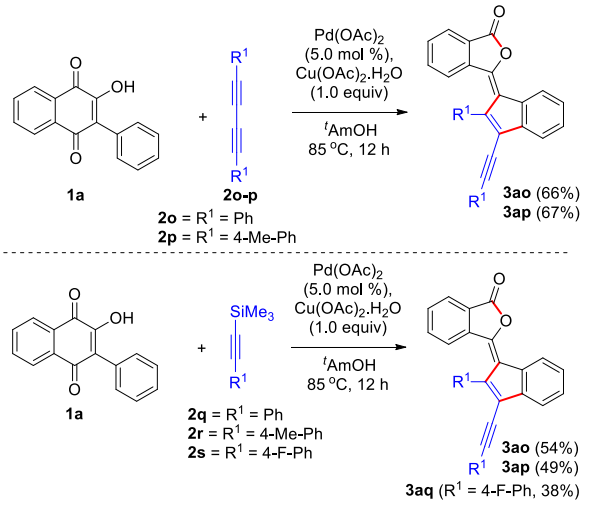
Scheme 4. Scope of Alkynes[a]

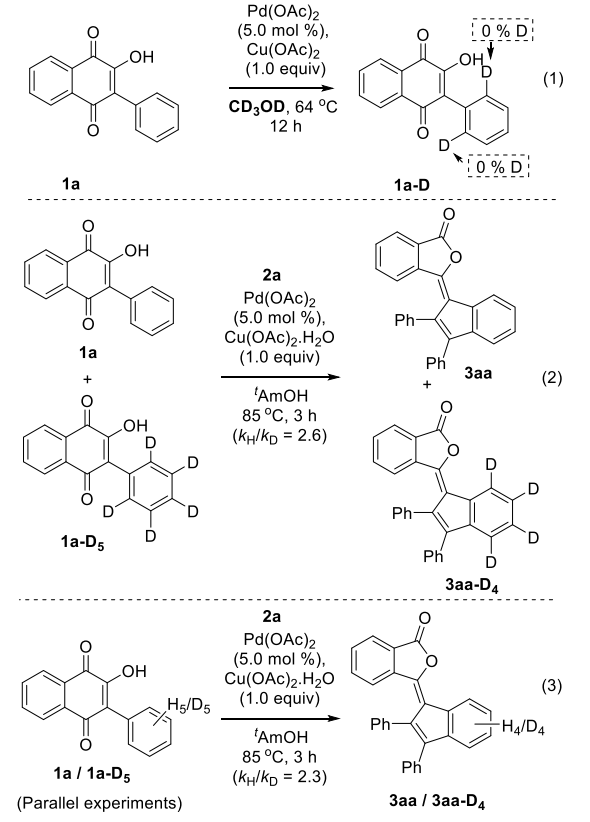


[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.2 mmol), Pd catalyst (5.0 mol %), and $Cu(OAc)_2.H_2O$ (1.0 equiv) in ^{t}AmOH (5.0 mL) heated at 85 °C for 12 h under air.

Scheme 5. Scope of Alkynes



Scheme 6. Experiments with Isotopically Labeled Compounds



competitive experiment performed with electron rich and electron poor hydroxynaphthoquinones **1b** and **1f** with **2a** revealed preferential formation of **3ba** [3:1 **3ba**:**3fa** (Scheme SI-4)]. **1a** under standard conditions and in CD_3OD could not afford the deuterated product **1a-D**, indicating the formation of a nonreversible Ru−C bond (Scheme 6, eq 1). The intermolecular competitive experiment performed with **1a** and **1a-D$_5$** with **2a** provided a k_H/k_D of 2.6 (Scheme 6, eq 2). Again, the competitive parallel experiments with **1a** and **1a-D$_5$** with **2a** provided a k_H/k_D of 2.3 (Scheme 6, eq 3). These k_H/k_D values indicate the possibility of the Ru−C bond formation step being the rate-determining step of this reaction. The elimination of CO gas from the reaction mixture was proven by performing the phosphomolybdic acid−$PdCl_2$ test (Figure SI-1 and the Supporting Information).[11]

On the basis of our experiments and literature reports, a possible mechanism is proposed for this reaction in Scheme 7. Initially, **1a** reacts with the catalyst $Pd(OAc)_2$ to form Pd complex **A** by eliminating two molecules of acetic acid. Insertion of the alkyne within the C−Pd bond provides complex **B**, which on subsequent intramolecular cyclization and cleavage of C−C bonds liberates one molecule of cabon monoxide to afford Pd complex **D**. Finally, in the presence of copper acetate and oxygen from air, reductive elimination of the metal provides compound **3aa** and it regenerates the catalyst as shown in Scheme 7.

In summary, we have developed a novel Pd(II)-catalyzed decarbonylative alkyne insertion reaction of six-membered ring compounds. This annulation reaction of hydroxynaphthoquinones and disubstituted alkynes proceeds via C−H/C−C

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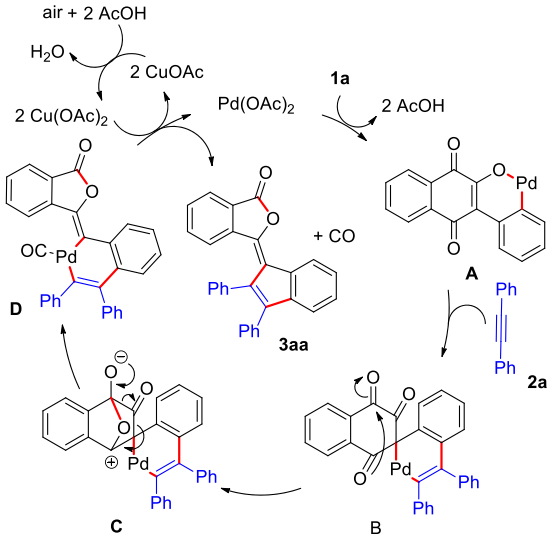
Scheme 7. Probable Mechanism



activation, alkyne insertion, intramolecular cyclization, and decarbonylation, providing good yields of alkylidene phthalides that are the key intermediates for the synthesis of biologically important compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00726.

Experimental procedures, spectroscopic data, and copies of ^{1}H NMR, ^{13}C NMR, and HRMS spectra of synthesized compounds (PDF)

Accession Codes

CCDC 1547365 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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