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Cyclopentadiene Construction via Rh-Catalyzed Carbene/Alkyne Metathesis Terminated with Intramolecular Formal [3 + 2] Cycloaddition

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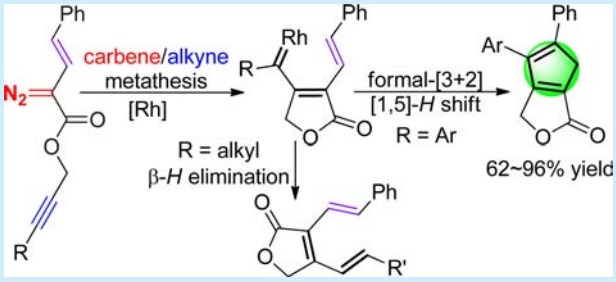
Supporting Information

ABSTRACT: A new type of intramolecular carbene cascade reaction of alkynyl-tethered styryl diazoesters is presented, which is terminated with a formal [3 + 2] cycloaddition to give the bicyclic cyclopentadiene derivatives in high yields and selectivity. Additionally, it was found that the β-H shift is the dominating process in the case of alkyl alkyne-tethered substrates.



Cyclopentadiene is a versatile synthon in cycloaddition reactions,[1] especially in the construction of the bicyclo[2.2.1]heptene framework, which is a pervasive unit in many drug candidates or compounds with various bioactivities.[2−5] For example, adducts of cyclopentadienes with *N*-substituted maleimide derivatives have drawn much attention in drug development studies (Figure 1), including compounds **A**

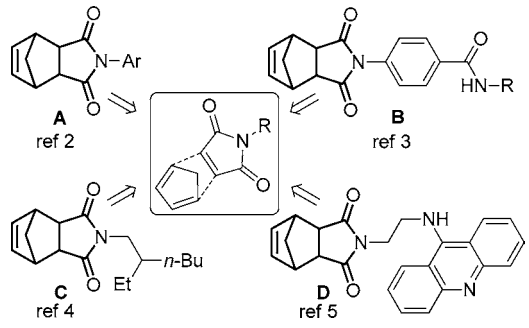


Figure 1. Representative bioactive compounds generated from cyclopentadiene via [4 + 2] cycloadditions.

as androgen receptor antagonists[2a] or potential antidepressants,[2b] compounds **B** as anticancer candidates[3a,b] and also as effective inhibitors of tankyrases,[3c−f] compound **C** as a molluscicide,[4] and compound **D** as a core unit in a new type of bisintercalator for DNA recognition.[5] With these studies, it is easy to find that all of these compounds are modified only at the *N*-substituted groups on maleimide derivatives, although it is equally important to have the derivatives decorated on the cyclopentadiene part to be tested.[2−5] Besides the advances in the formation of functionalized cyclopentadienes,[1,6] access to stable cyclopentadienes with structural diversity and various substitutions is rare.[6e]

Metal carbenes have been proven to be powerful species in modern organic synthetic chemistry,[7] especially in direct C−C bond formations.[8] Besides the typical carbene transformations, metal carbene cascade reactions show more efficiency in multibond formations. In this context, Padwa[9] and Hoye[10] reported the pioneering work on catalytic carbene/alkyne metathesis reactions with alkynyl-tethered diazo compounds, and the resultant vinyl metal carbenes were terminated with a typical metal carbene reaction, for example, with a carbonyl group to give the bicyclic furan derivatives in high yield[9] or intra- and intermolecular cyclopropanation with an alkenyl group[10,14] (Scheme 1). Later, Fox's group reported that the resultant intermediate could be trapped via a Buchner reaction.[11] Recently, May and co-workers reported a carbene cascade reaction terminating in C−H insertion,[12] which offers direct access to polycyclic ring frameworks. Although a few other variants have been reported by Doyle,[13] Cossy,[14] and others,[15] the synthetic potential of activated cyclopropene is going to become significant via utilization of the catalytically generated vinyl metal carbene intermediate. Here we report our recent discovery of stable bicyclic cyclopentadiene construction via catalytic carbene/alkyne metathesis terminated with intramolecular formal [3 + 2] cycloaddition (Scheme 1).

Initially, substrate **1a** was treated with 1.0 mol % $Rh_2(OAc)_4$ in DCM at room temperature. To our delight, the

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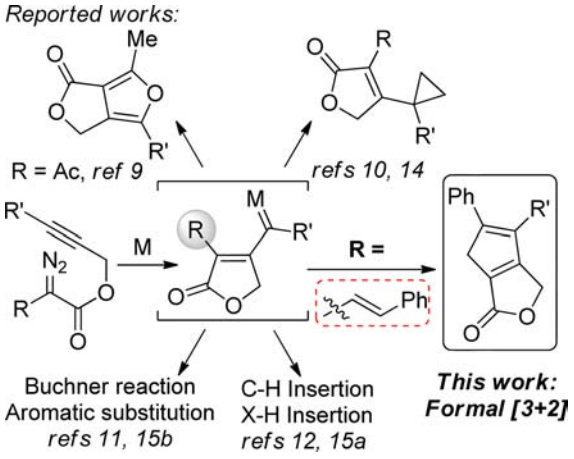
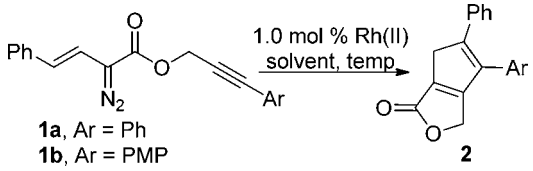
Scheme 1. Types of Metal Carbene Cascade Reactions



corresponding cyclopentadiene product **2a** was obtained in 90% yield (Table 1, entry 1). More importantly, the reaction

Table 1. Optimization of the Reaction Conditions[a]



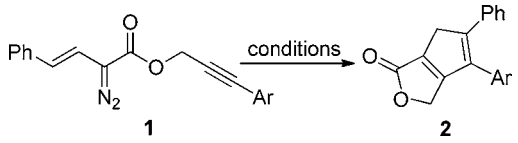
entry	cat.	1	solvent	temp (°C)	yield (%)[b]
1	$Rh_2(OAc)_4$	**1a**	DCM	25	90 (75)[c]
2	$Rh_2(OAc)_4$	**1b**[d]	DCM	25	56
3	$Rh_2(OAc)_4$	**1b**	DCM	0	46
4	$Rh_2(tfa)_4$	**1b**	DCM	25	60
5	$Rh_2(pfb)_4$	**1b**	DCM	25	30
6	$Rh_2(oct)_4$	**1b**	DCM	25	85
7	$Rh_2(oct)_4$	**1b**	toluene	50	95

[a]Each reaction was carried out at the indicated temperature on a 0.3 mmol scale in 2.0 mL of solvent with 1.0 mol % dirhodium catalyst for 5 h, unless otherwise noted. [b]Isolated yields after chromatography. [c]The reaction was carried out on a 5.0 mmol scale. [d]PMP = *p*-methoxyphenyl.

could be carried out on a gram scale in 75% isolated yield (entry 1, in parentheses). Subsequently, substrate **1b** bearing an electron-rich *p*-methoxyphenyl (PMP) group on the alkynyl chain was tested under the same conditions, and a yield of only 56% was obtained (entry 2). After further optimization with various dirhodium carboxylate catalysts in different solvents (entries 2−7), it turned out that $Rh_2(oct)_4$, which has better solubility in toluene, gave the best results for this substrate at 50 °C (95% yield; entry 7).

With the above results in hand, we set out to investigate the scope of this reaction under two sets of optimized conditions: 1.0 mol % $Rh_2(OAc)_4$ in DCM at room temperature (conditions A) and 1.0 mol % $Rh_2(oct)_4$ in toluene at 50 °C (conditions B) (Table 2). The tested substrates all performed well under either conditions A or B. In general, substrates containing an electron-withdrawing group gave lower yields (62−90%; entries 6−12) compared with electron-neutral or -rich ones (>90%; entries 1−5). The relative structures of these products were confirmed by single-crystal X-ray diffraction analysis of **2k** (Figure 2).[16]

Table 2. Substrate Generality



entry	Ar (**1**)	conditions[a]	**2**	yield (%)[b]
1	C_6H_5 (**1a**)	A	**2a**	90
2	4-$MeOC_6H_4$ (**1b**)	B	**2b**	95
3	4-MeC_6H_4 (**1c**)	B	**2c**	92
4	3-MeC_6H_4 (**1d**)	B	**2d**	95
5	2-MeC_6H_4 (**1e**)	B	**2e**	96
6	4-ClC_6H_4 (**1f**)	A	**2f**	70 (65)[c]
7	4-$CF_3C_6H_4$ (**1g**)	A	**2g**	67
8	4-BrC_6H_4 (**1h**)	A	**2h**	78 (69)[c]
9	4-$NO_2C_6H_4$ (**1i**)	A	**2i**	62
10	4-AcC_6H_4 (**1j**)	B	**2j**	84
11	4-$MeO_2CC_6H_4$ (**1k**)	B	**2k**	90
12	2-Me-4-$NO_2C_6H_3$ (**1l**)	B	**2l**	80

[a]Conditions A: **1** (0.3 mmol), $Rh_2(OAc)_4$ (1.0 mol %, 1.3 mg), DCM (2.0 mL), rt, 5 h. Conditions B: **1** (0.3 mmol), $Rh_2(oct)_4$ (1.0 mol %, 2.3 mg), toluene (2.0 mL), 50 °C, 5 h. [b]Isolated yields after chromatography. [c]Isolated yield under conditions B.

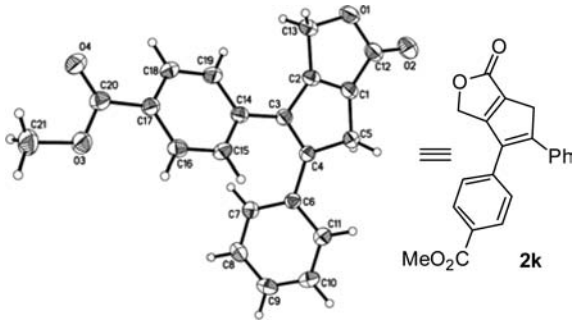


Figure 2. X-ray crystal structure of product **2k** (CCDC 1417641).

With these promising results, terminal-alkyl-substituted diazo compound **1m** was employed. Although a carbene cascade reaction still occurred, the resultant vinyl metal carbene was terminated with a *β*-H shift process instead of formal [3 + 2] cycloaddition to form triene **2m** in moderate yield (Scheme 2, eq 1). Substrate **1n** with a methyl group on the alkenyl part produced only the C−H insertion product **2n** in 50% yield (Scheme 2, eq 2), indicating the priority of carbene C−H insertion over carbene/alkyne metathesis because of the steric preponderance of the methyl group, which is closer to the carbene center. Some chiral dirhodium catalysts were tested for this cyclobutene formation reaction, and although 100% conversion was observed, only up to 11% ee was observed for the reaction catalyzed by Rh_2(*S*-TBPTTL)$_4$. With stable bicyclic cyclopentadienes in hand, Diels−Alder additions with *N*-aryl- and *N*-alkyl-substituted maleimide derivatives were tested, and the corresponding adducts were obtained in high yields (75% yield with R = Ph and 70% yield with R = Et; Scheme 2, eq 3). This constitutes a significant complementary method that provides access to derivatives of reported bioactive compounds.[2−5]

To gain insight into the mechanistic details, the reaction was carried out in an NMR tube with $CDCl_3$ as the solvent (Figure 3). After 5 min, the staring material **1a** decomposed completely, and the desired cyclopentadiene **2a** was formed as the major

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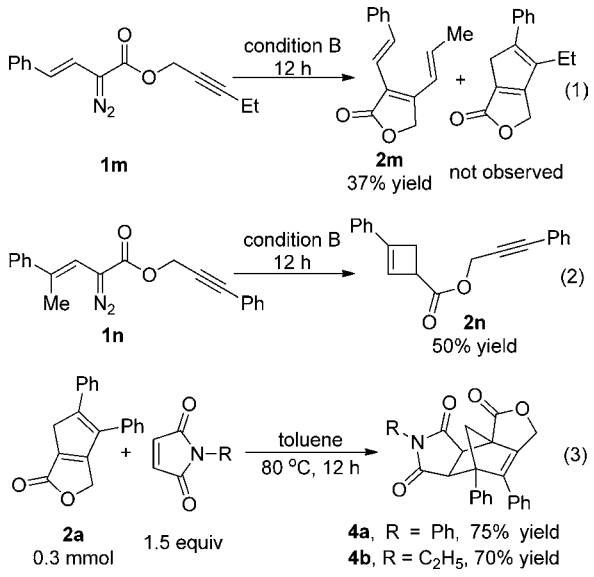
Scheme 2. Extended Experiments



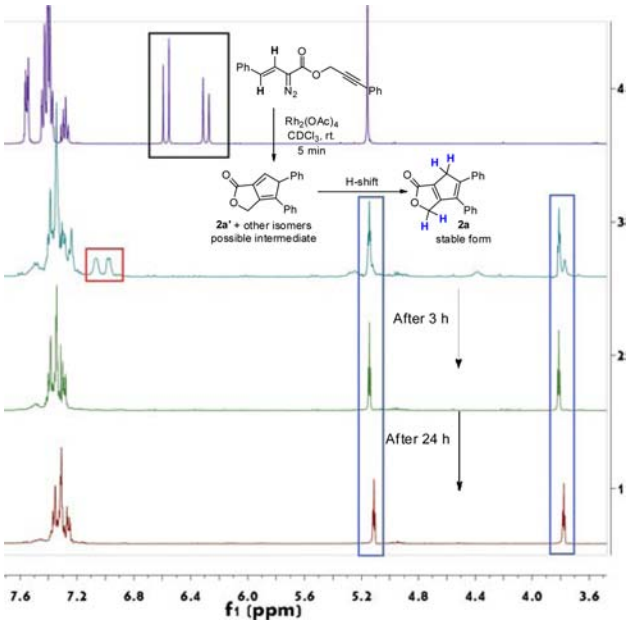


Figure 3. Proton NMR observations of the cascade reaction.

product; meanwhile, some peaks around 7 ppm were observed (Figure 3, red box), which might be the proton signals of cyclopentadiene **2a′** and other isomers. These signals disappeared after 3 h, and no further change was observed even after 24 h. This result suggested that a hydrogen shift may occur to form the final product **2a** from other isomers. In addition, the cyclopropene intermediate in the carbene/alkyne metathesis has been isolated for the first time by Le and May.[12b]

In conclusion, a new dirhodium-catalyzed intramolecular carbene cascade reaction for the construction of bicyclic cyclopentadiene frameworks with alkyne-tethered styryl diazo compounds has been presented for the first time. The process is initiated by catalytic metal carbene formation, followed by carbene/alkyne metathesis and termination with a formal [3 + 2] cycloaddition. A quick hydrogen shift of the initially formed cyclized adducts was observed to give the final stable products in high yield. The generated products could be applied to Diels–Alder reactions, and potential bioactivity of the generated adducts could be envisioned on the basis of relevant investigations.[2−5]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02912.

Detailed experimental procedures and characterization data for the products (PDF)
Crystallographic data for **2k** (CIF)

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Notes

The authors declare no competing financial interest.

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(16) CCDC 1417641 contains the supplementary crystallographic data for **2k**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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