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One-Pot Synthesis of Decahydropyrene via Tandem C−H Activation/Intramolecular Diels−Alder/1,3-Dipolar Cycloaddition

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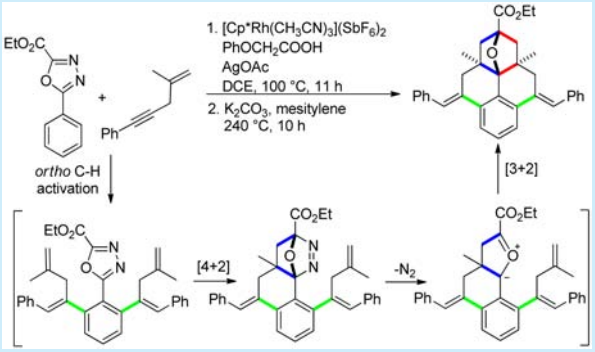
Supporting Information

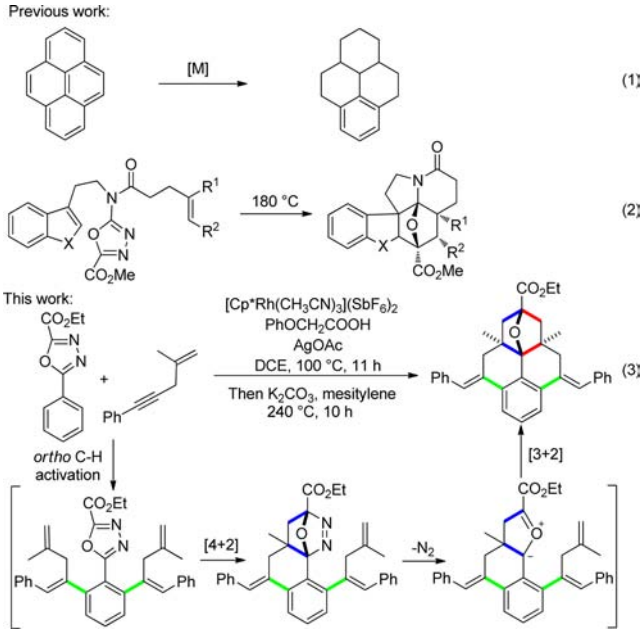
ABSTRACT: A novel decahydropyrene synthesis has been successfully developed involving a tandem rhodium-catalyzed C−H activation/intramolecular Diels−Alder reaction/1,3-dipolar cycloaddition cascade process by using diazole as a traceless directing group. The advantage of this one-pot strategy is a quite simple, efficient, highly stereoselective, and unique product structure.



Tandem reactions, sometimes referred to as domino reactions, are attractive strategies for the construction of complex bridged or polycyclic structures bearing several contiguous stereocenters from simple precursors without the need to isolate intermediates.[1] Especially with the rapid development of the C−H activation reaction in the past decades,[2] tandem reactions following the first rhodium-catalyzed C−H bond cleavage have been extensively studied due to the high efficiency and atom-economy.[3,4] For example, various amides or oximes coupling with multiple alkynes to obtain polycyclic heteroaromatic compounds via a multiple chelation-assisted *ortho*-C−H bond cleavage process and annulation in one-pot have been discovered by many groups.[4] Despite the significant developments, cascade reactions via rhodium-catalyzed C−H activation to build a more complex polycyclic system still face huge challenges. Therefore, exploring a versatile and novel cascade route is highly desirable.

Recently, decahydropyrene has received certain attention by virtue of its unique molecular struture; however, traditional approaches for the synthesis of these structures usually suffer from low yields, complex operations, and inadequate structural modification (Scheme 1, eq 1).[5] Very recently, a powerful intramolecular [4 + 2]/[3 + 2] cycloaddition cascade reaction was utilized in the total synthesis of a series of indole alkaloids (Scheme 1, eq 2).[6] Inspired by the structure of decahydropyrene derivatives and based on this cascade work, herein, we report a highly efficient and powerful strategy for the one-pot synthesis of a series of decahydropyrenes through a tandem rhodium-catalyzed C−H activation/intramolecular Diels−Alder reaction/1,3-dipolar cycloaddition cascade process (Scheme 1, eq 3). It is worth mentioning that the diazole in this cascade reaction can act as a traceless directing group,[2p,7] releasing N_2 during the pericyclic cascade after the Rh catalyst.

Scheme 1. Strategies to Polycyclic Structures



We commenced our examination by investigating the cascade annulation of 1,3,4-oxadiazole **1a** and (4-methylpent-4-en-1-yn-1-yl)benzene **2a**. Although **3aa** should be the key intermediate in the proposed cascade reactions, the initial experiments were performed by optimizing the reaction conditions for the first

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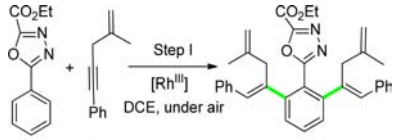
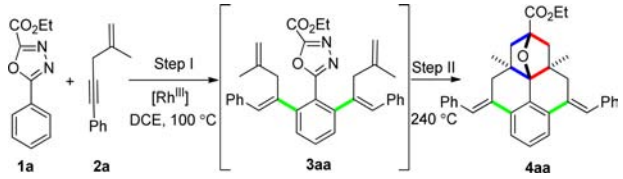
Table 1. Optimization of the Reaction Conditions To Form Intermediate 3aa[a]



entry	t (°C)	acid	additive	yield of **3aa** (%)[b]
1[c,d]	110	AcOH		31
2[c,d]	110	PivOH		34
3[c,d]	100	PivOH		63
4[c,d]	100	$PhOCH_2COOH$		62
5[d]	100	$PhOCH_2COOH$		63
6	100	$PhOCH_2COOH$		69
7	100	$PhOCH_2COOH$	$Cu(OAc)_2$	63
8	100	$PhOCH_2COOH$	CuOAc	74
9	100	$PhOCH_2COOH$	$Cu(acac)_2$	46
10	100	$PhOCH_2COOH$	$AgCO_3$	74
11	100	$PhOCH_2COOH$	AgOAc	80

[a]Reaction conditions unless otherwise specified: 0.03 mmol of **1a**, 2.2 equiv of **2a**, 8 mol % of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$, 0.5 mL of DCE, 1 equiv of acid, 0.4 equiv of additive, 11 h, under air. $[Rh^{III}]$ = $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$. [b]Isolated yield of **3aa**. [c]Under Ar. [d]With 5 mol % of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$.

Table 2. Optimization of the One-Pot Reaction Conditions[a]



entry	additive/equiv	solvent	yield of **4aa** (%)[b]
1		mesitylene	27
2		1,2-dichlorobenzene	17
3		diphenyl oxide	20
4	NaOAc/1	mesitylene	NP
5	Na_2CO_3/1	mesitylene	40
6	K_2CO_3/1	mesitylene	48
7	K_2CO_3/2	mesitylene	65
8	**K_2CO_3/3**	**mesitylene**	**90**
9	K_2CO_3/4	mesitylene	80

[a]Reaction conditions unless otherwise specified: 0.03 mmol of **1a**, 2.2 equiv of **2a**, 8 mol % of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$, 0.5 mL of DCE, 1 equiv of $PhOCH_2COOH$, 0.4 equiv of AgOAc, 100 °C, 11 h, under air (step I). Subsequently, 0.4 mL of solvent was directly added to the mixture of step I, and the temperature was increased to 240 °C, 10 h (step II). $[Rh^{III}]$ = $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$. [b]Isolated yield of **4aa**.

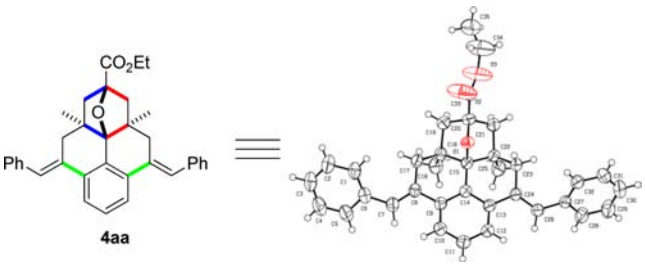
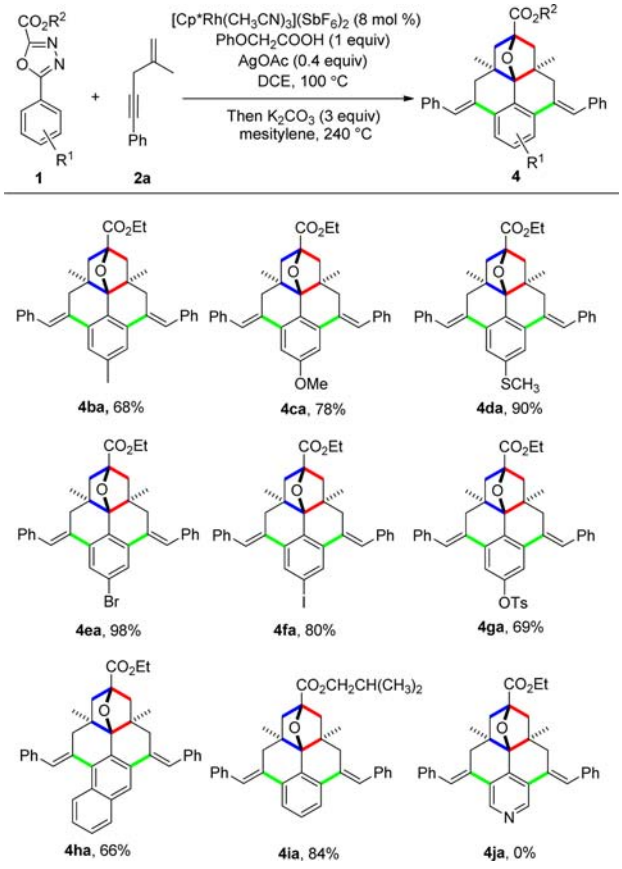


Figure 1. X-ray crystal structure of **4aa**.

Scheme 2. Substrate Scope of 1,3,4-Oxadiazoles[a]



[a]Reaction conditions unless otherwise specified: 0.03 mmol of **1**, 2.2 equiv of **2a**, 8 mol % of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$, 0.5 mL of DCE, 1 equiv of $PhOCH_2COOH$, 0.4 equiv of AgOAc, 100 °C, 10–24 h, under air. Subsequently, 0.4 mL of mesitylene was directly added to the mixture, and the temperature was increased to 240 °C, 6–11 h. Isolated yield of **4**.

ortho-C–H activation step (Table 1, step I).[8] Compared to other acids, $PhOCH_2COOH$ gave the higher yield (Table 1, entries 1–3). Lowering the reaction temperature and even being open to the air did not influence the reaction efficiency (Table 1, entries 4 and 5). Raising the catalytic loading gave a slightly better yield (Table 1, entry 6). Among the additives investigated, AgOAc was the best choice to afford **3aa** in 80% yield (Table 1, entries 7–11).

Next, reaction conditions of the one-pot process to directly generate decahydropyrene product **4aa** without isolated intermediate **3aa** are examined with the best conditions of C–H activation in hand (Table 2). To our delight, the cascade polycyclic product **4aa** can be detected when we directly added high-boiling-point solvents into the mixture of step I and then increased the temperature to 240 °C (Table 2, entries 1–3). However, low yields imply that the acid environment in step I might affect the cascade reaction to continue smoothly. Throughout further additive screening, 3 equiv of K_2CO_3 was best suited for this [4 + 2]/$-N_2$/[3 + 2] reaction, giving the final product **4aa** in 90% yield (Table 2, entries 4–9). It is possible that a pH value in step II was crucial to this cascade cyclization reaction. The structure of the final product **4aa** was characterized by X-ray crystallography (Figure 1).[9]

With the optimized one-pot reaction conditions in hand, we explored the generality of the substrate scope of 1,3,4-

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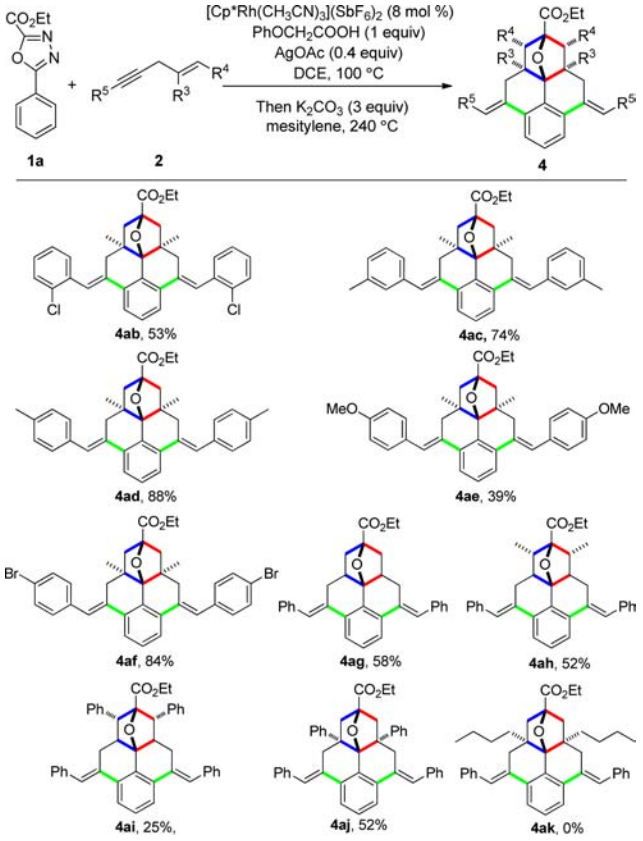
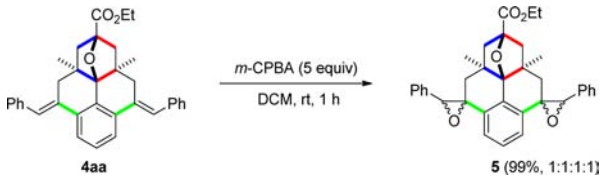
Scheme 3. Substrate Scope of Alkynes[a]



[a]Reaction conditions unless otherwise specified: 0.03 mmol of **1a**, 2.2 equiv of **2**, 8 mol % of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$, 0.5 mL of DCE, 1 equiv of $PhOCH_2COOH$, 0.4 equiv of AgOAc, 100 °C 10−24 h, under air. Subsequently, 0.4 mL of mesitylene was directly added to the mixture, and the temperature was increased to 240 °C, 6−11 h. Isolated yield of **4**.

Scheme 4. Oxidization of Decahydropyrene 4aa



oxadiazoles, as shown in Scheme 2. 1,3,4-Oxadiazoles bearing either an electron-donating or -withdrawing group at the 4-position of the phenyl ring are well-tolerated, affording the corresponding polycyclic products in good to excellent yields (**4ba**−**4ga**). Good results were also obtained with a naphthalene ring, generating **4ha** in 66% yield. In addition, using ester **1i** resulted in the smooth cyclization to **4ia**. However, **1j** and some other substrates were not suitable for this cascade reaction.[8]

To further demonstrate the versatility of this tandem catalytic process, a variety of substituted pent-4-en-1-yn-1-ylbenzenes are synthesized and tested, as shown in Scheme 3. Gratifyingly, alkyne moieties with several different substituents on the benzene ring were all applicable for the tandem reactions to afford the cyclization products **4ab**−**4af** in good to excellent yields. When **2g** was applied, only 58% yield was obtained because **2g** as a coupling partner was not stable in this catalytic system. Notably, substituents on the end position of the vinyl group were suitable coupling partners but were proven to be less efficient in this cascade reaction, applying the desired products **4ah** and **4ai** only in low yields due to the steric hindrance. Furthermore, a phenyl group instead of a methyl group was installed in the alkene, leading to **4aj** in 52% yield. Meanwhile, attempts to use butyl substituent **2k** as a coupling partner failed.

To make better use of this special structure of decahydropyrenes, we subjected it to further transformation (Scheme 4). As we expected, **4aa** could be oxidized to diepoxy product **5** in high total yield by *m*-CPBA, while four isomers were detected. After recrystallization, one of the isomers can be observed (**5′**).

In summary, we have successfully developed a unique cascade annulation for the one-pot synthesis of decahydropyrenes from 1,3,4-oxadiazoles and 1,4-enynes (a special case of alkynes) by using diazole as a traceless directing group. This powerful methodology involves multistep reactions and various transformations: (1) tandem rhodium-catalyzed *ortho*-C−H activation; (2) [4 + 2] cycloaddition reaction; (3) nitrogen release; (4) [3 + 2] cascade cycloaddition reaction. Furthermore, this cascade cyclization strategy allows the formation of six new C−C bonds, three new rings together with an oxygen bridge ring. This type of structure is the first constructed by using transition-metal-catalyzed cascade reactions. Further applications of decahydropyrenes are still under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02768.

Experimental procedures, structural proofs, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(8) For more details, see the Supporting Information.

(9) Crystallographic data for **4aa**: CCDC 1509293, $C_{35}H_{34}O_3$, M = 502.62, space group $\bar{P}1$, cell: a = 9.4048(4) Å, b = 11.0851(4) Å, c = 13.4547(4) Å, α = 76.126(3)°, β = 82.803(3)°, γ = 86.051(3) °, temperature = 291 K, calcd 1.237 mg/mm^3.

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